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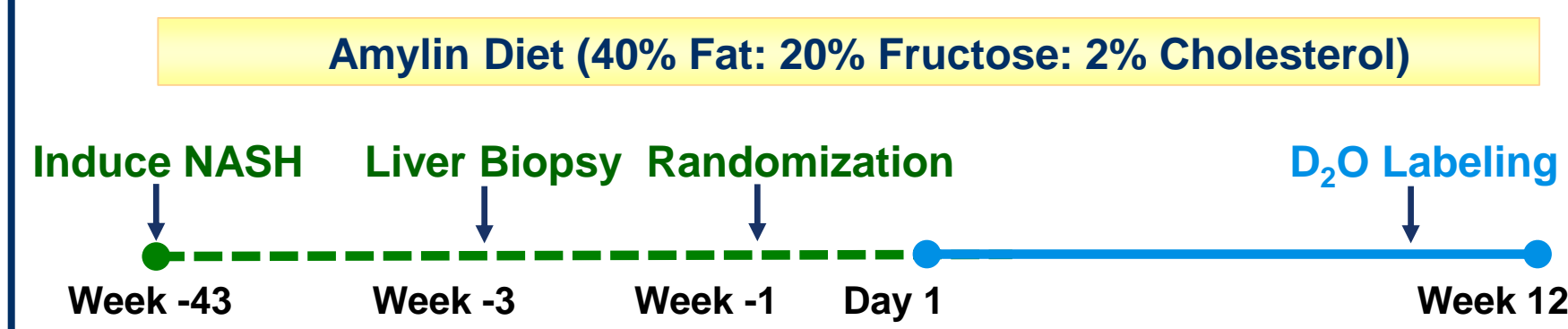
BACKGROUND

Seladelpar, a selective PPAR δ agonist, is in clinical development for the treatment of nonalcoholic steatohepatitis (NASH) and primary biliary cholangitis. Unlike the selective tissue distributions of PPAR α and PPAR γ , PPAR δ is ubiquitously expressed. Seladelpar exerts peripheral and hepatic effects through regulation of lipid metabolism, energy expenditure, and inflammation, and by reducing hepatic fibrosis. The efficacy of seladelpar on hepatic lipids, inflammation, and fibrosis was evaluated in a diet-induced and biopsy-confirmed NASH mouse model.

METHODS

Male C57BL/6J mice were fed a diet high in fat, fructose, and cholesterol for 43 weeks to induce NASH. Mice (n=11-12/group) with biopsy confirmed histologic steatosis (score ≥ 2) and fibrosis (stage ≥ 1) were randomized into vehicle, seladelpar (10 mg/kg), or obeticholic acid (OCA, 30 mg/kg, comparator) groups and treated daily for 12 weeks. Biochemical and liver histological parameters were assessed. Liver fibrogenesis was evaluated by LC/MS-MS analysis of the guanidine-soluble (less cross-linked ECM) fraction after D₂O (heavy water) labeling for 7 days.

