

The selective PPAR-delta agonist seladelpar reduces ethanol-induced liver disease by restoring gut barrier function and bile acid homeostasis in mice

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Conflict of Interests

- Bernd Schnabl is consulting for Ferring Research Institute.
- This study was supported by a laboratory service agreement from CymaBay to the University of California San Diego.
- Edward Cable is an employee from CymaBay Therapeutics (Newark, CA).

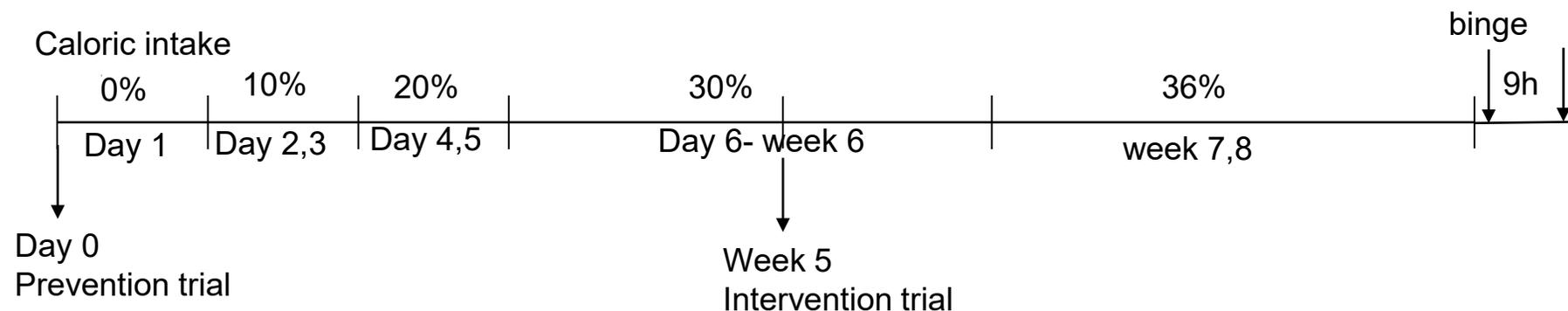
Background

- Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors of nuclear hormone receptor superfamily.
- Activation of PPAR- β/δ enhances fatty acid metabolism.
- PPAR δ is expressed on many tissues including gut and liver

Aim

To evaluate effects of the selective PPAR-delta agonist seladelpar (MBX-8025) on gut barrier function, gut microbiome and bile acid homeostasis in a mouse model of ethanol-induced liver disease

