Lysophosphatidic acid receptor 1 antagonist (EPGN2154) improves murine MASH.

Jashdeep Bhattacharjee[1], Graham Beaton[2], Satheesh B. Ravula[2], Suk Joong Lee[2], Mikako Warren[1], Fabio C. Tucci[2], Rohit Kohli[1]

[1]Gastroenterology, Hepatology and Nutrition, Children's Hospital Los Angeles, Los Angeles, CA, United States. [2]Epigen Biosciences Inc, San Diego, CA, United States.

Introduction

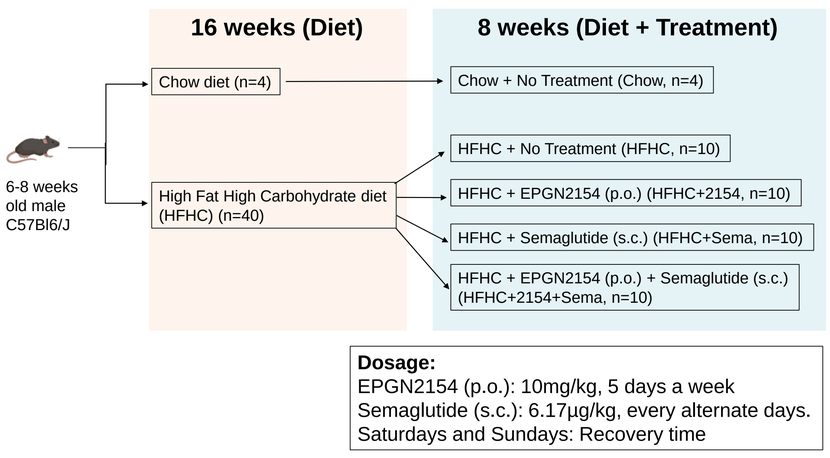
Metabolic dysfunction-associated steatohepatitis (MASH) includes hepatic inflammation and fibrosis in the background of obesity and steatosis. MASH has become the second leading cause of liver transplantation in the United States. Although MASH imposes a significant burden on healthcare worldwide, the FDA has not approved any medication for MASH.
A Lysophosphatidic acid receptor 1 (LPAR1) antagonist, EPGN2154 (2154), has shown anti-fibrotic activity in preclinical kidney and liver disease models. In contrast, the Glucagon-like peptide 1 (GLP-1) receptor agonist, Semaglutide (Sema), has improved obesity and hepatic steatosis. The present study investigated MASH-related outcomes post-EPGN2154 and/or Semaglutide treatment on a diet-induced preclinical MASH model.

Hypothesis

LPAR1 antagonist, EPGN2154, will show additive effects when treating GLP-1 agonist Semaglutide in MASH remission.

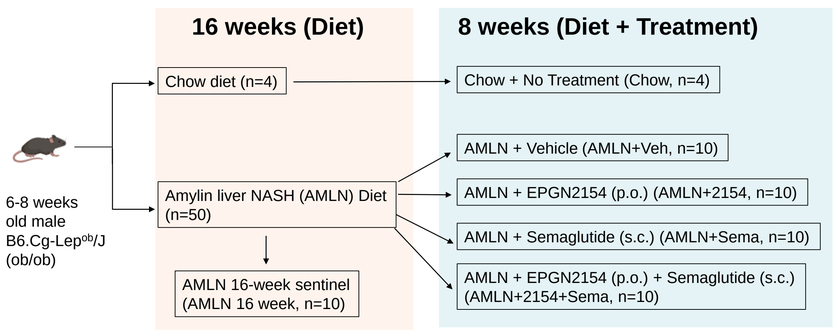
Methods

Experiment 1 Layout



Dosage:
EPGN2154 (p.o.): 10mg/kg, 5 days a week
Semaglutide (s.c.): 6.17µg/kg, every alternate days.
Saturdays and Sundays: Recovery time

Experiment 2 Layout



Dosage:
EPGN2154 (p.o.): 10mg/kg, 5 days a week
Semaglutide (s.c.): 6.17µg/kg, every alternate days.