Study Design



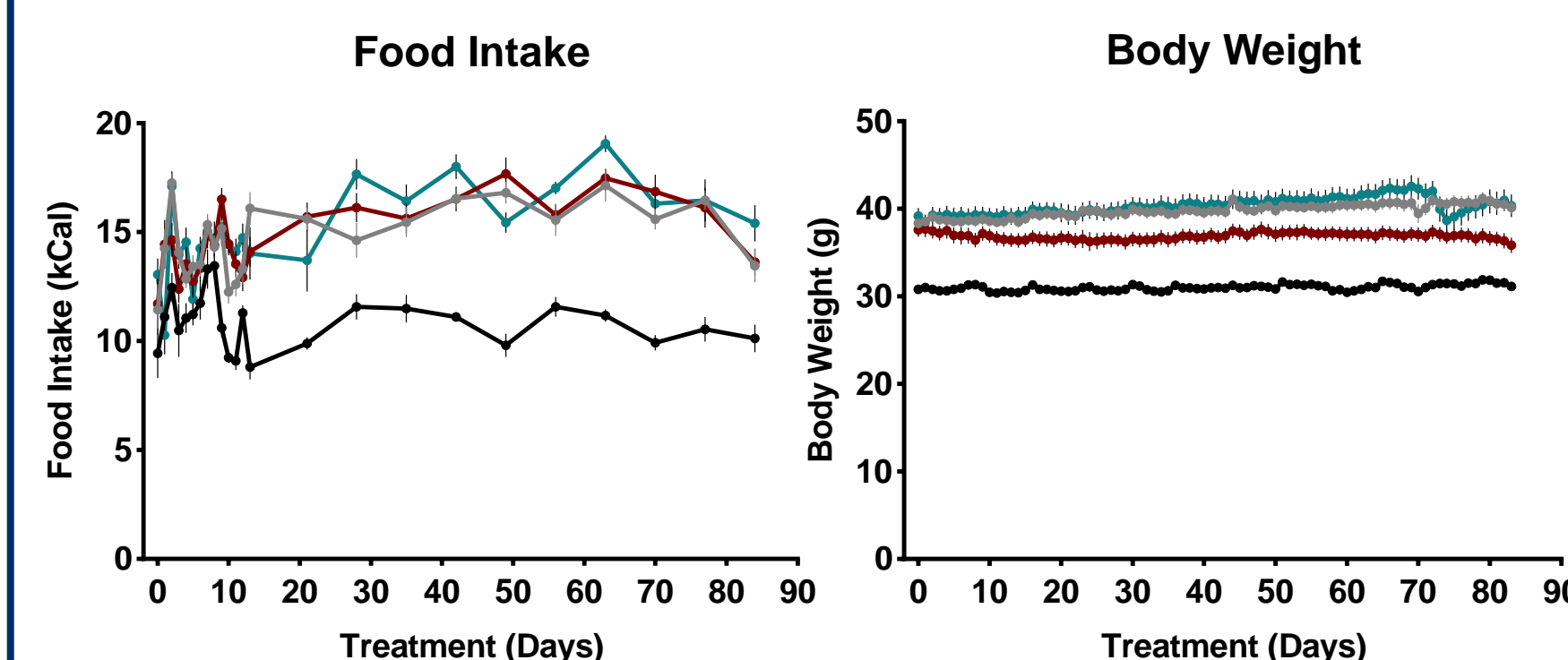
Treatment Groups

1. NASH Vehicle
2. Seladelpar
3. OCA
4. Chow Vehicle

P-Values vs. NASH Vehicle: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001
Data are presented as Mean \pm SE

