CYMABAY THERAPEUTICS

H.C. Wainwright
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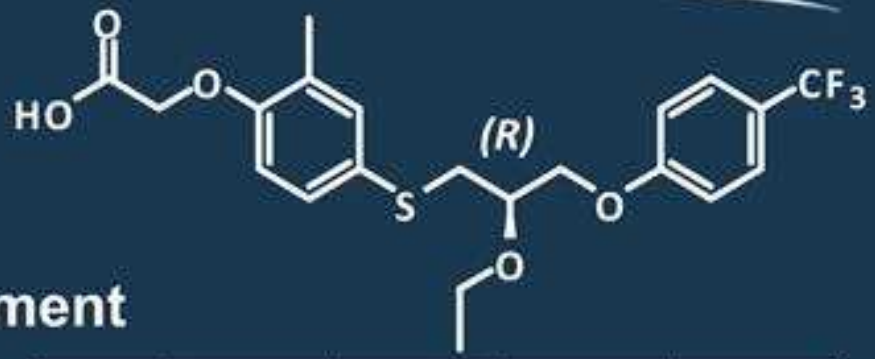
Seladelpar as a Potential Agent to Treat NASH

Seladelpar (MBX-8025)



- Once daily orally administered
- Only truly selective PPARδ in development
- PPARδ profile ideal for liver disease
  - Hepatocytes, Kupffer and stellate cells
- 90-fold more potent than elafibranor

EC_{50}	PPARδ	PPARα	PPARγ	FXR
nM	2	1,630	Inactive	Inactive

Potency for PPARδ drives potential as foundational therapy:

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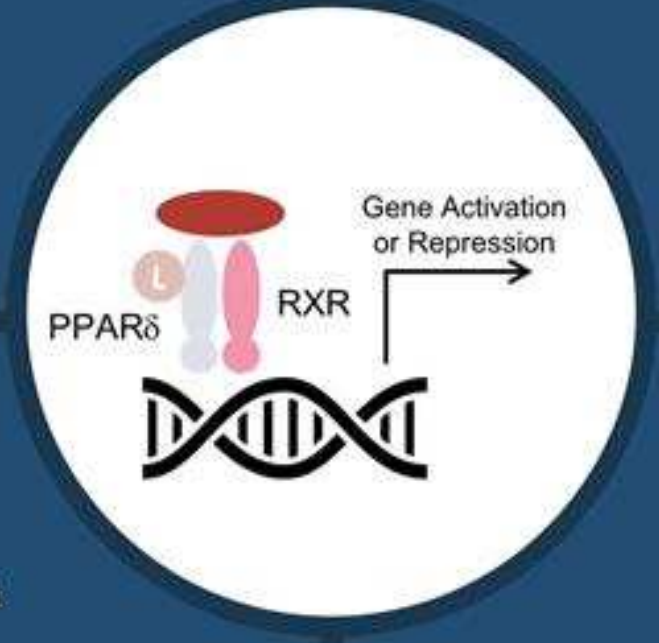
PPARδ Mediated Pharmacological Actions
Multiple potential benefits in NASH

Cardiovascular & Metabolic Effects

- ↓ LDL-C, TG and Fatty acids
- ↑ Insulin sensitivity
- ↑ Hepatic lipid metabolism

Fibrosis

- ↓ Connective Tissue Growth Factor (CTGF), TIMP, αSMA
- ↓ Stellate cells
- ↓ Collagen deposition



Inflammation

- ↑ Anti-inflammatory (M2) Kupffer cells
- ↓ NFκB-dependent cytokines
- ↓ ALT
- ↓ hs-C-Reactive Protein (CRP)

Peripheral Metabolic Effects

- ↑ Lipid metabolism
- ↑ Insulin sensitivity
- ↓ Cholesterol absorption

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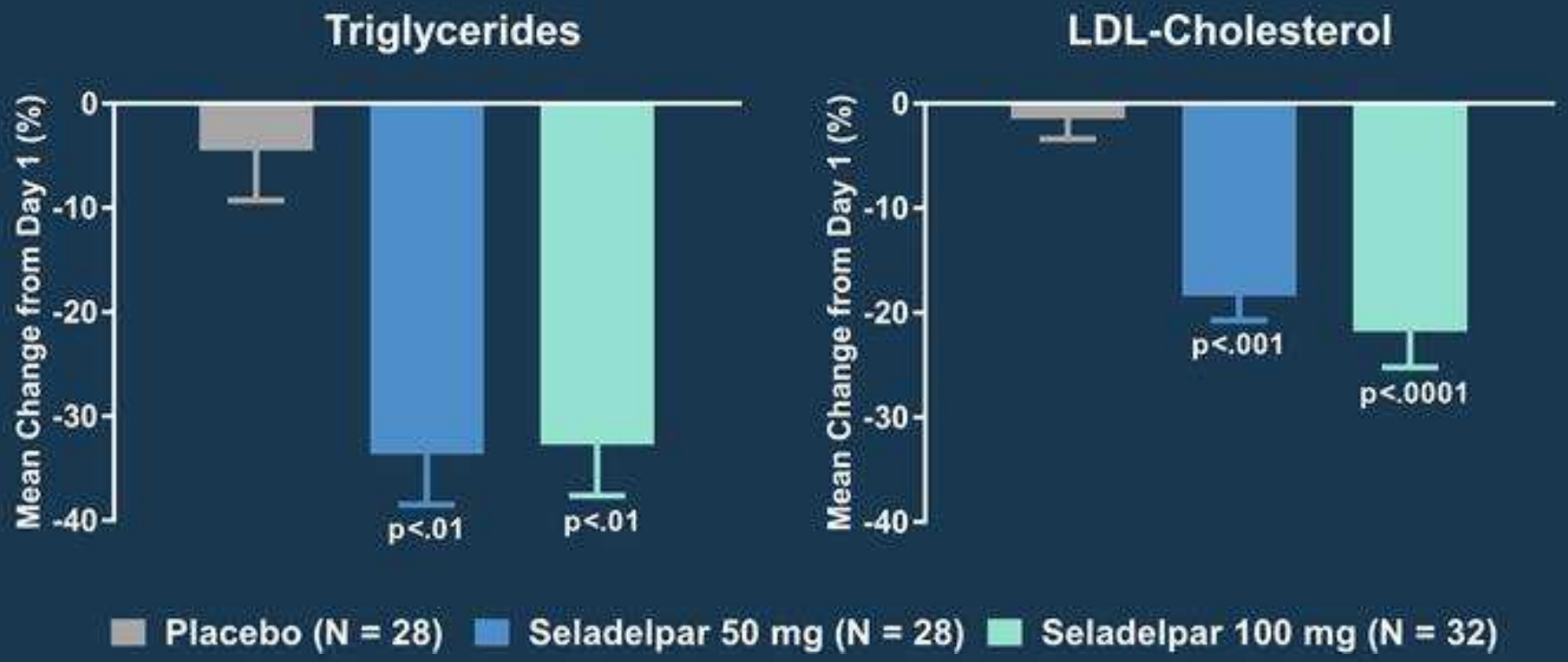
8-Week Phase 2 Study of Seladelpar in Mixed Dyslipidemia
Cardiovascular, metabolic and anti-inflammatory activity

