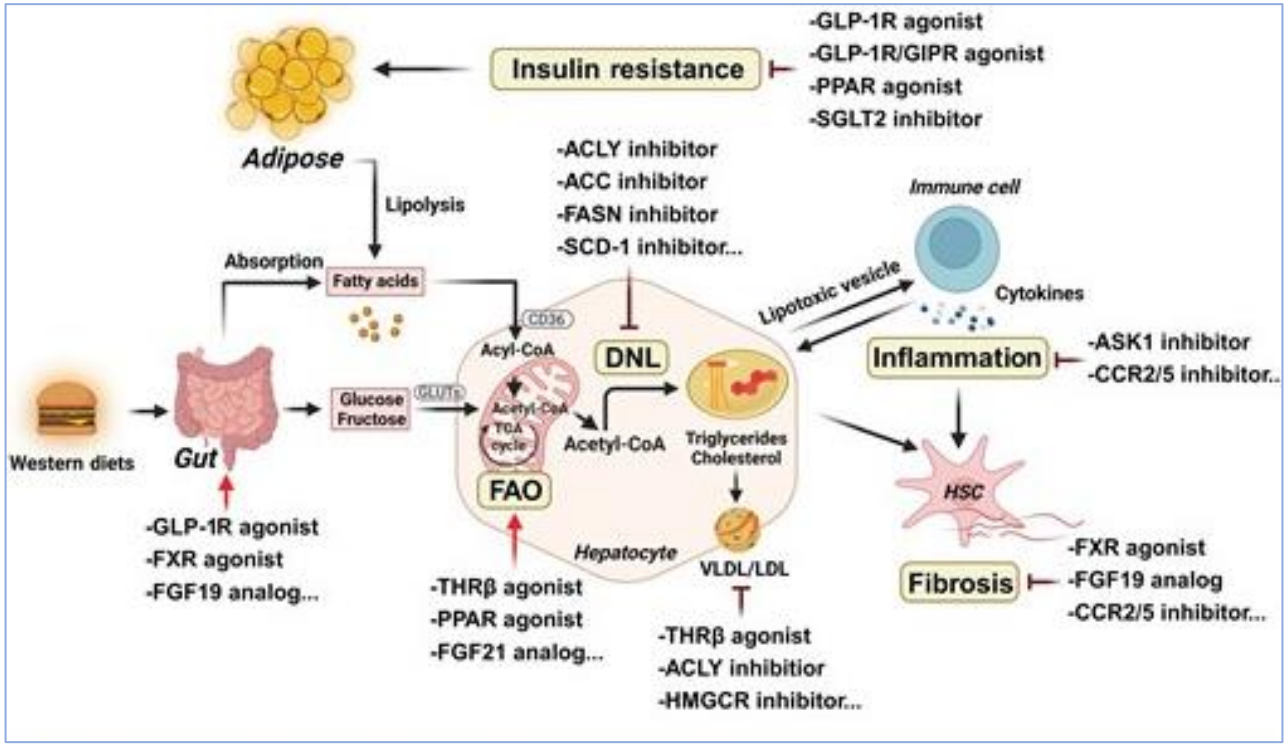
Evaluation of Combination Therapies in a Mouse Model of MASH

2025.07

OncoWuXi Newsletter

Therapeutic Landscape for MASH

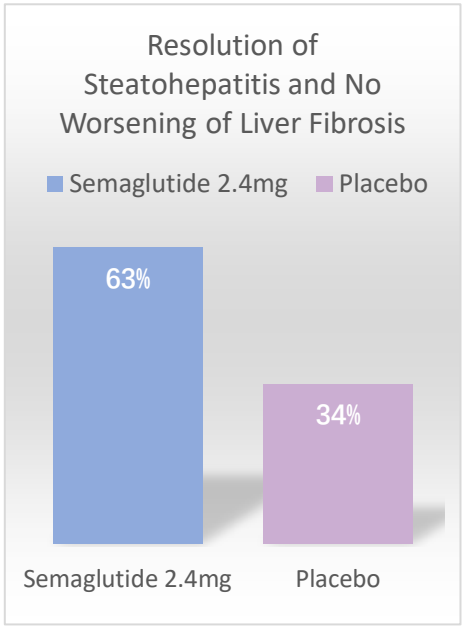
- Metabolic Associated Steatotic Liver Disease (MASLD) affects approximately **25%** of the world population and is becoming a global health issue. Among all MASLD patients, **20-30%** may progress to Metabolic Associated Steatohepatitis (MASH).
- The main characteristics of MASH include fat accumulation, inflammation, fibrosis, and hepatocyte ballooning in the liver.
- The pathogenesis of MASH involves complex interactions and **"multiple hits."** Recent developments in therapeutic strategies focus on various pathogenic pathways, including lipid metabolism, inflammation, insulin sensitivity, and the gut microbiome.