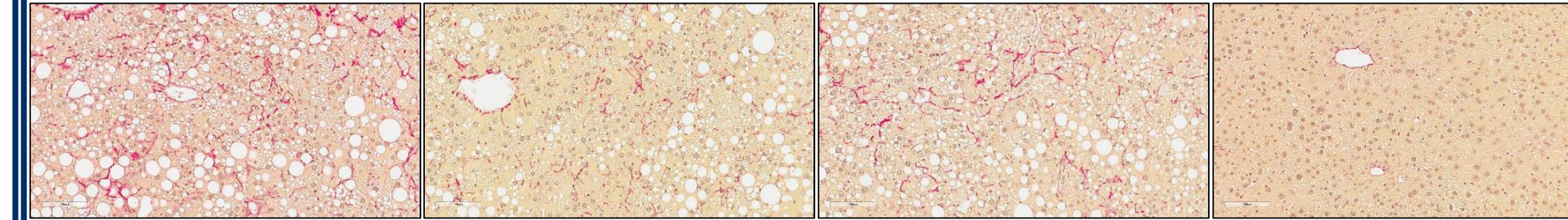
RESULTS

Food Intake & Body Weight



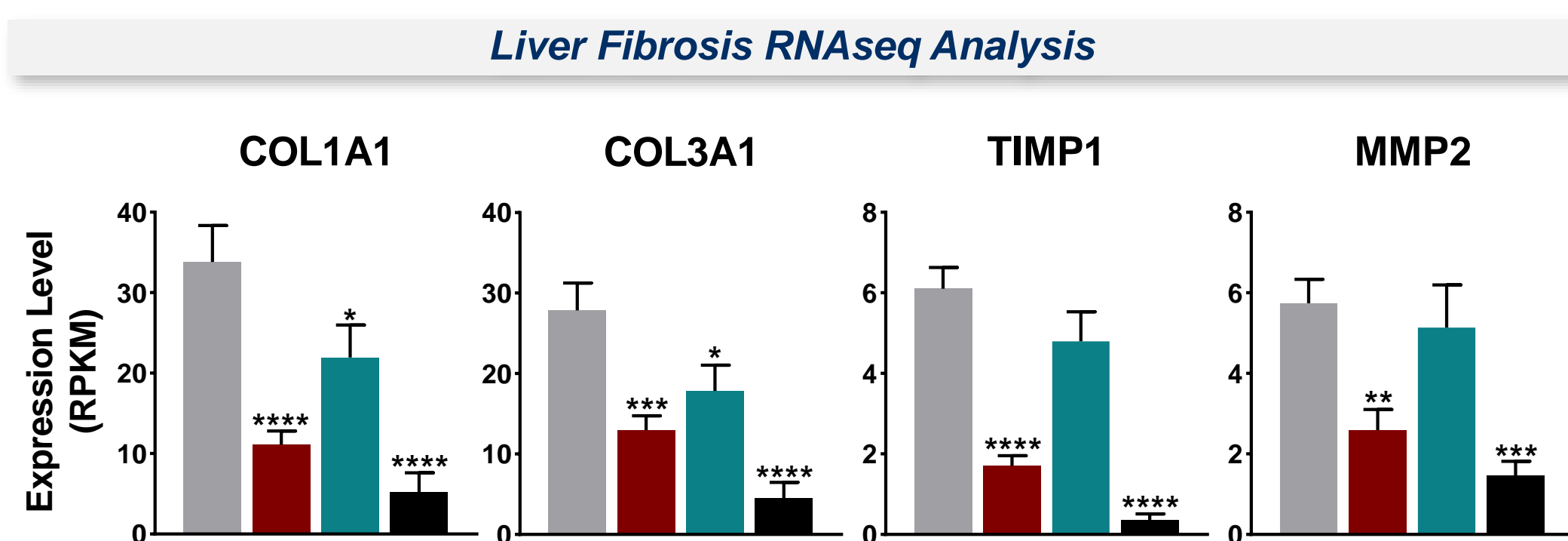