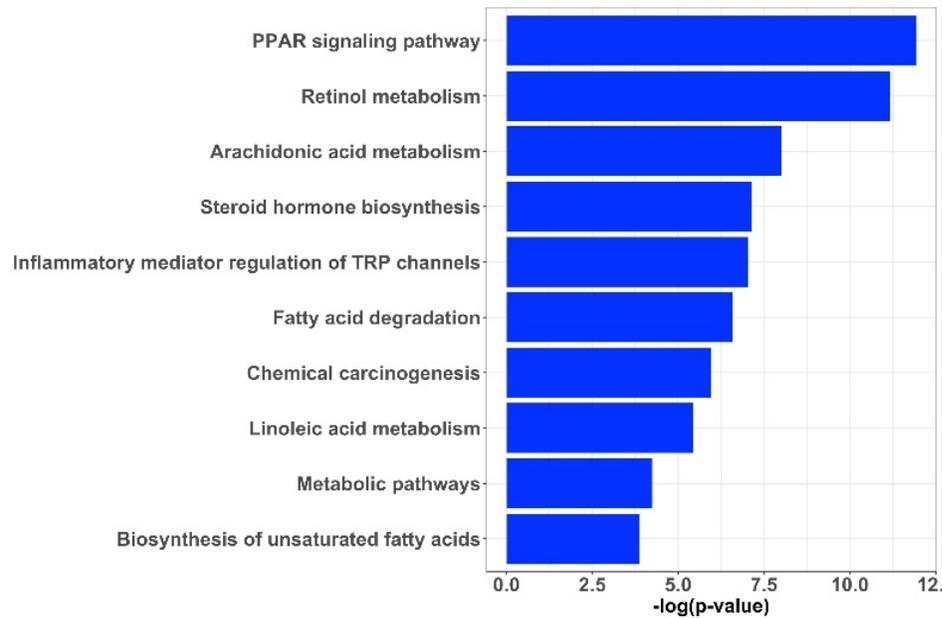
Method



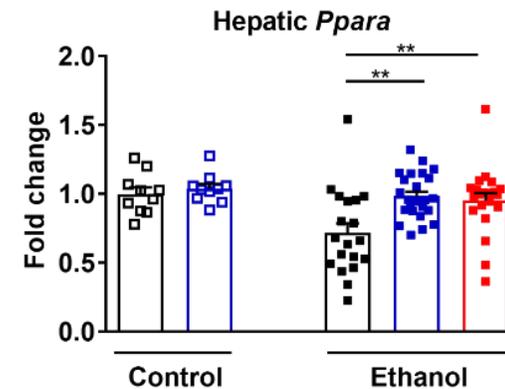
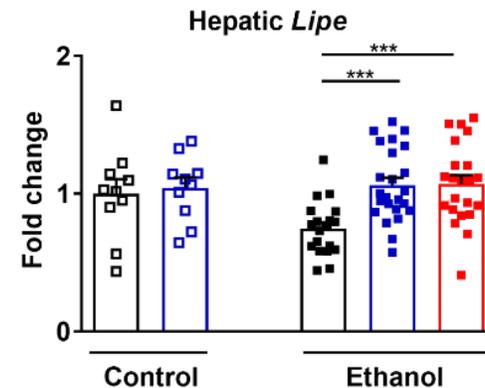
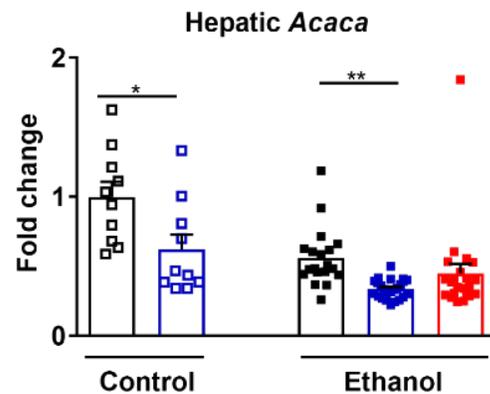
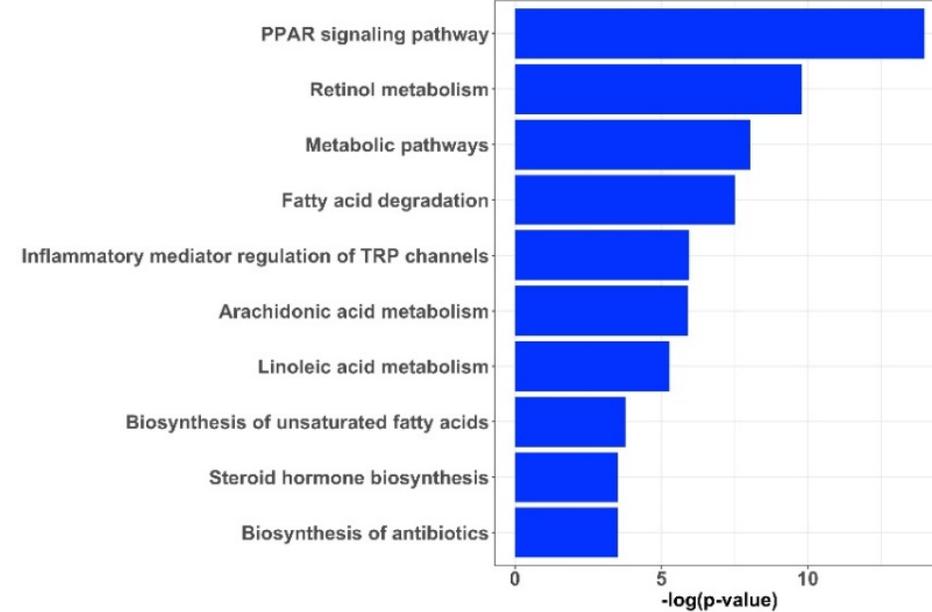
Single binge of ethanol (5g/kg body weight)
Seladelpar 10mg/kg/d