Data

Experiment 1

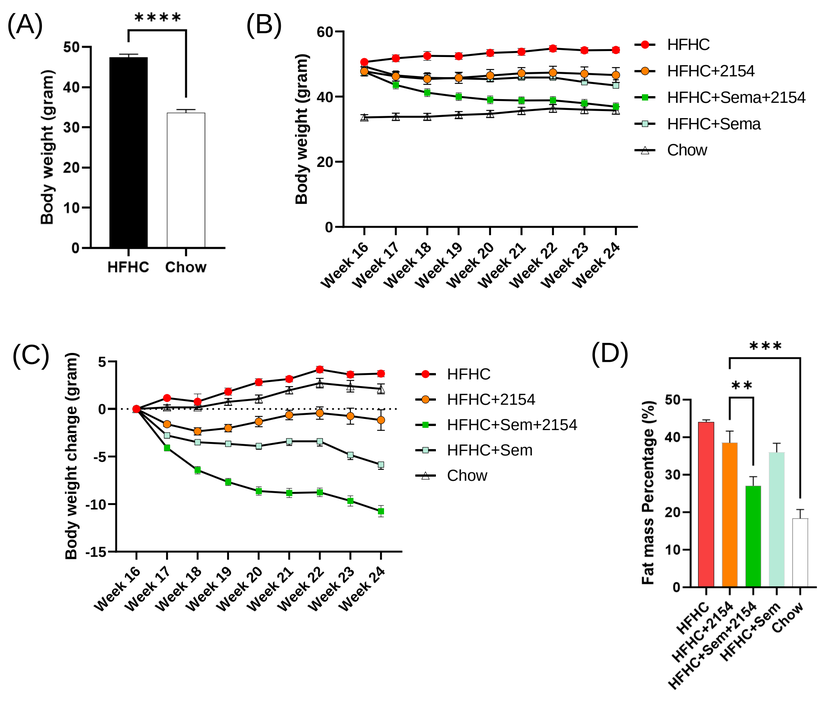


Figure 1. EPGN2154 and Semaglutide combination therapy lowers bodyweight and adiposity. (A) Body weight at week 16 on HFHC diet , (B) Body weight of WT mice from week 16 to week 24 during drug dosing, (C) Bodyweight change of WT mice compared to week 16 bodyweight from week 16 to week 24 during drug dosing (D) Fat mass percentage of mice. Mean± SEM. **** P< 0.0001, *** P<0.001, ** P<0.01.

LPAR1 antagonist, EPGN2154, causes regression of hepatic fibrosis independent of bodyweight loss in preclinical MASH models

Key Results

Experiment 1

EPGN2154 treatment on HFHC-fed C57Bl6/J mice

- Reduces plasma ALT
- Reduces NAS
- Reduces hepatic fibrosis

Experiment 2

EPGN2154 treatment on AMLN-fed ob/ob mice

- Reduces NAS
- Reduces hepatic fibrosis
- Reduces expression of hepatic fibrosis markers α-smooth muscle actin (αSMA), galectin-3 (Gal-3), collagen1a1 (Col1), and laminin (Lam)

However, this was not observed in the Semaglutide treatment group.