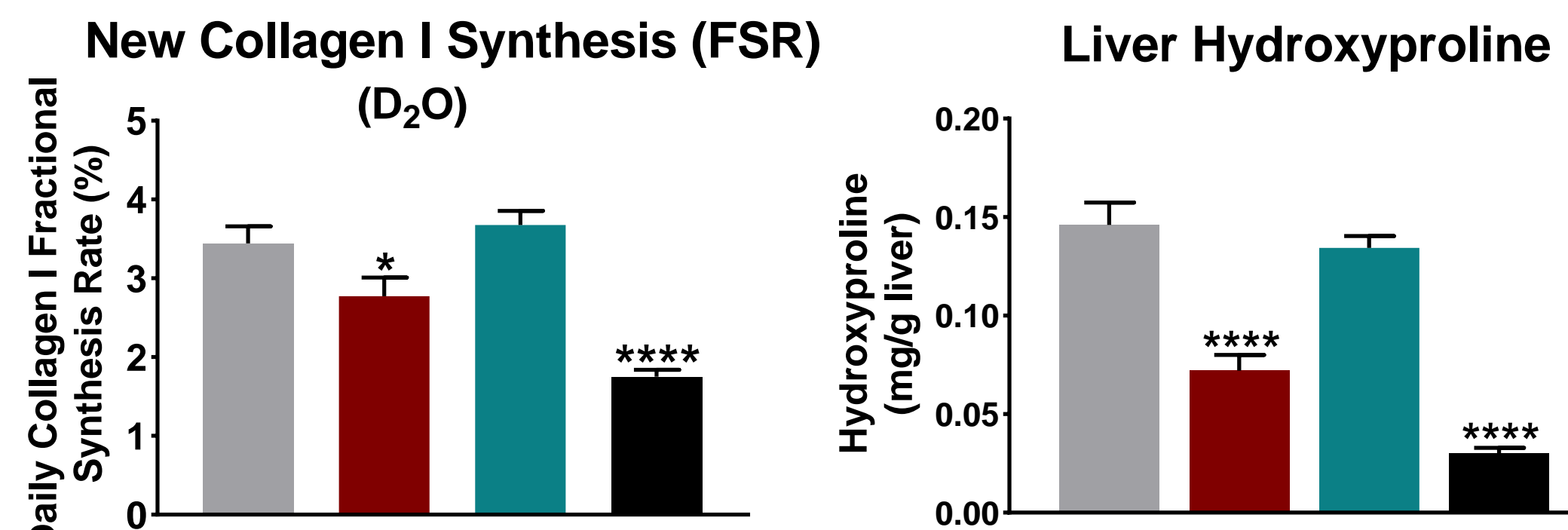
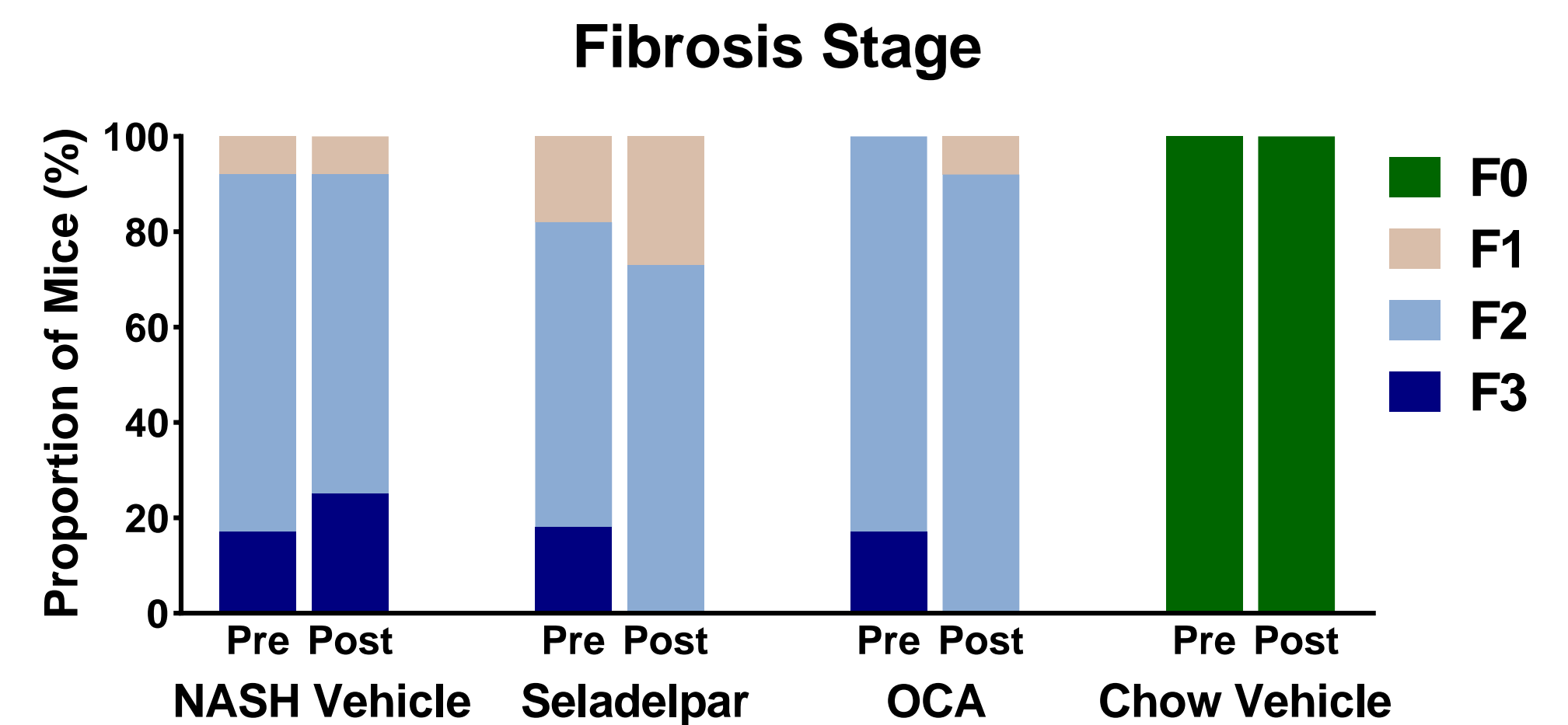
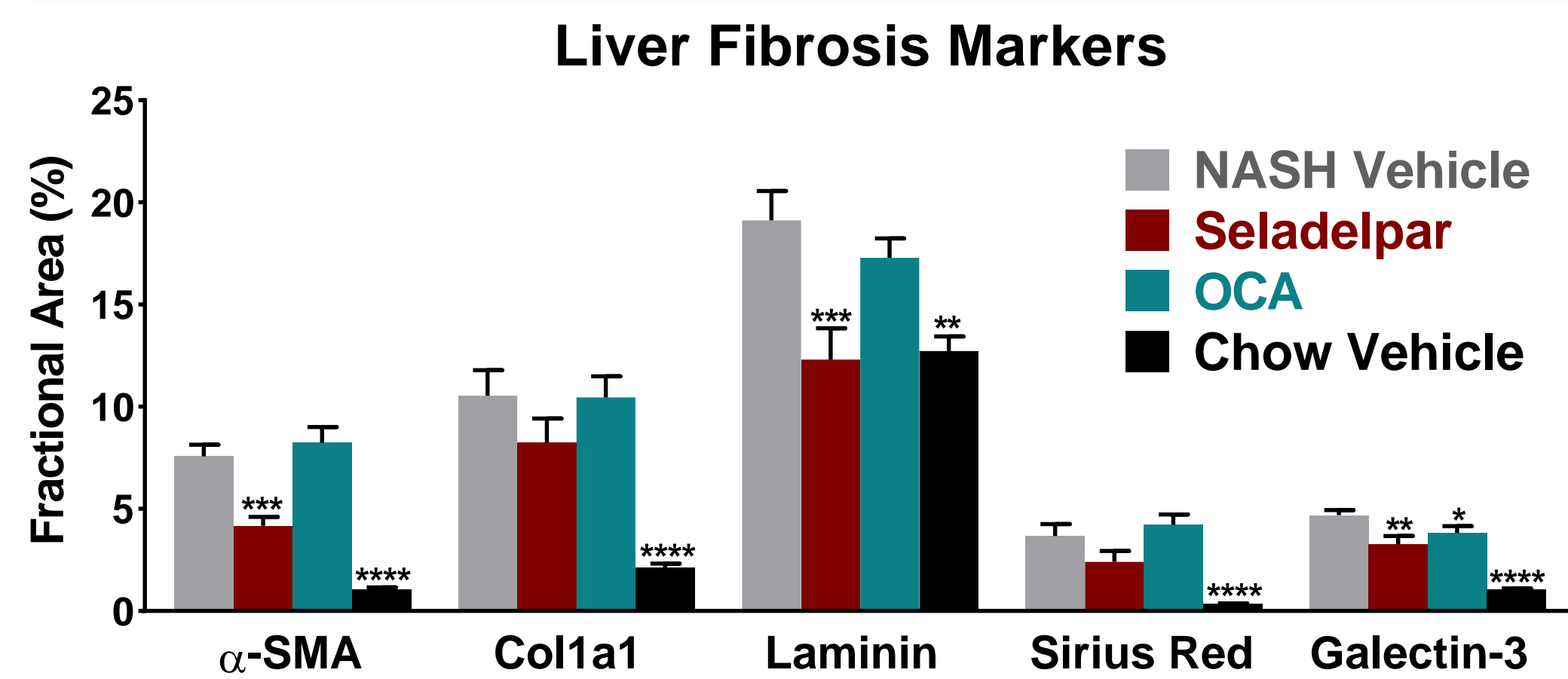
Liver Fibrosis