MBX-8025 regulates liver inflammation and lipid metabolism

MBX-8025/Prevention vs Vehicle

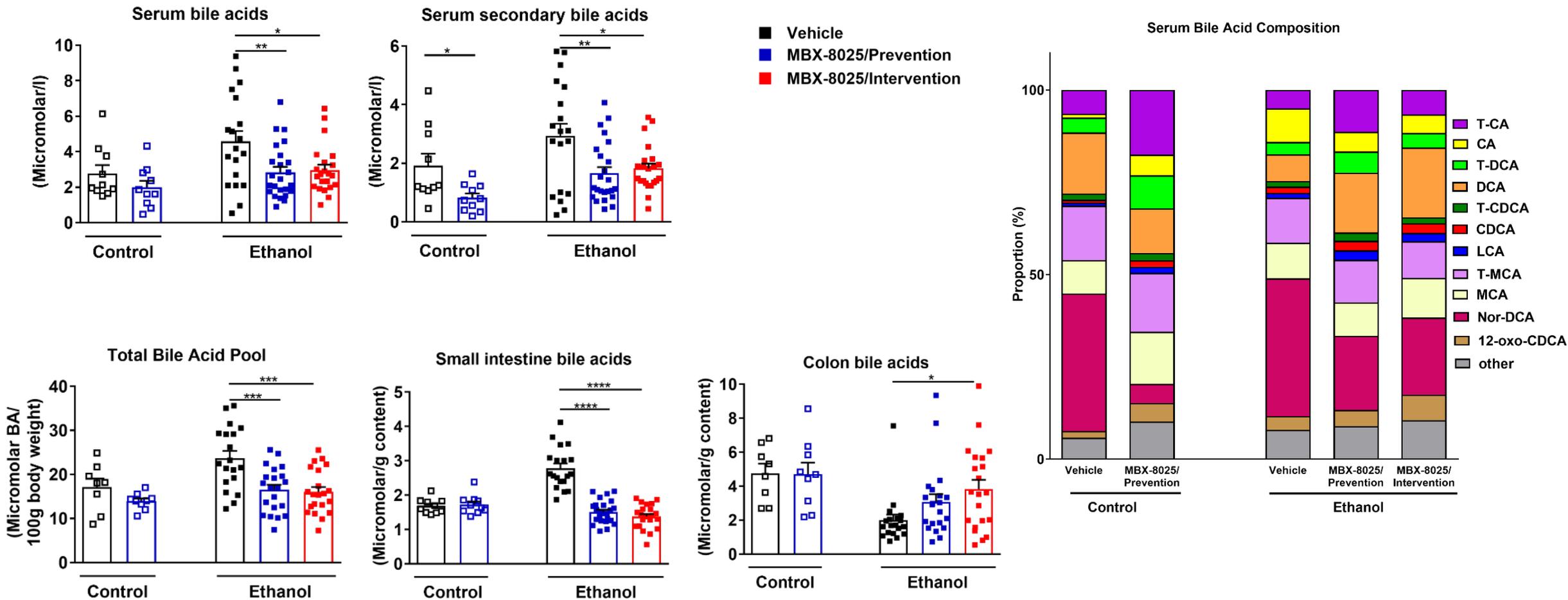


MBX-8025/Intervention vs Vehicle

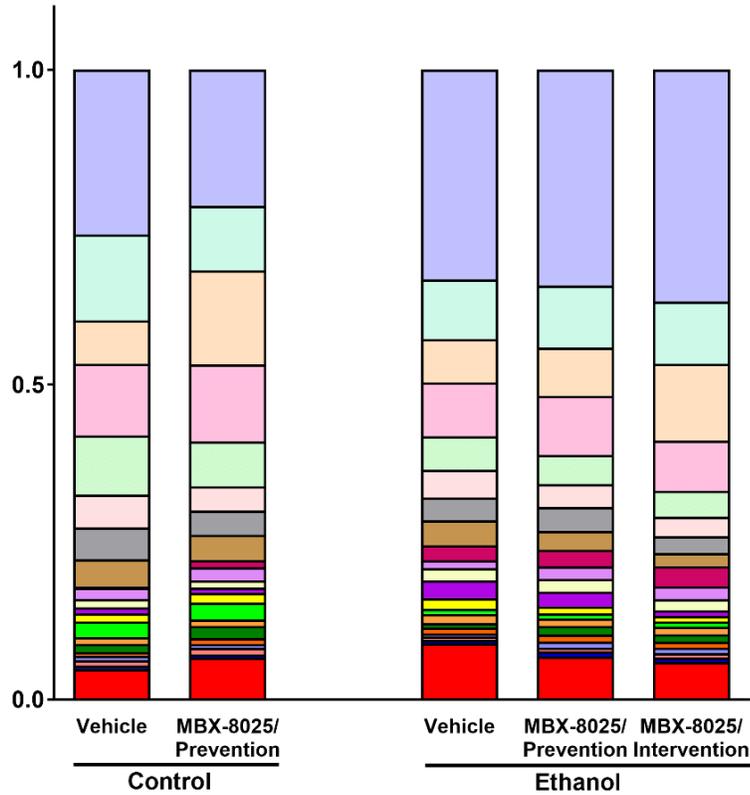
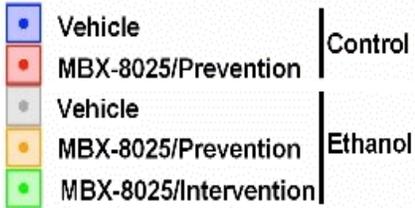
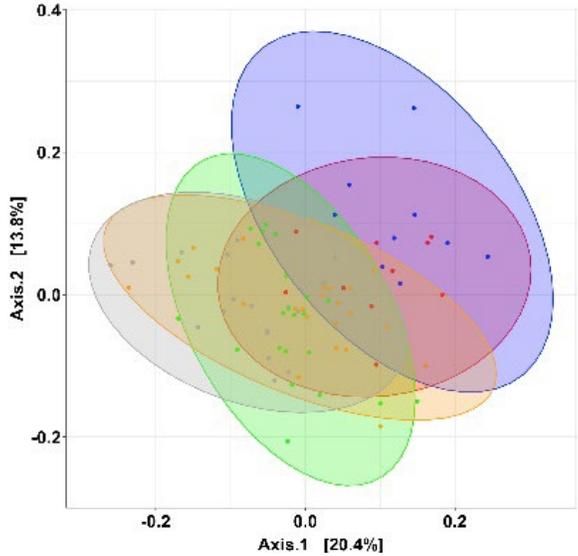