The Research supported by **R43DK129071** and **R44DK129071** was awarded to Epigen Biosciences Inc. (PD/PI – Dr. Fabio Tucci).
Contact**: rokohli@chla.usc.edu**

Data

Experiment 1

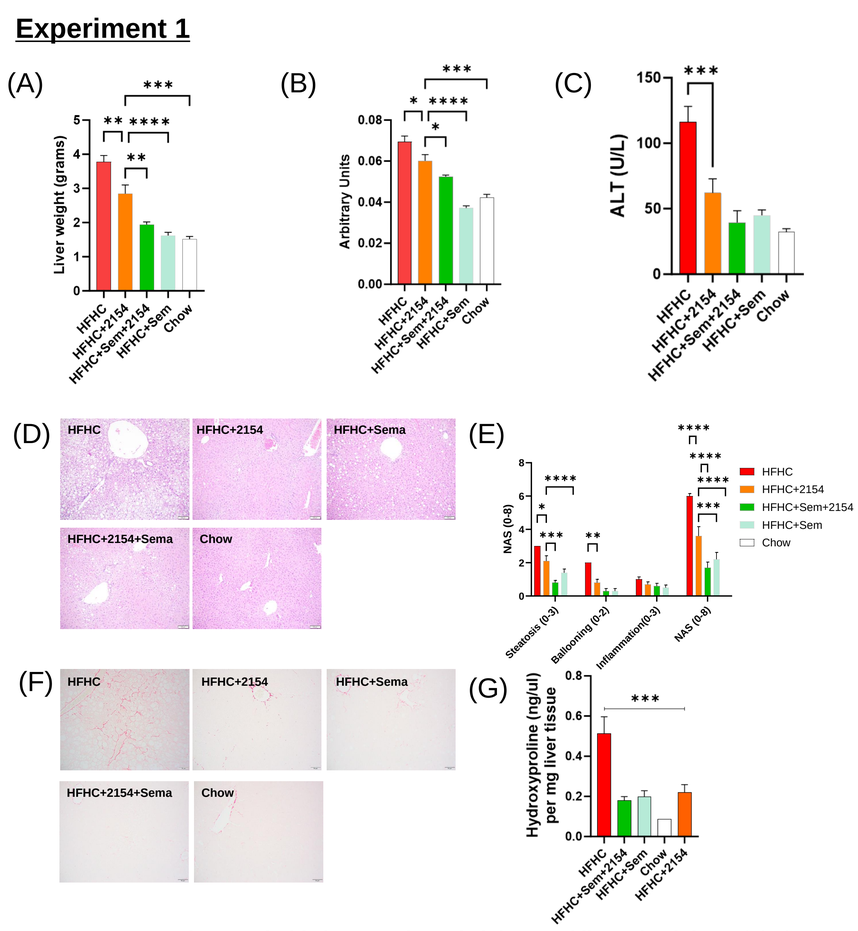


Figure 2. EPGN2154 and Semaglutide improve hepatic injury and liver physiology. (A) Liver weight of mice, (B) Liver to body weight ratio (C) Plasma ALT (alanine transaminase) concentration of mice, (D) H&E staining of liver cross-section of experimental groups, (E) NAS of the liver cross-section of experimental groups (F) Sirius Red staining of liver cross-section of experimental groups, (G) Hydroxy proline concentration in the liver of the experimental groups at week 24. Mean± SEM. **** P< 0.0001, *** P<0.001, ** P<0.01, *P<0.05