Sirius Red Staining



NASH Vehicle Seladelpar OCA Chow Vehicle

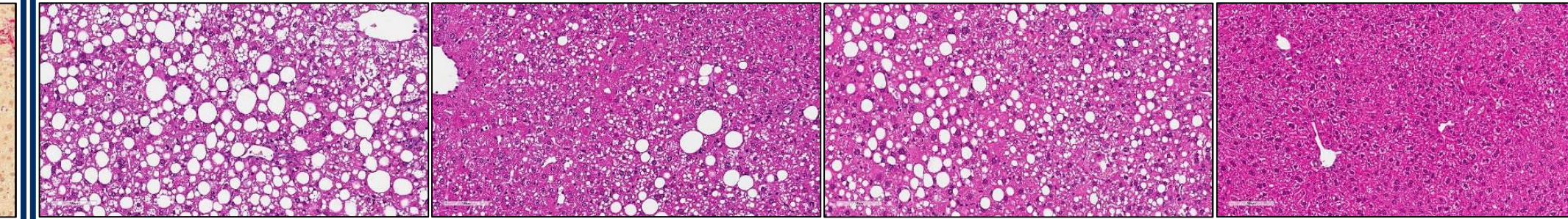
Fibrosis Morphometric Analysis (IHC)



RESULTS

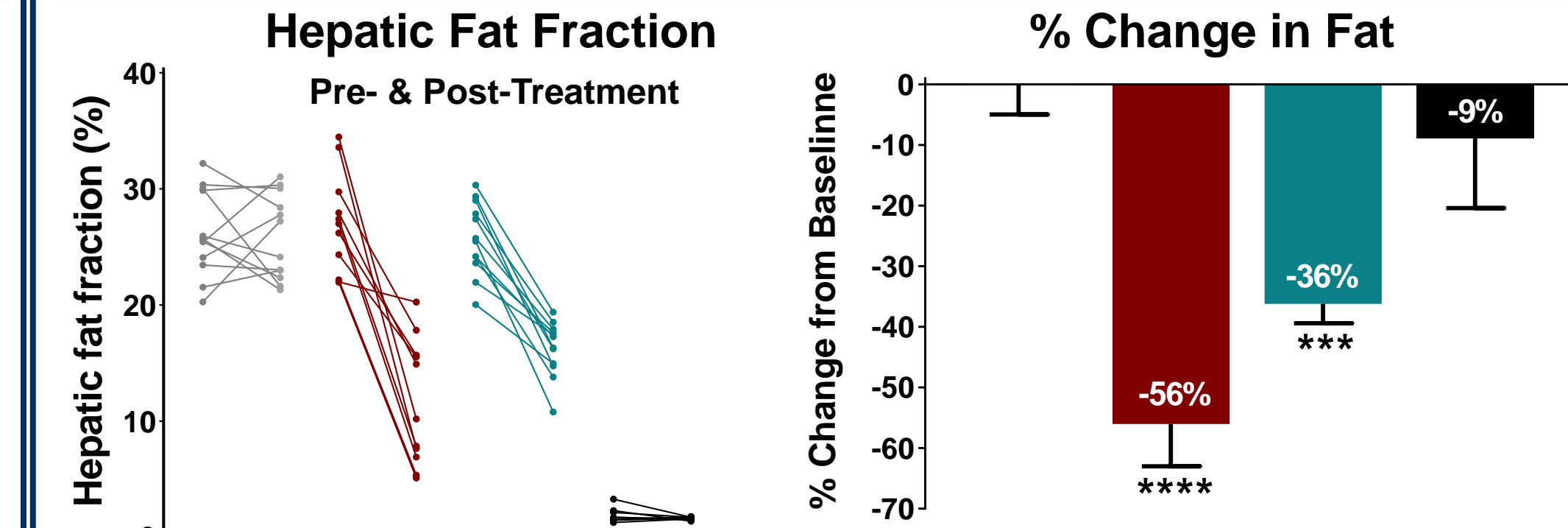