■ Vehicle
■ MBX-8025/Prevention
■ MBX-8025/Intervention

MBX-8025 restores bile acid homeostasis during chronic ethanol feeding

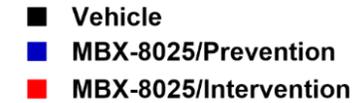
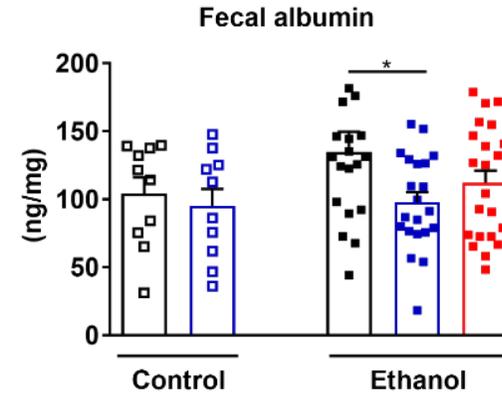
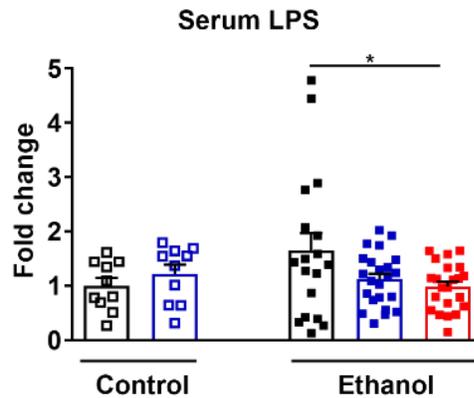


