FXR AGONISTS WITH SUSTAINED ACTIVITY EXHIBIT EFFICACY COMPARABLE TO ANTI-IL-12P40 IN TREATING COLITIS INDUCED BY ADOPTIVE T-CELL TRANSFER

Xueqing Liu[1], Harry Dedman[1], Robert O'Connell[2], Alison Bendele[2], Connor Ohlsen[2], Steve Govek[1], Johnny Nagasawa[1], Karensa Douglas[1], Andiliy Lai[1], Angelica Milik[1], Nhin Lu[1], Jing Qian[1], Alvaro Ortiz[1], Douglas Zook[1], Kyoung-Jin Lee[1], Nicholas Smith[1], Hubert Chen[1], Brandee Wagner[1], Ken Song[1]

1. Metacrine, San Diego, CA; 2. Bolder BioPath, Inc., Boulder, CO.

3985 Sorrento Valley Blvd., Suite C
San Diego, CA 92121
www.metacrine.com

INTRODUCTION

The farnesoid X receptor (FXR) is a ligand-activated nuclear hormone receptor that is highly expressed in the liver and gastrointestinal tract. FXR agonists are in development for the treatment of nonalcoholic steatohepatitis (NASH) and other hepatobiliary diseases. Preclinical and clinical data suggest that sustained as opposed to transient FXR activation is required for maximal efficacy in NASH. We have previously shown that FXR agonists with novel, non-steroidal structures can demonstrate anti-colitis activity comparable to anti-IL-12p40.

AIMS

The aims of this study were to examine the efficacy of M480, a potent, non-bile acid *sustained* FXR agonist, in adoptive T-cell transfer colitis model and compare that activity to a *transient* FXR agonist M1217.

MATERIAL & METHODS

Hepatic and intestinal FXR target gene expression in C57BL/6 mice was examined at 4, 8 and 24 hours after a 10 mg/kg single dose. Sustained activation is defined as significant target gene engagement at 24 hours. Colitis was induced by transferring CD4+CD45RB^{hi} T-cells to recipient C.B-17 SCID mice. All treatments were started 21 days post transfer and lasted for 4 weeks. FXR agonists M480 (10 mg/kg), M1217 (10mg/kg) were orally dosed daily (n=10). Anti-IL-12p40 (0.5mg/mouse) was dosed intraperitoneally weekly (n=5). Efficacy was assessed by terminal colon weight to length ratio (W/L) and colon histopathology. Histopathology scores were determined for inflammation, erosion, gland loss and hyperplasia, each with a score of 0-5, and cumulative sum score of 0-20.

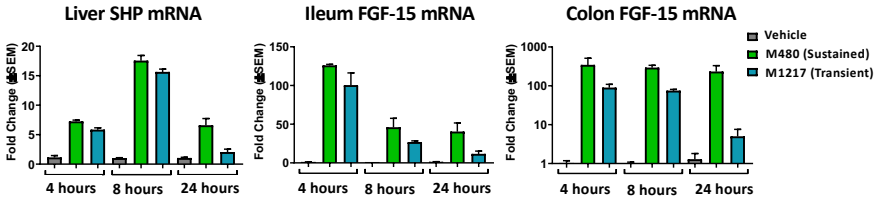
CONCLUSIONS

Sustained FXR agonist M480 improved parameters of colitis with magnitude comparable to anti-IL-12p40. Transient FXR agonist M1217 only led to moderate improvements in colitis.

Sustained activation of FXR is required to achieve maximal efficacy. These findings support the development of FXR agonists as a novel oral therapeutics for treating IBD.

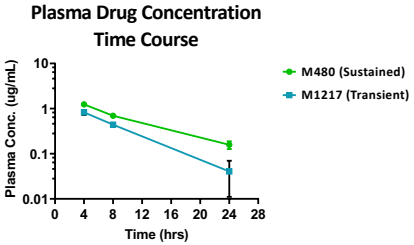
RESULTS

In Vitro Potencies and Mouse PK/PD Analysis

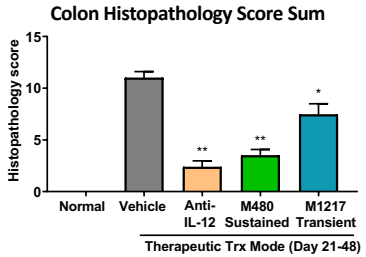


M480 and M1217 were administered with 10mg/kg dose level

In Vitro Potency	Mouse EC50 (nM)	Human EC50 (nM)
M480 (Sustained)	4	33
M1217 (Transient)	3	13



Sustained FXR Activation Required For Maximum Improvement In Histopathology

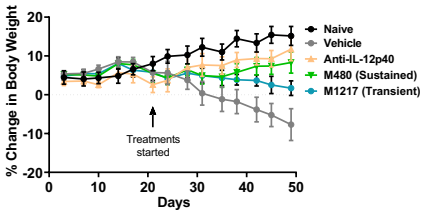


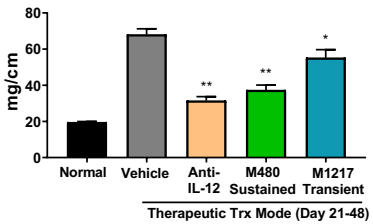
** p<0.001, * p<0.05, vs Vehicle

Treatments	Inflammation Score (0-5)	Hyperplasia Score (0-5)	Gland loss Score (0-5)	Histopathology Sum (0-20)
Naïve	0.0	0.0	0.0	0.0
Vehicle	4.6[a]	4.0[a]	2.2[a]	11.0[a]
Anti-IL-12p40	1.5[b]	0.4[b]	0.5[b]	2.4[b]
M480 (Sustained)	1.8[b]	1.2[b]	0.6[b]	3.5[b]
M1217 (Transient)	3.5[b]	2.7[b]	1.3[b]	7.5[b]

Data shown is mean; a, p<0.05, vs Naïve, b, p<0.05, vs Vehicle, One-Way ANOVA

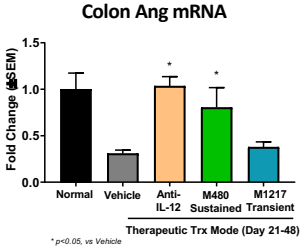
Sustained FXR Activation Improves Colon Weight /Length and Reduces Body Weight Loss



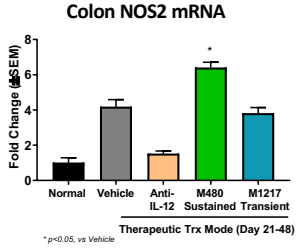


** p<0.001, * p<0.05, vs Vehicle

FXR Activation Increases Expression of Anti-microbial Barrier Function Genes



* p<0.05, vs Vehicle



* p<0.05, vs Vehicle

DISCLOSURES

B.W., S.G., J.N., K.D., H.D., A.M., K.L., A.O., J.Q., N.L., X.L., E.B., K.S. and N.S. are employees and equity holders in Metacrine, Inc.

DDW Digestive Disease Week®