Experiment 2

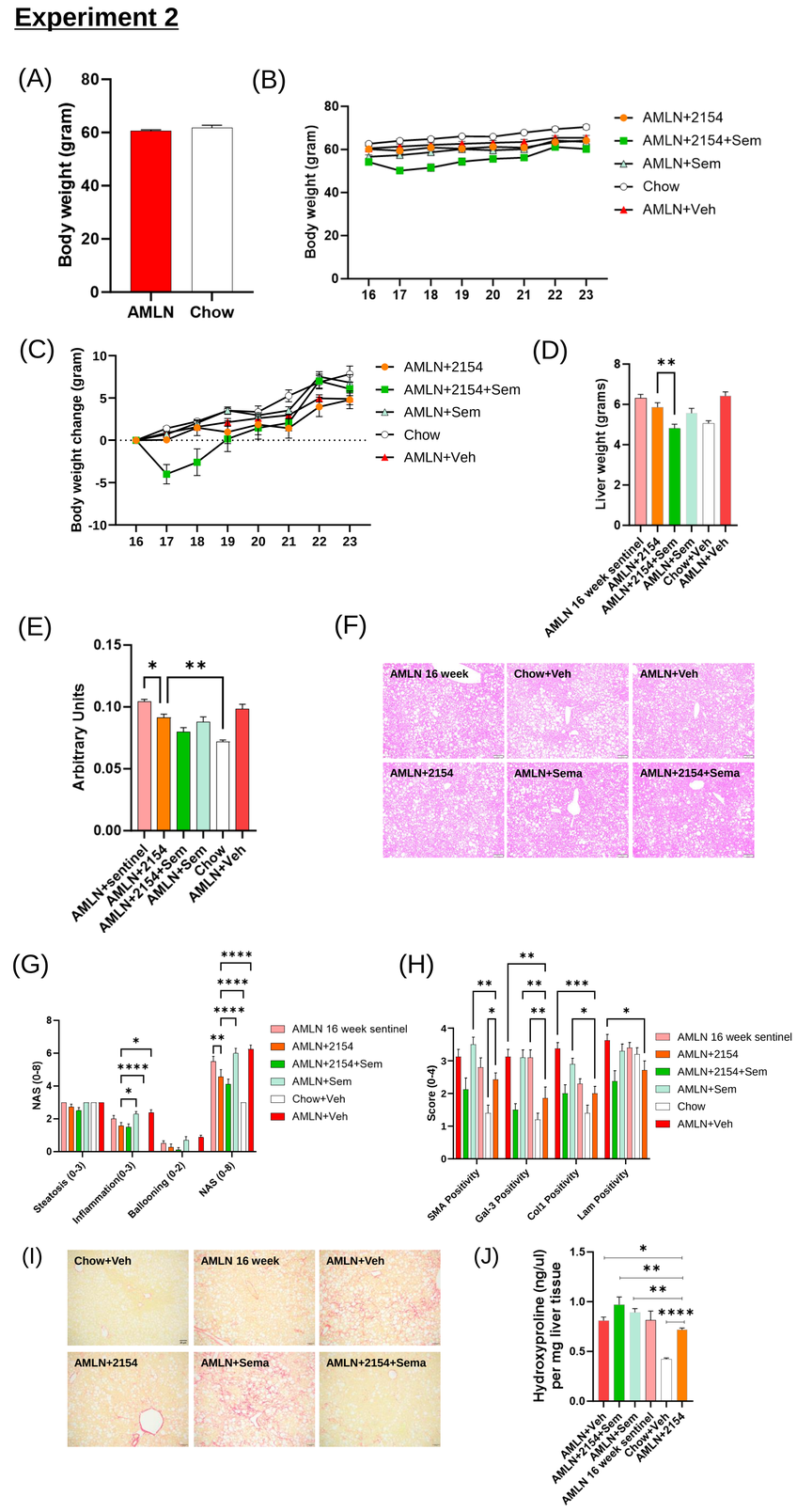


Figure 2. EPGN2154 improves hepatic fibrosis in AMLN-fed ob/ob mice . (A) Body weight of ob/ob mice before drug doing,(B) Body weight of WT mice from week 16 to week 24 during drug dosing, (C) Bodyweight change of ob/ob mice compared to week 16 bodyweight from week 16 to week 24 during drug dosing, (D) Liver weight of mice, (E) Liver to Body weight ratio, (F) H&E staining of liver cross-section of experimental groups, (G) NAS of the liver cross-section of experimental groups, (H) Immuno-histochemistry of the liver cross-section for α-smooth muscle actin (αSMA), galectin-3 (Gal-3), collagen1a1 (Col1), and laminin (Lam), (I) Sirius Red staining of liver cross-section of experimental groups, (J) Hydroxy proline concentration in the liver of the experimental groups at week 24. Mean± SEM. **** P< 0.0001, *** P<0.001, ** P<0.01, *P<0.05.