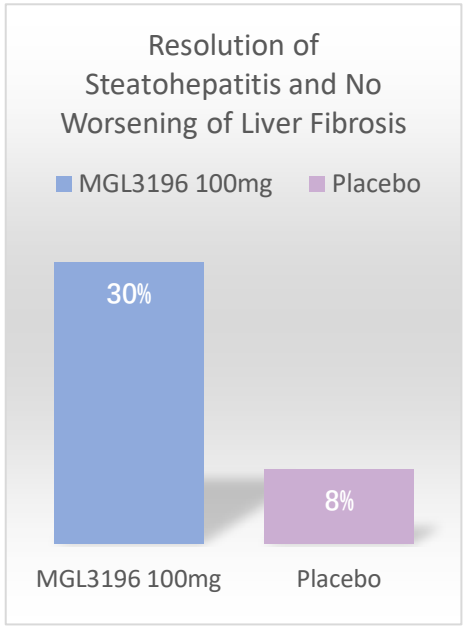


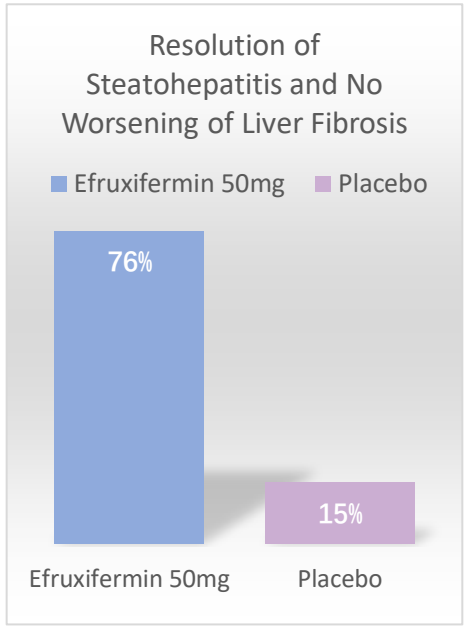
Xie Z et al. Life Metabolism (2024)

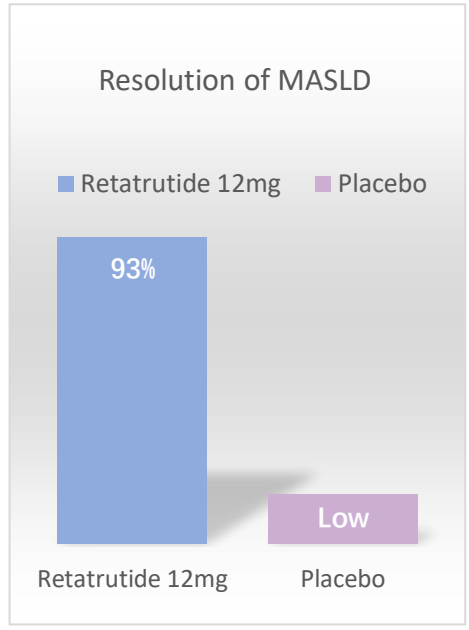
Key MASH Targets and Drug Candidates

- **Semaglutide - GLP-1:** Enhances insulin secretion and slows gastric emptying
- **Resmetirom (MGL3196) - THR-β:** Regulates metabolism and cholesterol
- **Efruxifermin - FGF:** Involved in tissue growth and repair
- **Retatrutide - GLP-1/GIP/GCG:** Enhances insulin secretion, inhibits glucagon release, and regulates glucose metabolism