- Obese patients with elevated TG, LDL-C and insulin resistance ("NAFLD")
- Decreases in hs-CRP, HOMA-IR, Free FA, small dense LDL, GGT and ALP



Bays et al. (2011) *J Clin Endocrinol Metab, 96: 2889-2897;* Choi et al. (2012) *Atheroclerosis*; 220: 470-477

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Evaluation of Seladelpar in the *foz/foz* Obese Diabetic Mouse Model for NASH

- Geoff Farrell & Fahrettin Haczeyni, Australian National University
- Matthew Yeh & George Haigh, UW Seattle
- Genetic loss of function mutation in *alms1* gene produces hyperphagic mice[1]
  - Obese
  - Insulin resistant and diabetic
  - Hyperlipidemic
  - Hepatic steatosis and lipotoxicity
  - Inflammation and hepatocellular damage
  - NASH established by 20 weeks
  - Liver fibrosis

Australian National University

UW Medicine PATHOLOGY

- Groups: Seladelpar 10 mg/kg & Vehicle oral, once daily

[1] Haczeyni et al (2015), *Obesity*.

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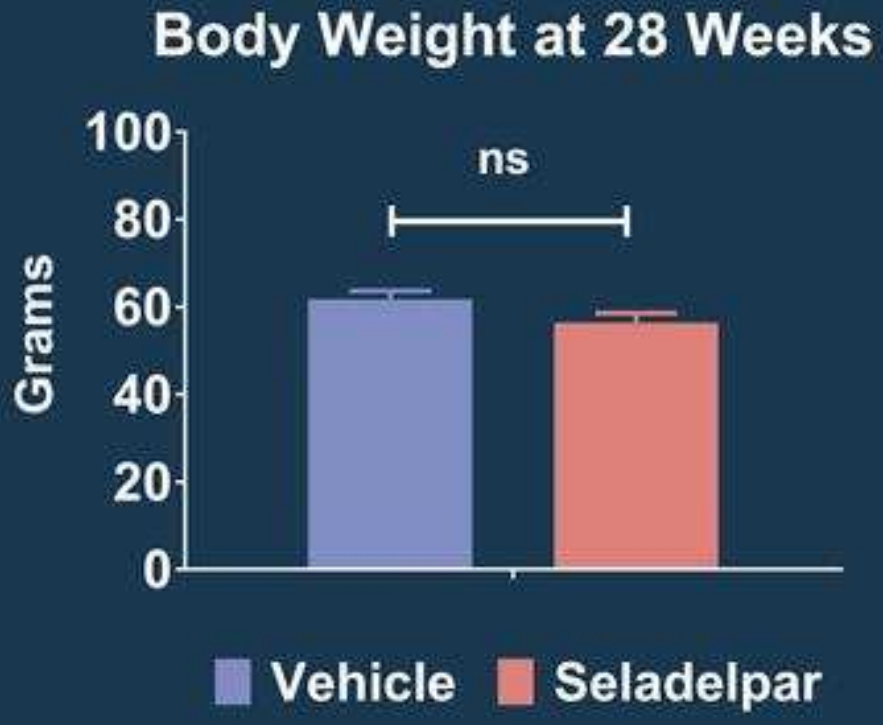
Effects of Seladelpar on Body Weight