Liver Steatosis

H&E Staining

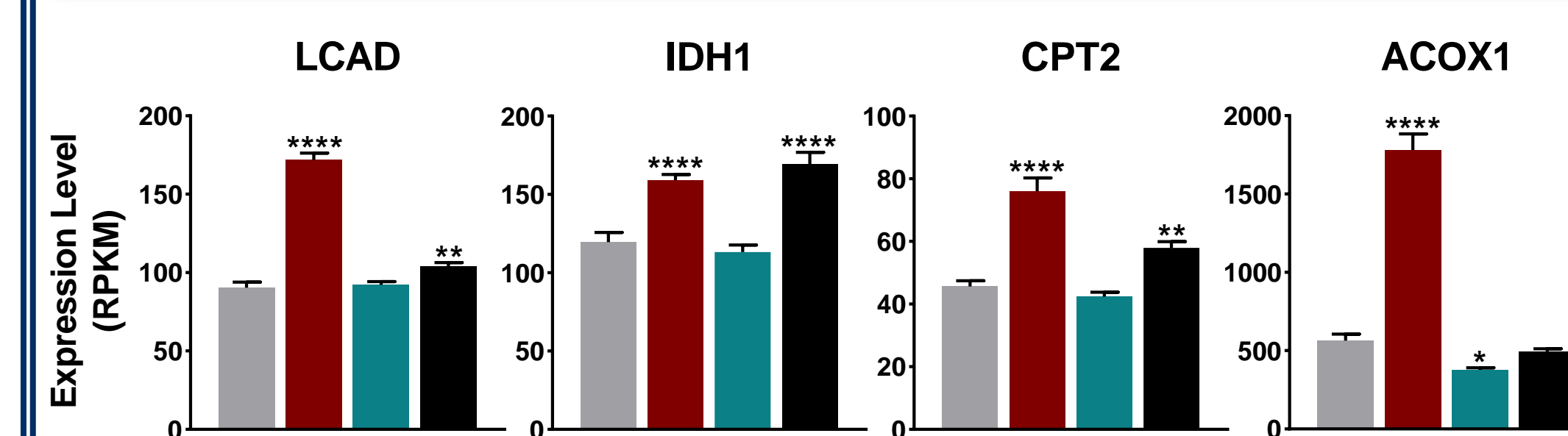
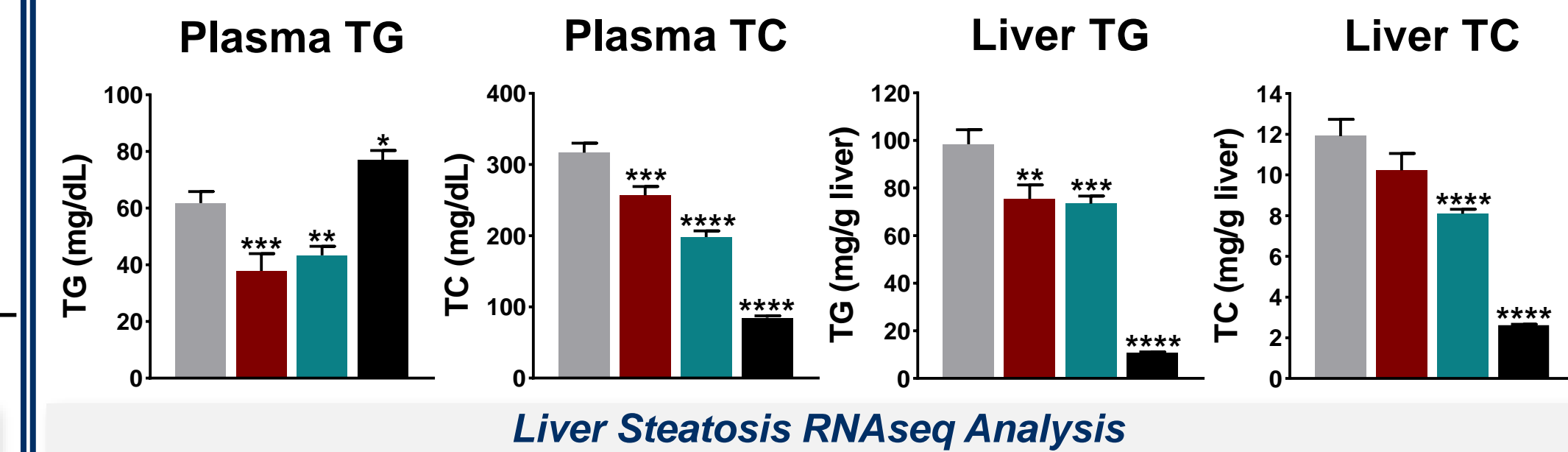
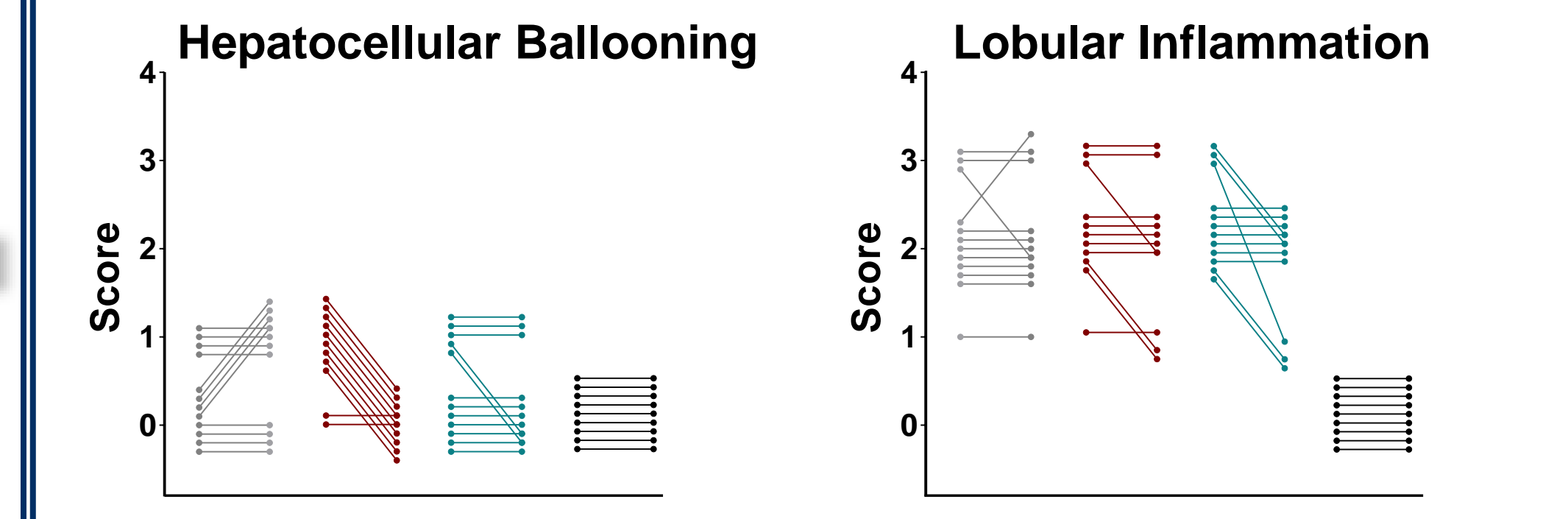
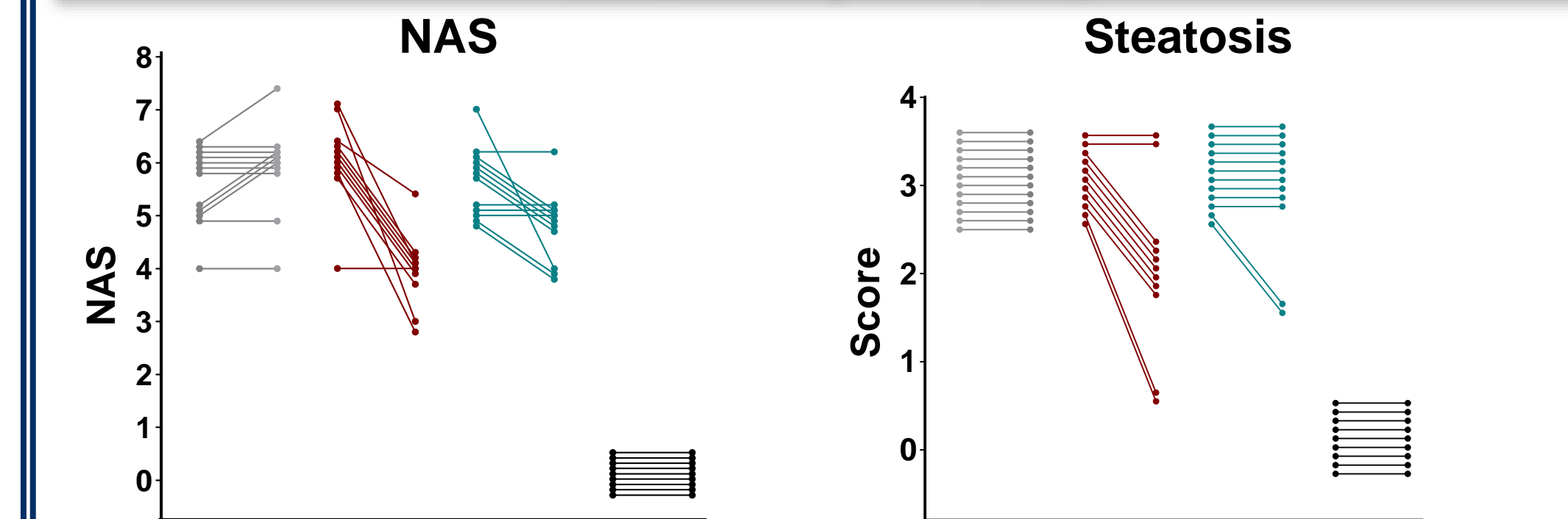