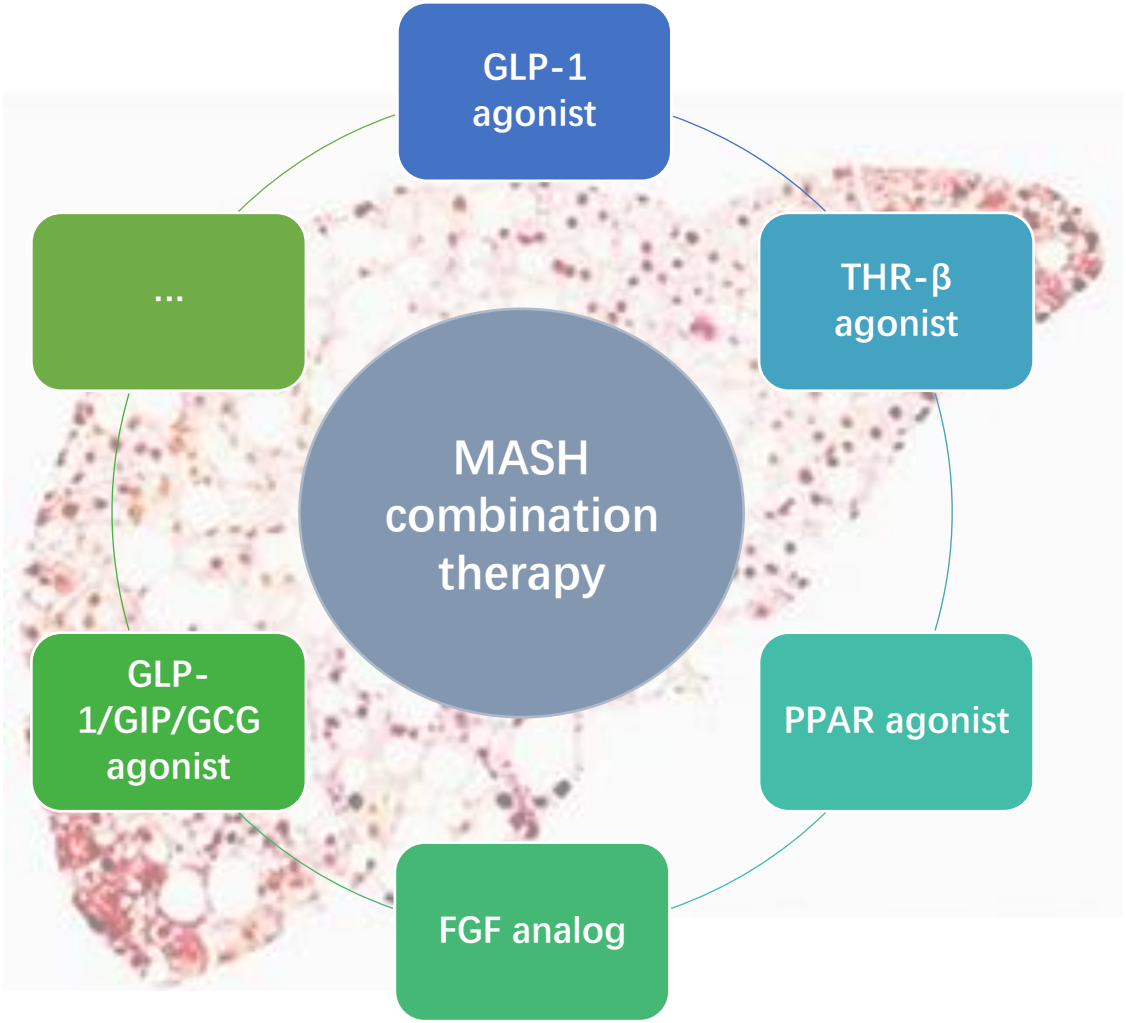






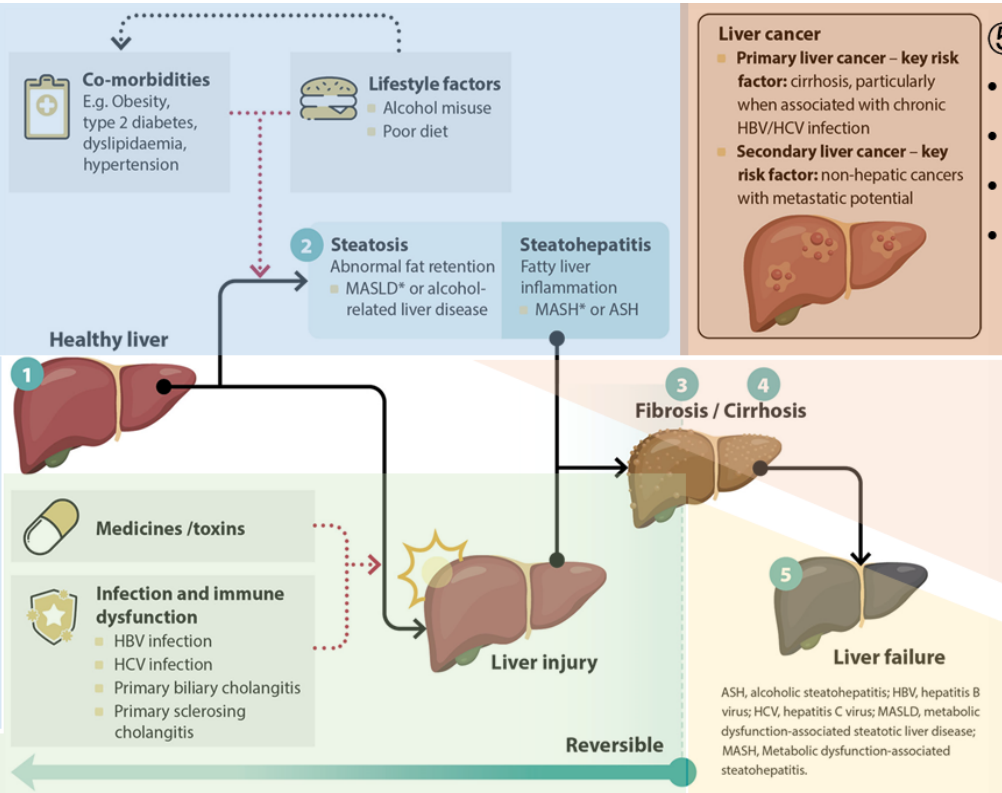
Status of Combination Therapy in Metabolic Diseases

- Due to the complex pathogenesis mechanisms of metabolic diseases, **combination therapies** targeting multiple pathways can potentially **improve efficacy, increase potency, and reduce side effects.**
- **Combination therapies have entered clinical trials for metabolic diseases to pursue better efficacy.** For example, initial combination therapy with metformin, dapagliflozin, and saxagliptin showed marked efficacy in patients with T2D.
- Given the current landscape of efficacy across different agents for MASH, the only approved resmetirom exhibited a resolution rate of 30%. **Combination therapy gives hope for improving MASH therapeutic effects.**



WuXi Biology Liver Disease Pharmacology Platform

② **Steatosis/ Steatohepatitis**
- HFD induced mice MASLD model
- HFD+CCl4 induced mice MASH model
- CDHFD induced Rat/mice MASH model
- GAN Diet induced mice MASH model
- Western Diet induced mice MASH model
- HFD+Fruc/gluc in drinking water induced mice MASH model
- CDAA diet induced mice MASH model
- MCD induced mice MASH model
- STZ+HFD induced mice MASH model
- Ethanol liquid diet induced Rat/mice ASH model



⑤ **Liver Cancer**
- Primary HCC& Metastatic HCC
- DEN+CCl4 induced mice liver cancer model
- CDX models
- PDX models

③ **Fibrosis**
- CCl4 induced mice/rat liver fibrosis model
- TAA induced mice liver fibrosis model
- BDL induced mice/rat liver fibrosis model
- HFCD induced hamster liver fibrosis model

④ **Cirrhosis**
- CDHFD induced rat cirrhosis model
- CCl4 induced rat cirrhosis model

② **Infectious liver diseased**
- HBV infected mice

② **Drug/Toxicant-induced liver injury**
- APAP induced mice acute liver injury model
- ConA induced mice acute liver injury model
- LPS/D-GalN induced mice acute liver injury model