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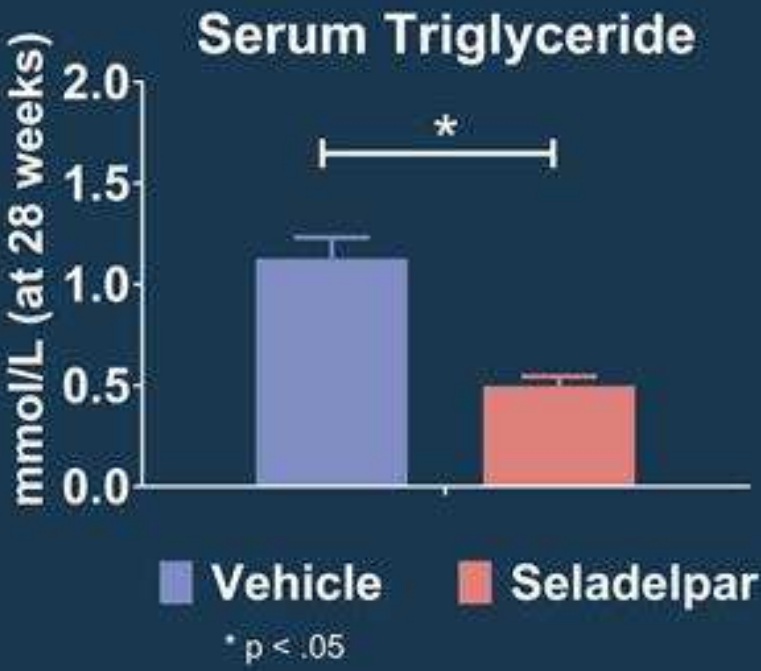
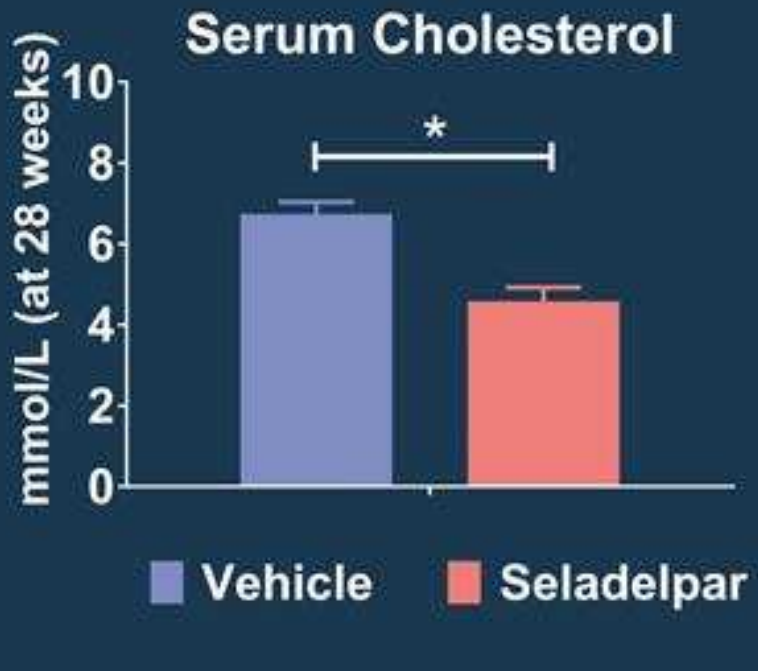
Evaluation of Seladelpar in the *foz/foz* NASH Model
Reductions in mice parallel clinical observations





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Evaluation of Seladelpar in the *foz/foz* NASH Model
Liver parameters and histopathology

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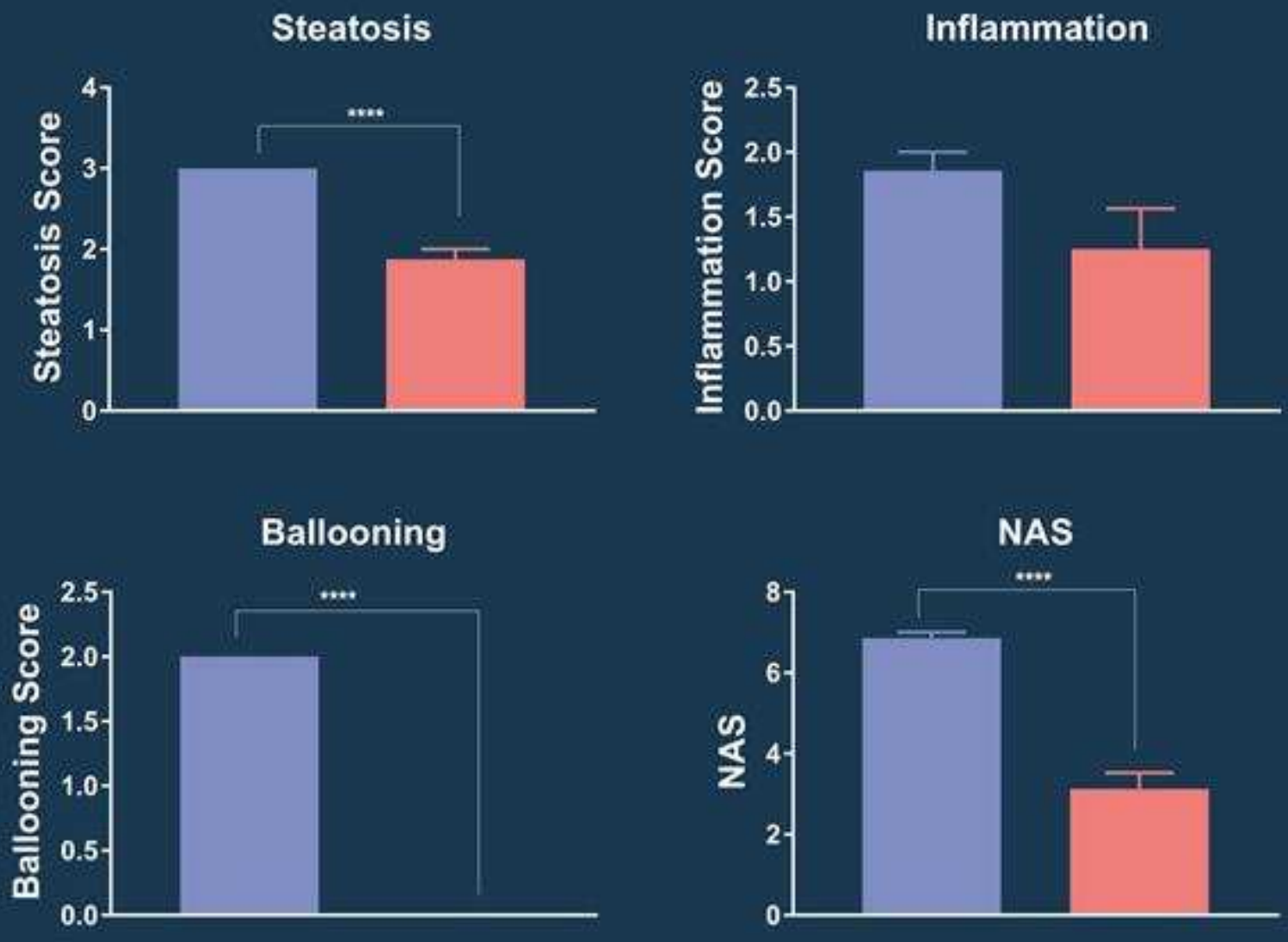
Evaluation of Seladelpar in the *foz/foz* NASH Model
Reduction in steatosis, inflammation and ballooning