NASH Vehicle Seladelpar OCA Chow Vehicle

Steatosis Morphometric Analysis

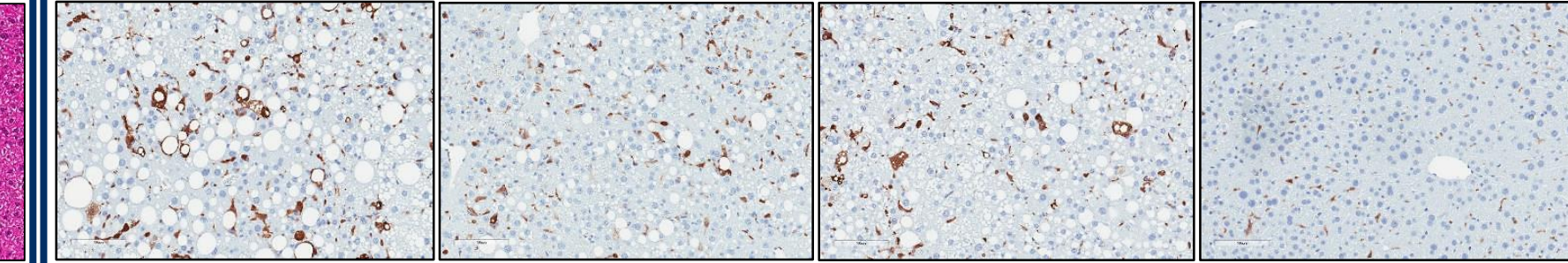


NAFLD Activity Score (NAS)