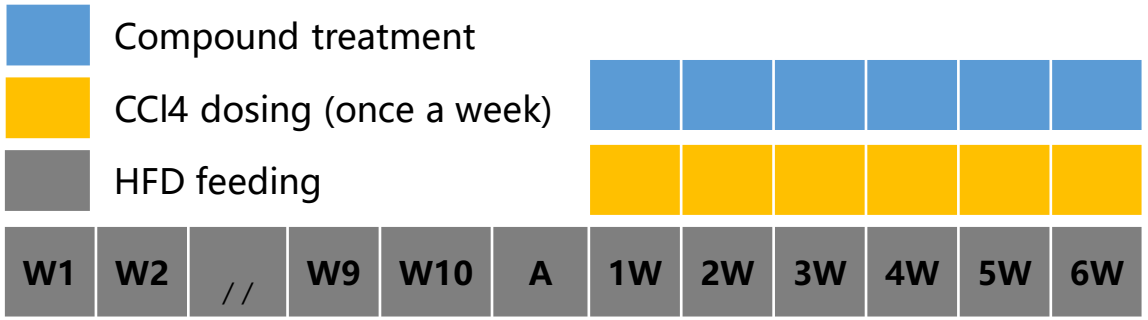
② **Liver biliary tract diseases (Autoimmune)**
- ANIT diet induced rat/mouse PBC model
- DDC diet induced mice PSC model
- Cholesterol and cholic acid induced mice cholelithiasis model

⑤ **Liver Failure**
- APAP induced mice acute liver Failure model
- Liver ischemia and reperfusion mouse model

⑤ **Hepatectomy Liver Regeneration**
- 70% partial hepatectomy mouse model

In Vivo Evaluation of Combination Therapies in HFD + CCl_4 Induced Mouse MASH Model

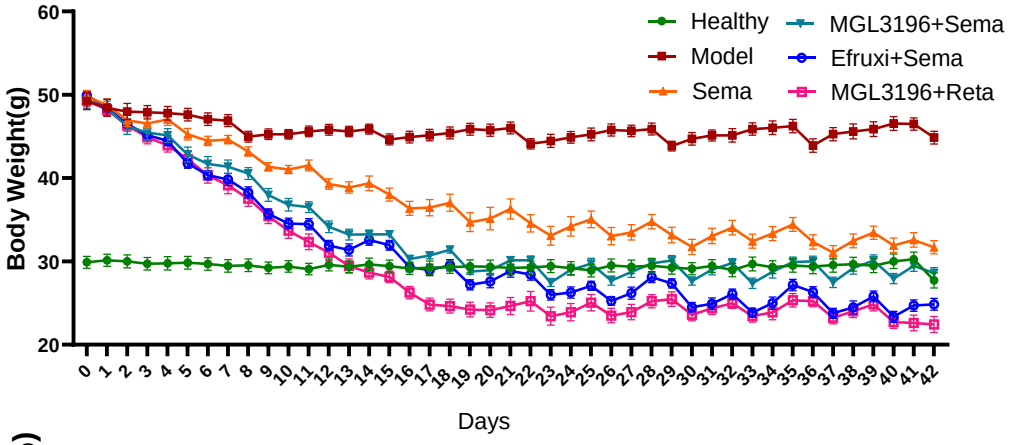
A



B

Animal Group	Number	CCl_4	Diet	Treatment
1	8	N	Chow	Vehicle
2	7	Y	HFD	Vehicle
3	8	Y	HFD	Semaglutide (Sema)
4	8	Y	HFD	MGL3196 + Sema
5	8	Y	HFD	Efruxifermin (Efruxi) + Sema
6	8	Y	HFD	MGL3196 + Retatrutide (Reta)

C



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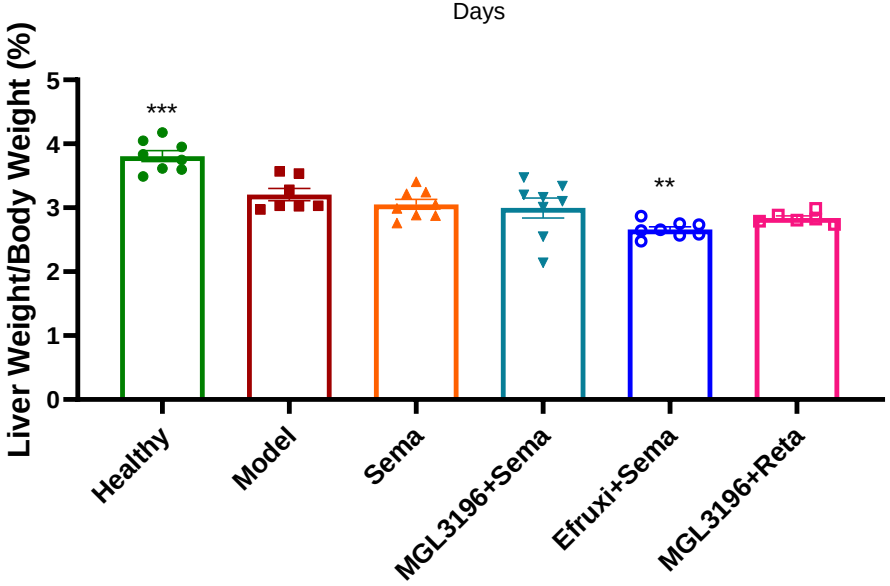