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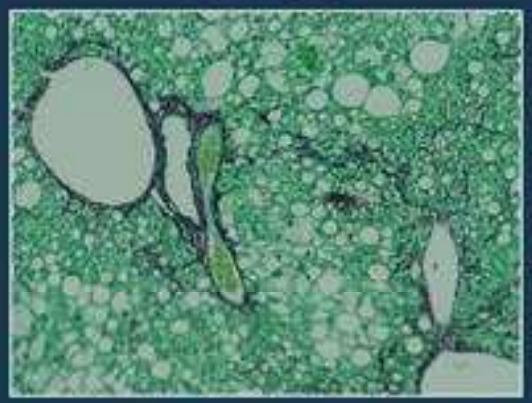
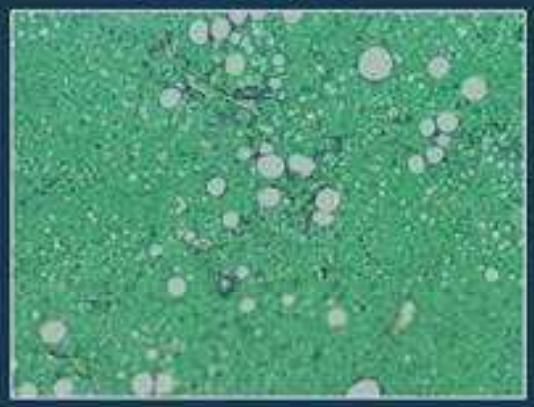
Evaluation of Seladelpar in the *foz/foz* NASH Model
Reduction in fibrosis

Vehicle



Seladelpar



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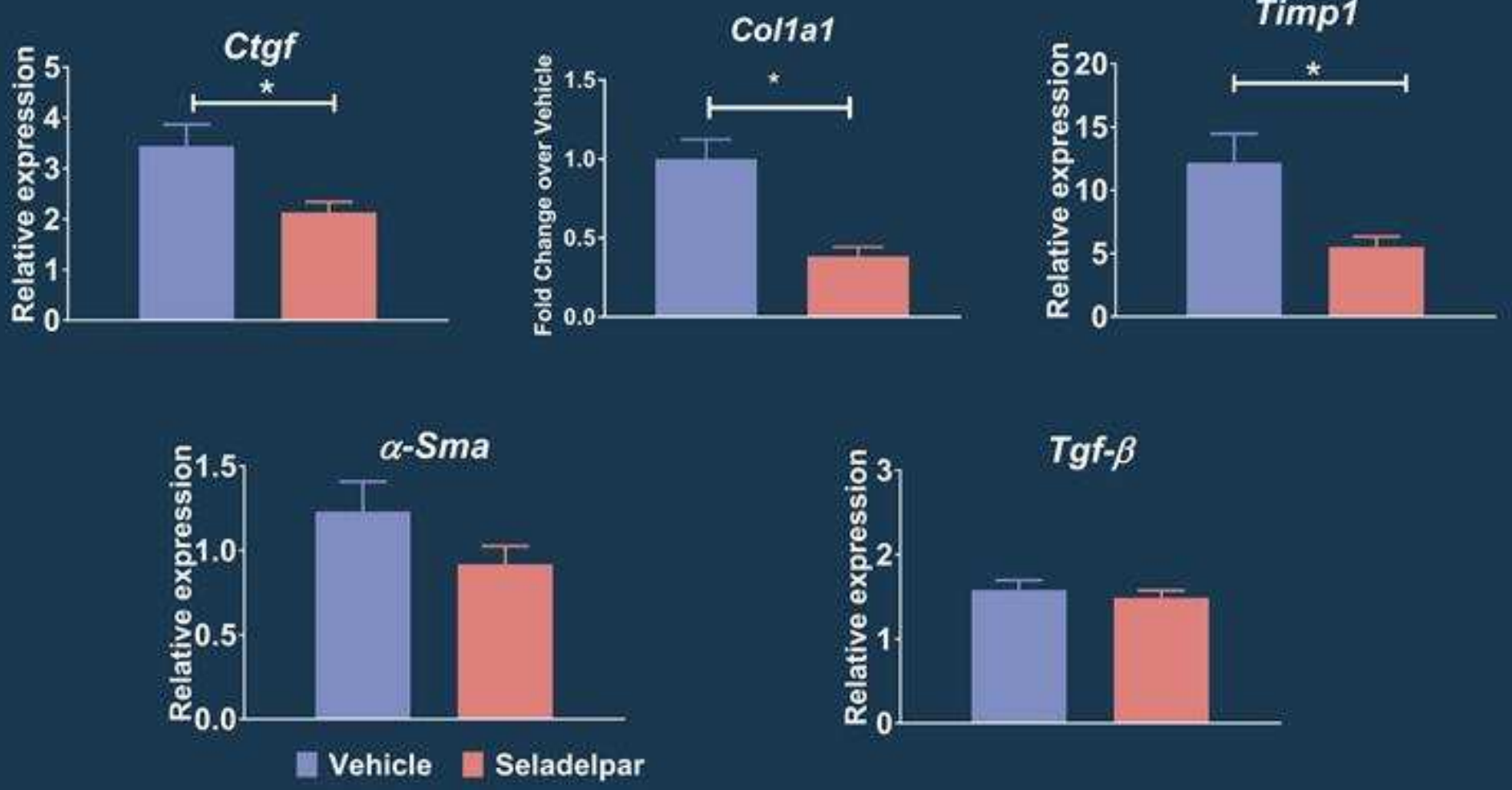
Evaluation of Seladelpar in the *foz/foz* NASH Model