MBX-8025 modulates ethanol-associated dysbiosis

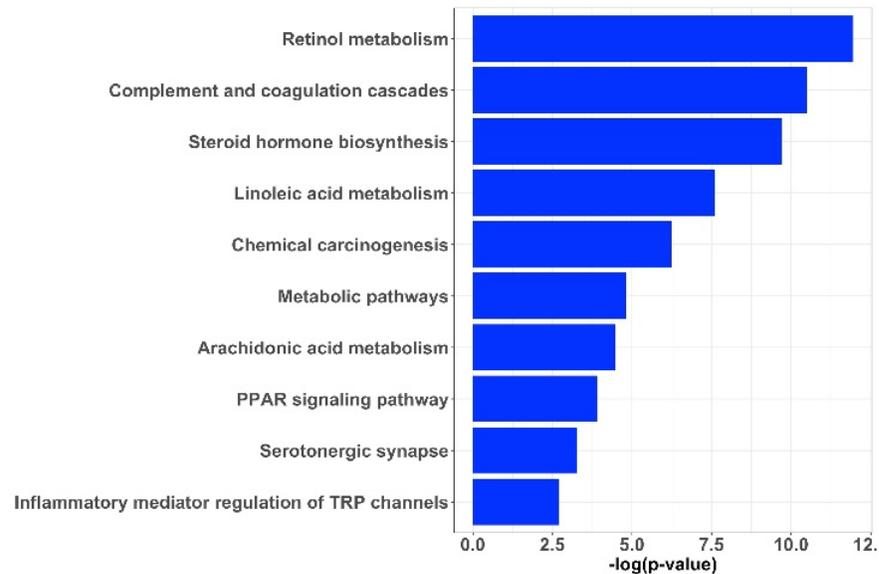


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- o_Bacteroidales.f_Bacteroidaceae.g_Bacteroides
- o_Verrucomicrobiales.f_Verrucomicrobiaceae.g_Akkermansia
- o_Bacteroidales.f_S24.7.g_
- o_Clostridiales.f_.g_
- o_Clostridiales.____
- o_Clostridiales.f_Lachnospiraceae.g_
- o_Clostridiales.f_Ruminococcaceae.g_Oscillospira
- o_Erysipelotrichales.f_Erysipelotrichaceae.g_Allobaculum
- o_Bacteroidales.f_Porphyromonadaceae.g_Parabacteroides
- o_Clostridiales.f_Lachnospiraceae.____
- o_Lactobacillales.f_Lactobacillaceae.g_Lactobacillus
- o_Clostridiales.f_Ruminococcaceae.g_Ruminococcus
- o_Desulfovibrionales.f_Desulfovibrionaceae.g_Bilophila
- o_Clostridiales.f_Lachnospiraceae.g_Ruminococcus
- o_Bacteroidales.f_Rikenellaceae.g_
- o_Clostridiales.f_Peptostreptococcaceae.____
- o_Burkholderiales.f_Alcaligenaceae.g_Sutterella
- o_Bacteroidales.f_Rikenellaceae.____
- k_Bacteria.____
- Others