Figure A. HFD + CCl_4 induced mouse MASH model and treatments for 6 weeks. **Figure B.** Grouping information. **Figure C.** Body weight. **Figure D.** Liver weight to body weight ratio.

In Vivo Evaluation of Combination Therapies in HFD + CCl_4 Induced Mouse MASH Model

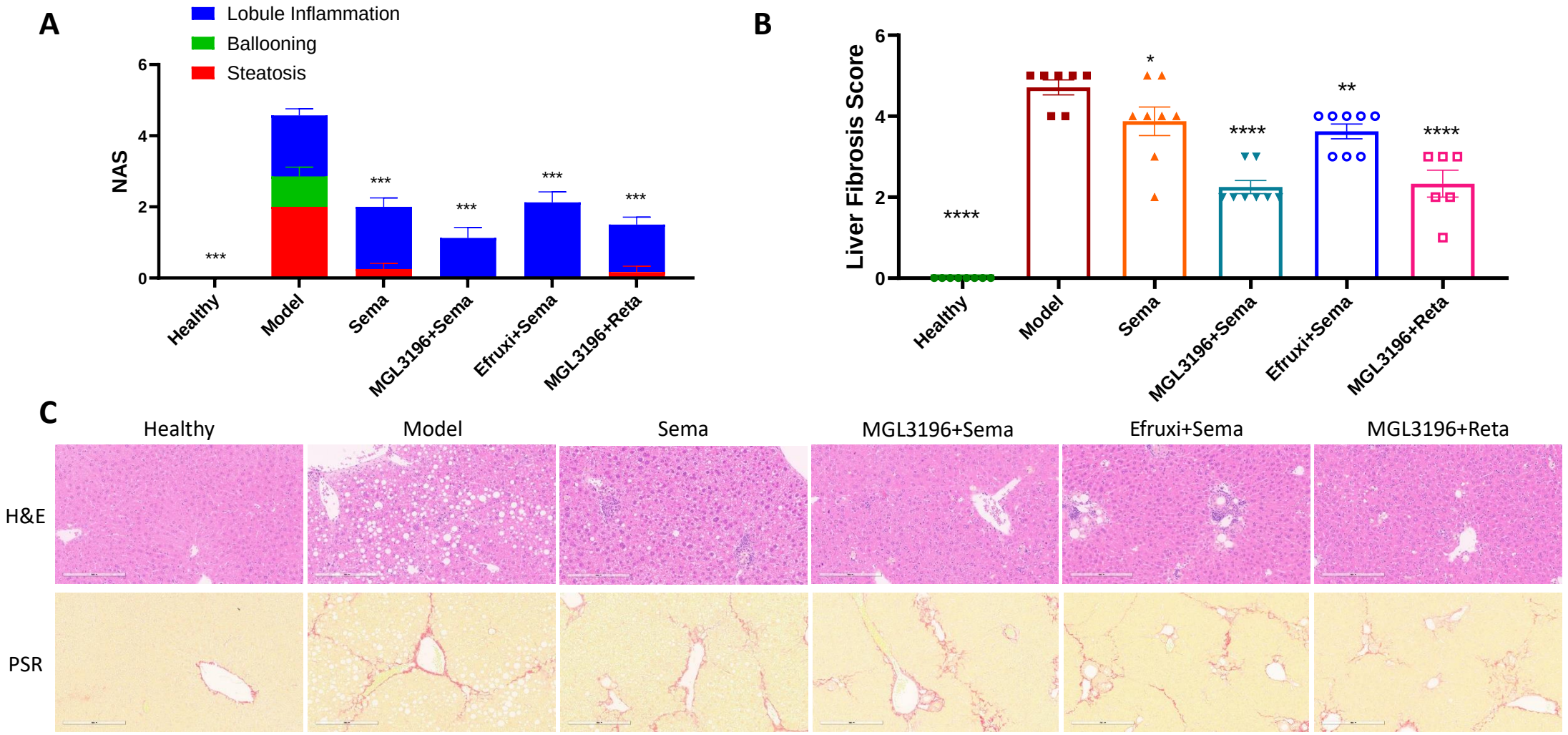

Figure A. NAS score. **Figure B.** Liver fibrosis score. **Figure C.** H&E and PSR images.