Changes in expression of genes associated with fibrosis



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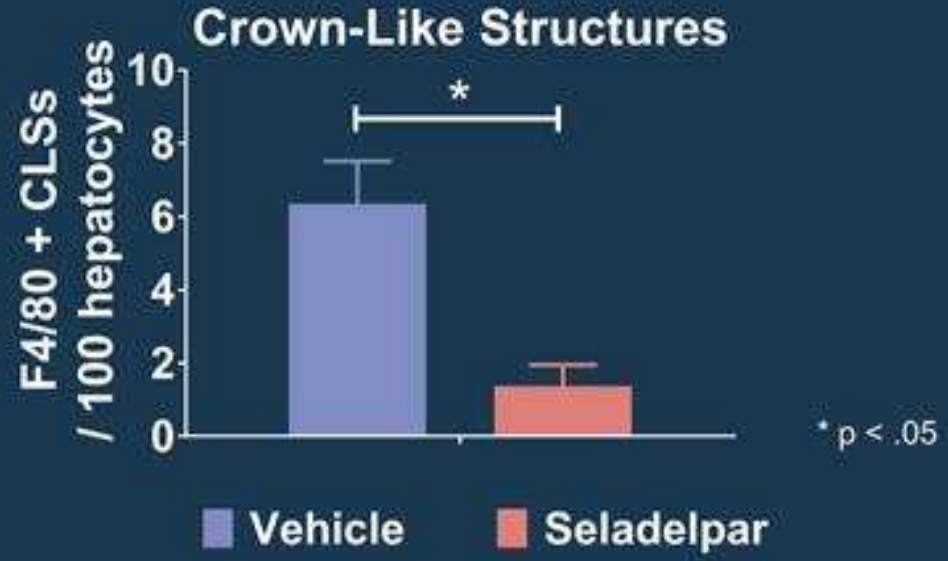
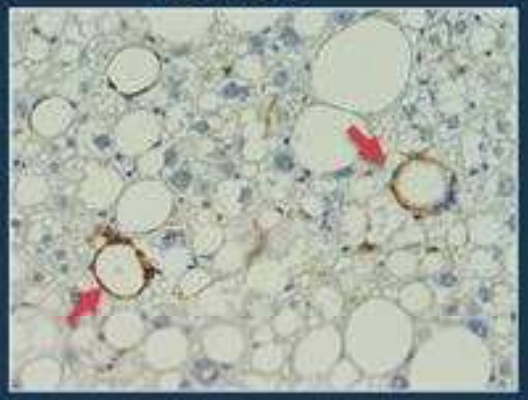
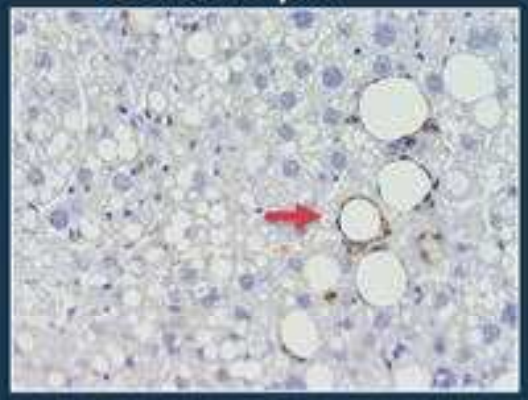
Evaluation of Seladelpar in the *foz/foz* NASH Model
Seladelpar reduces hepatic inflammation