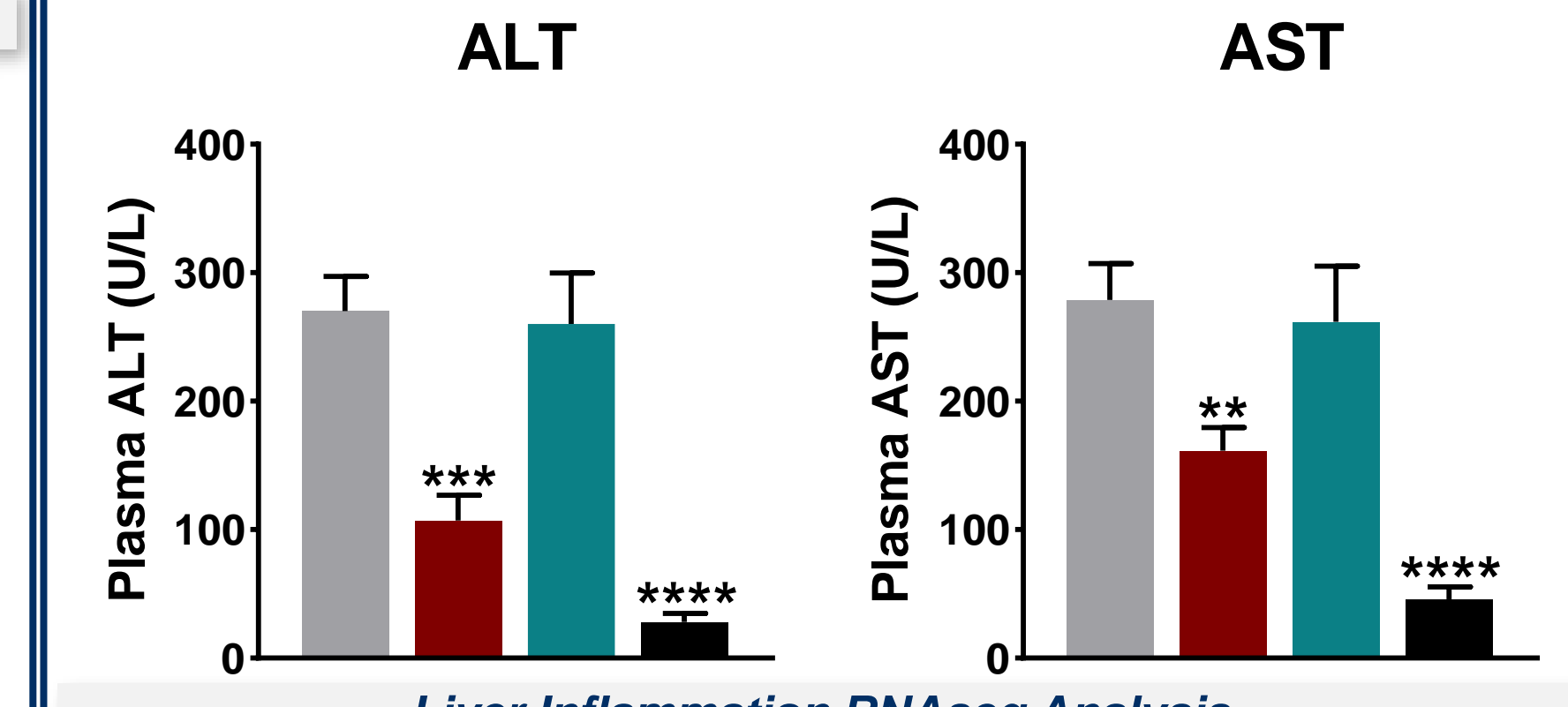


Inflammation

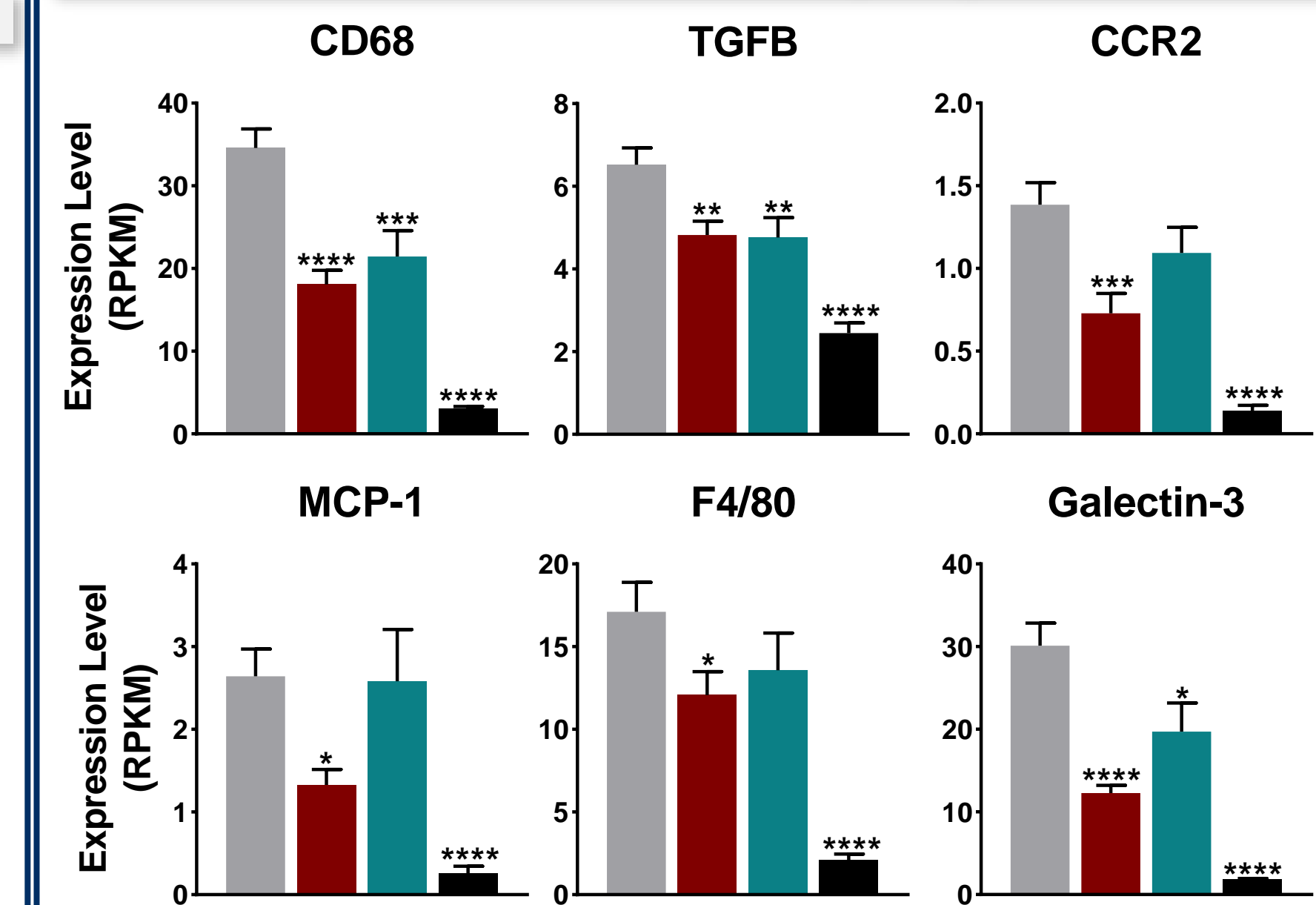
Galectin-3 Staining



NASH Vehicle Seladelpar OCA Chow Vehicle



Liver Inflammation RNAseq Analysis



CONCLUSION

In a diet-induced obesity mouse model of NASH, seladelpar treatment for 12 weeks

- Improved NASH pathology
- Significantly reduced liver fibrotic markers
- Profoundly decreased hepatic fat
- Decreased NAS
 - Improvement of steatosis score
 - Mean decrease of 2.1 points
 - Complete resolution of hepatocellular ballooning
 - Reduction in inflammatory markers
 - Eliminate bridging fibrosis
- Decreased liver collagen I synthesis (fibrogenesis)

Phase 2b NASH study is ongoing
NCT03551522