In Vivo Evaluation of Combination Therapies in HFD + CCl_4 Induced Mouse MASH Model

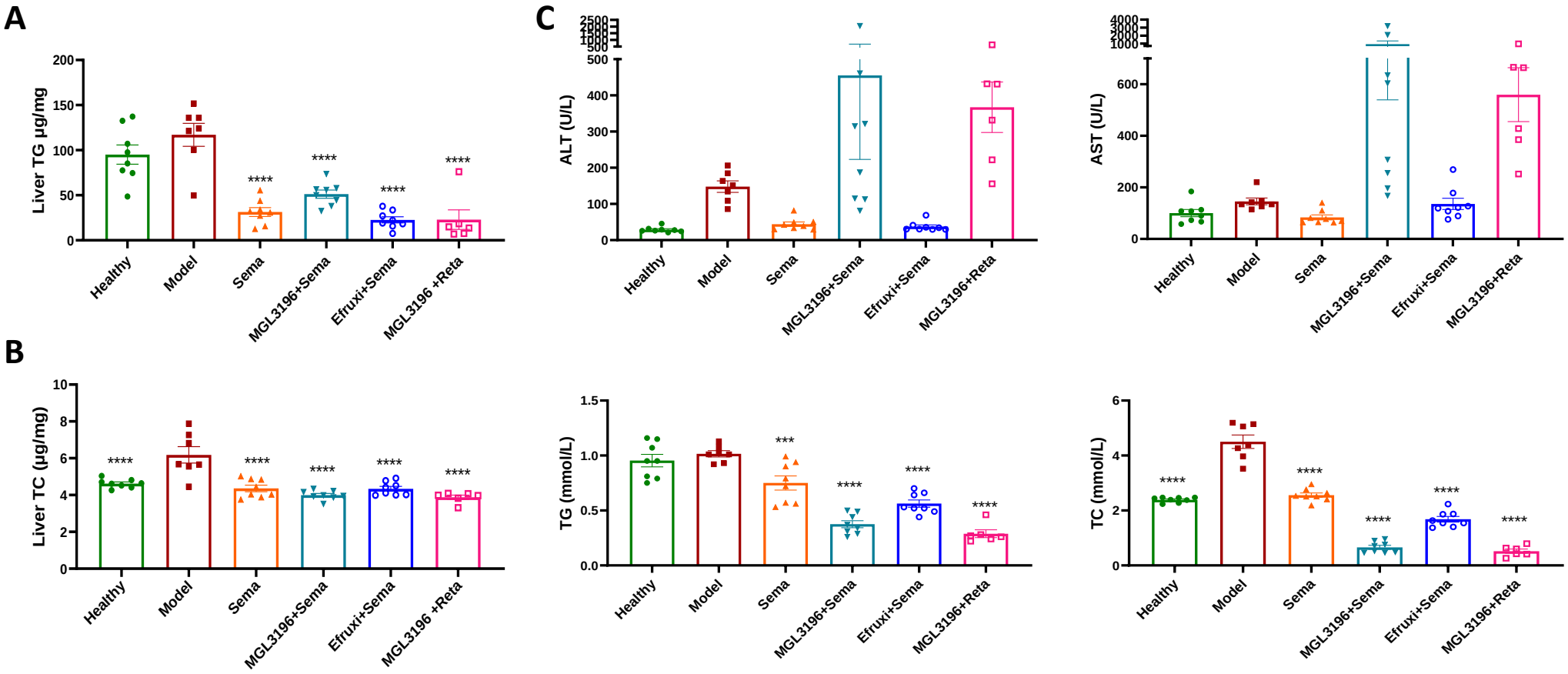

Figure A. TG (triglycerides) level in liver. **Figure B.** TC (total cholesterol) level in liver. **Figure C.** Serum chemistry profile of the model and effects by combination therapies.

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For questions and requests, please email to Pharmacology-BD-Translation@wuxiapptec.com

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