Vehicle



Seladelpar



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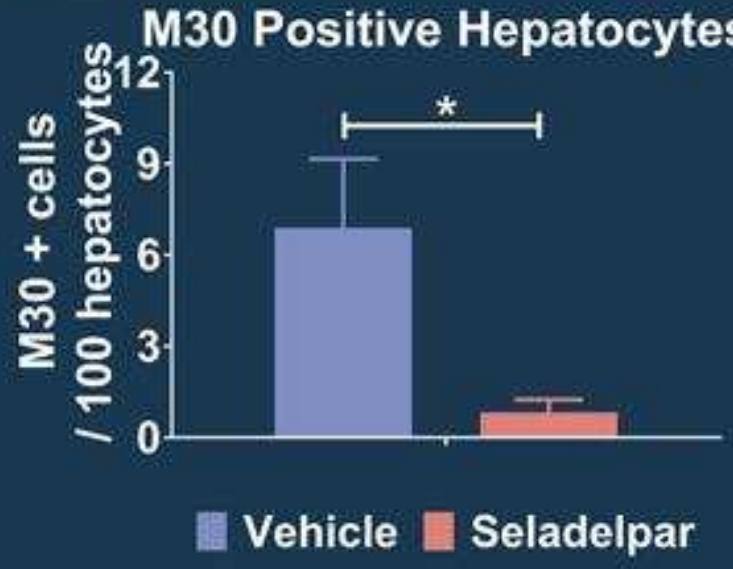
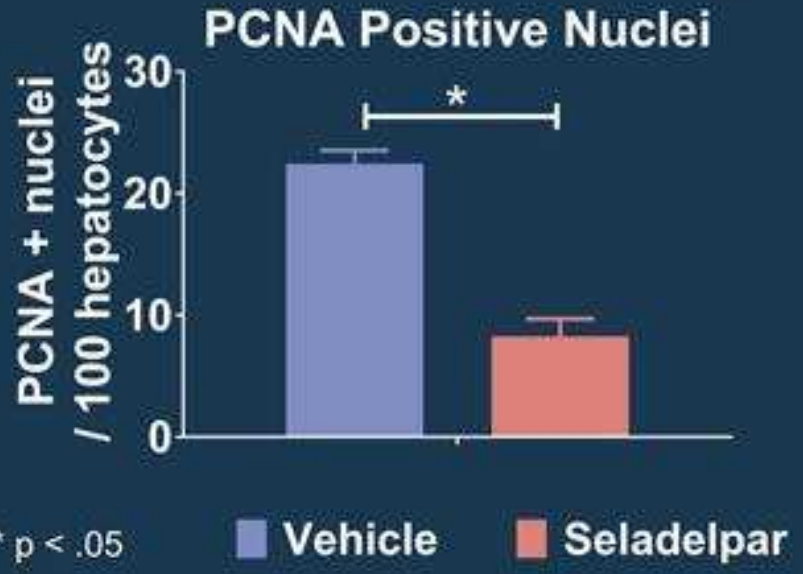
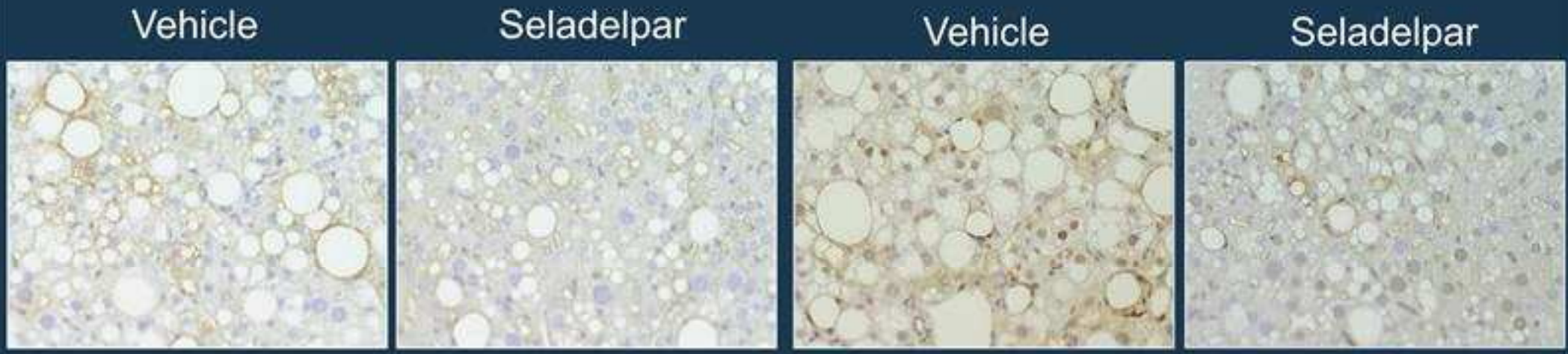
Seladelpar Decreases Hepatocyte Proliferation and Apoptosis