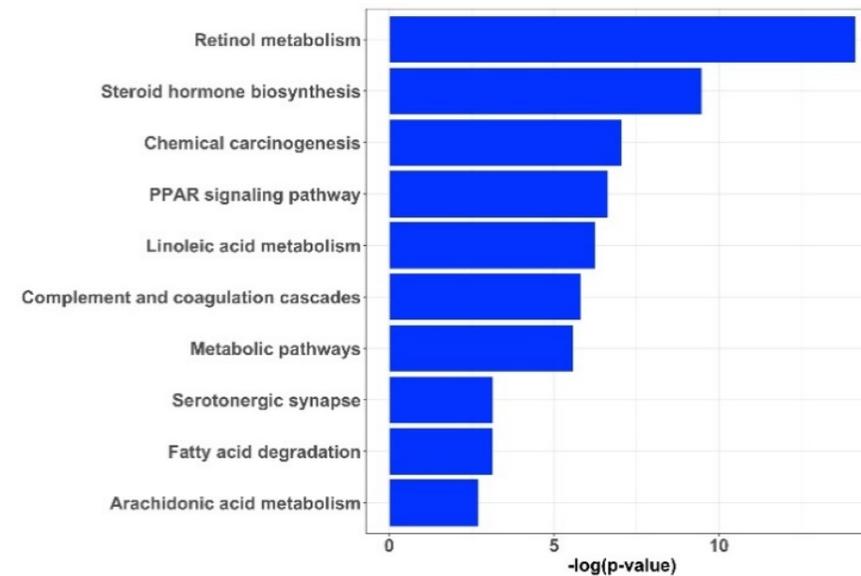
MBX-8025 reduces ethanol-induced gut barrier dysfunction



MBX-8025/Prevention vs Vehicle



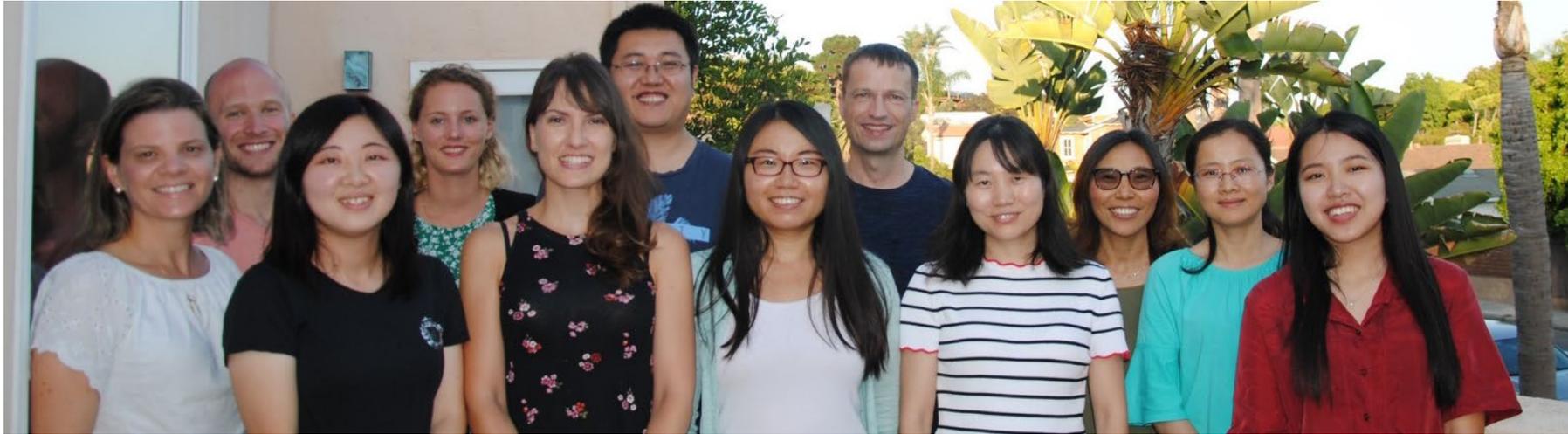
MBX-8025/Intervention vs Vehicle



Conclusions

- MBX-8025 reduces ethanol-induced liver injury, steatosis and inflammation.
- MBX-8025 restores bile acid homeostasis during chronic ethanol feeding.
- MBX-8025 modulates ethanol-associated dysbiosis and reduces ethanol-induced gut barrier dysfunction.

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