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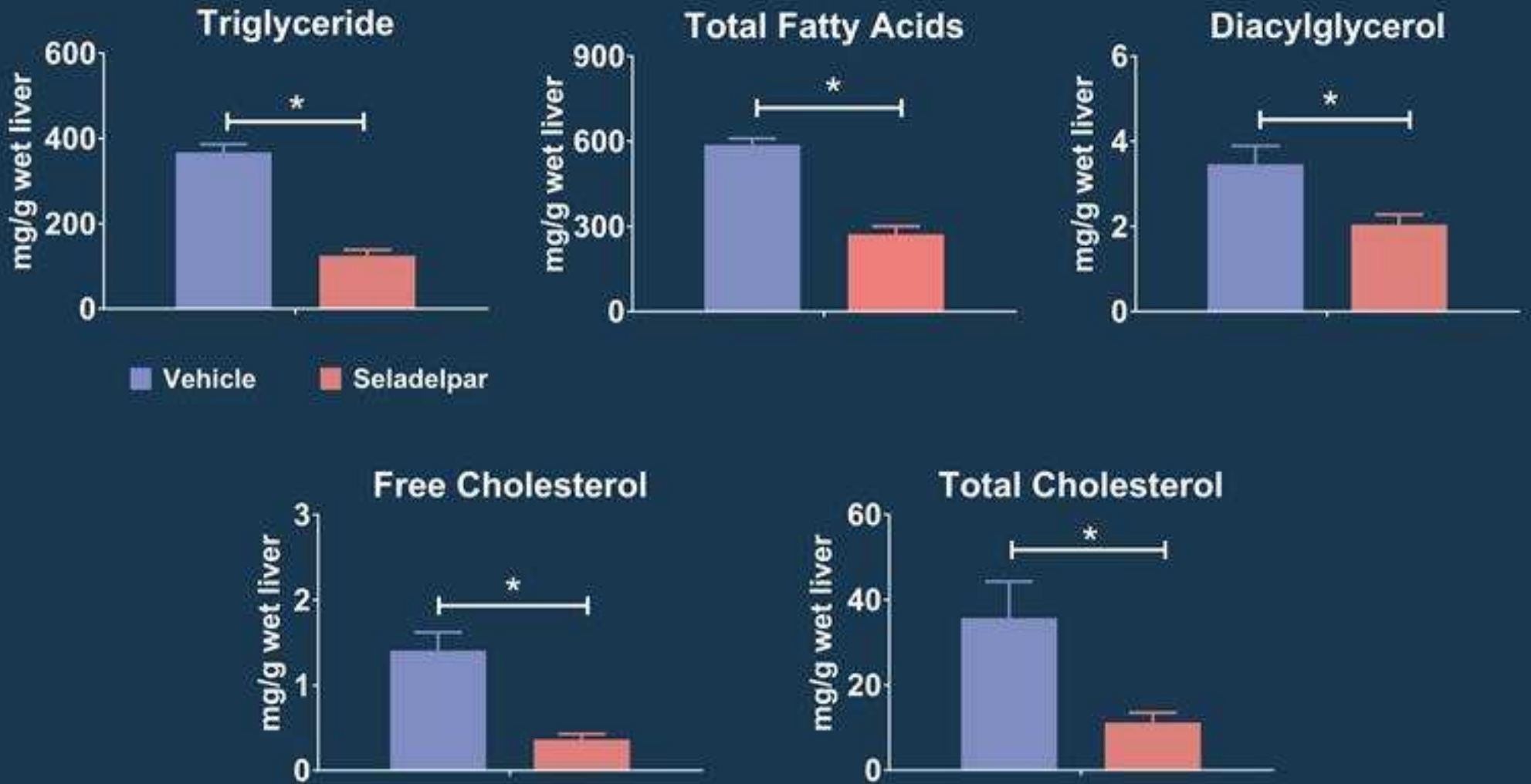
Seladelpar Reduces Hepatic Lipids



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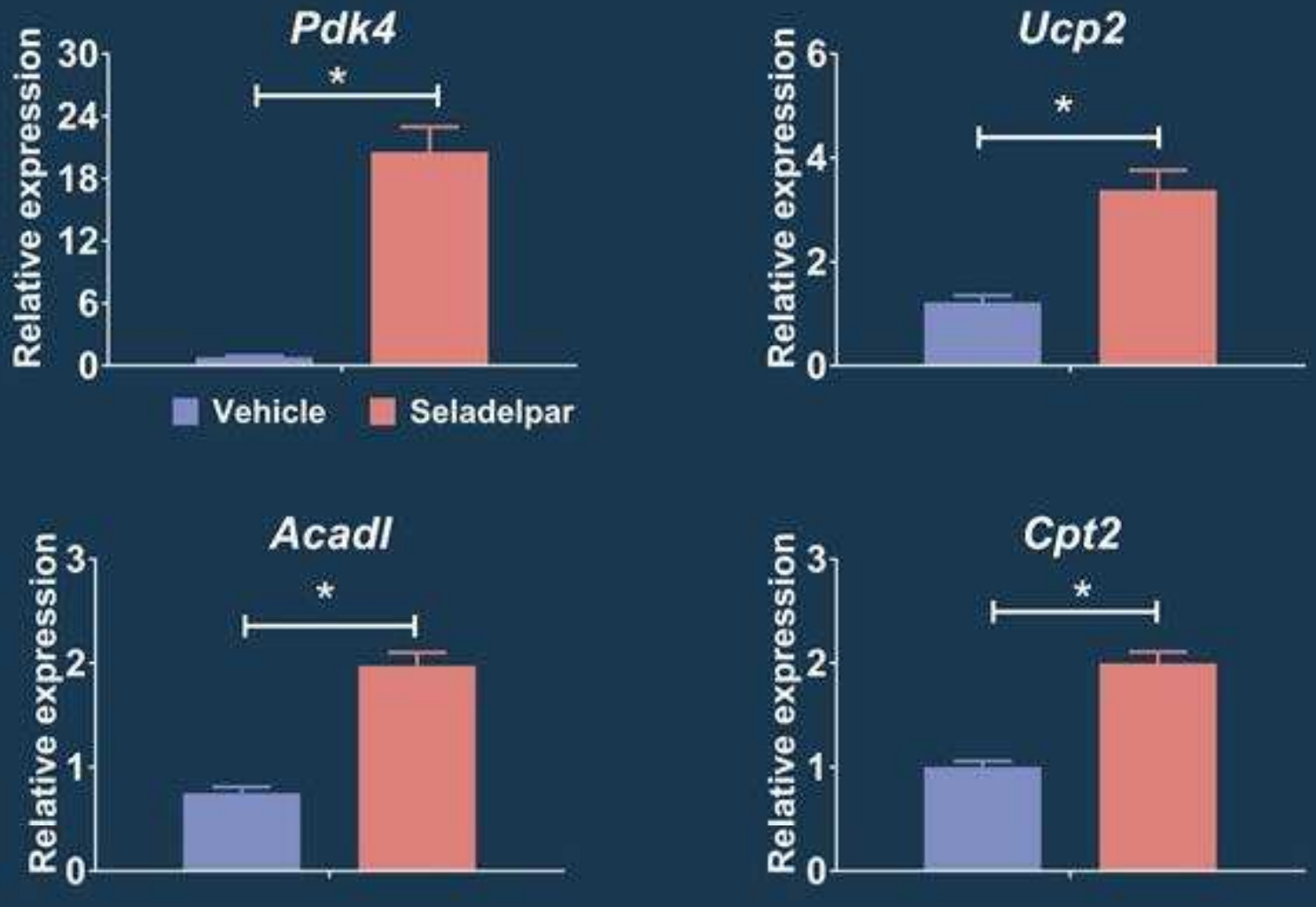
Seladelpar Increases Mitochondrial Fatty Acid Oxidation



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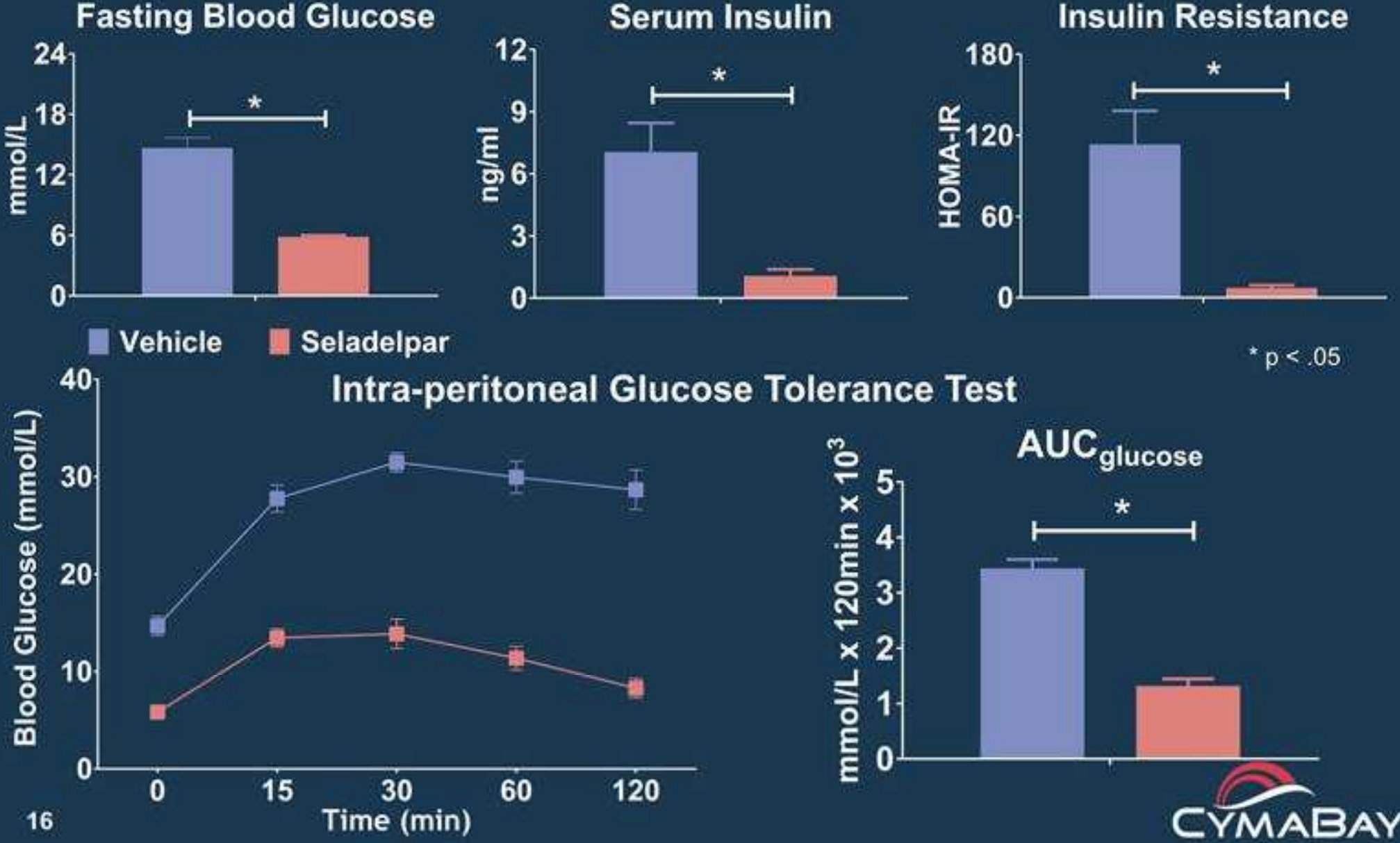
Effects of Seladelpar on Glycemic Control



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Evaluation of Seladelpar in the *foz/foz* NASH Model
Summary

- **Seladelpar reverses NASH, blocks fibrosis and provides multiple metabolic benefits**
  - Decreases inflammation
    - Macrophage infiltration and liver enzymes
    - Blocks inflammatory gene expression
  - Inhibits fibrosis
    - Strong reductions in collagen deposition
    - Reduced expression of fibrotic genes
  - Reduces hepatic lipid pools, free cholesterol and lipotoxic lipids
  - Improves fasting and prandial glucose
  - Reverses insulin resistance

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CymaBay's Development Strategy for Seladelpar

- **Second-line therapy for Primary Biliary Cholangitis**
  - Anti-cholestatic activity and profile potential for best in class
  - Inhibition of bile acid and cholesterol synthesis
  - Anti-inflammatory
  - PRIME designation in EU
  - Phase 2 study (26 weeks) to select Phase 3 doses in progress
    - Interim results early 3Q

- **Results provide a strong rationale for development of seladelpar as a foundational therapy for NASH**
  - Planning for a Phase 2 proof-of-concept study in NASH
  - Discussing with FDA and thought leaders

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