The Liver Meeting® 2017 in Washington D.C.

Significant anti-fibrotic efficacy of EDP-305, a highly potent and selective farnesoid X receptor (FXR) agonist, in a rat model of thioacetamide-induced liver fibrosis and cirrhosis

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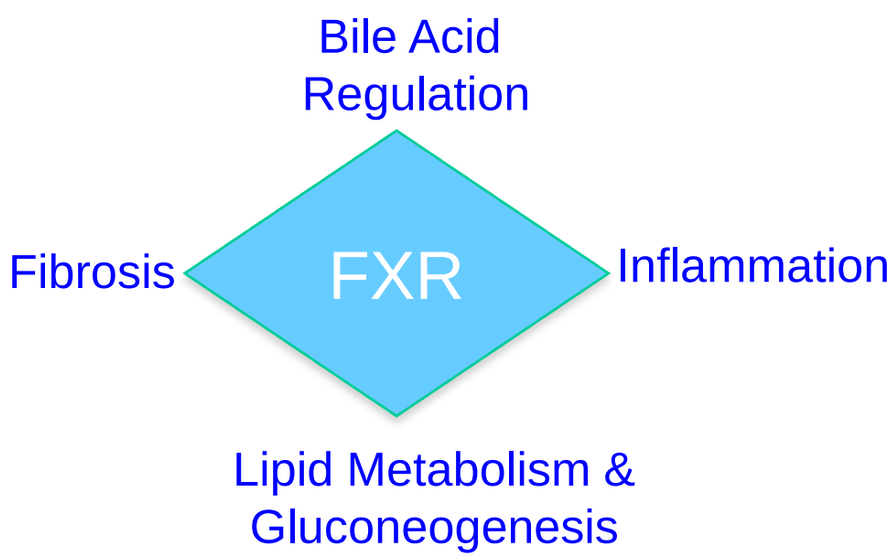
Icahn School of Medicine at Mount Sinai

FXR has emerged as an attractive target for the treatment of NASH & PBC

NASH = nonalcoholic steatohepatitis; PBC = primary biliary cholangitis

- Clinical validation has been achieved in NASH and PBC with the FXR agonist obeticholic acid (OCA)
- FXR is a nuclear receptor and main regulator of bile acid levels in the liver and small intestine
- FXR responds to bile acids by regulating transcription of key enzymes and transporters
- FXR agonists have ameliorated a number of the pathologies in NASH, including effects on fibrosis, inflammation, lipid metabolism & gluconeogenesis



Matsubara Mol Cell Endocrinol 2013;
Neuschwander-Tetri *et al*, Lancet, 2014

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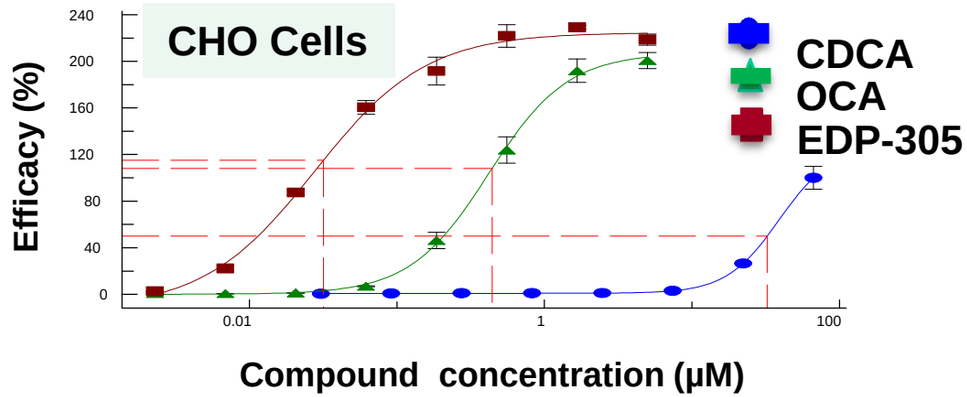
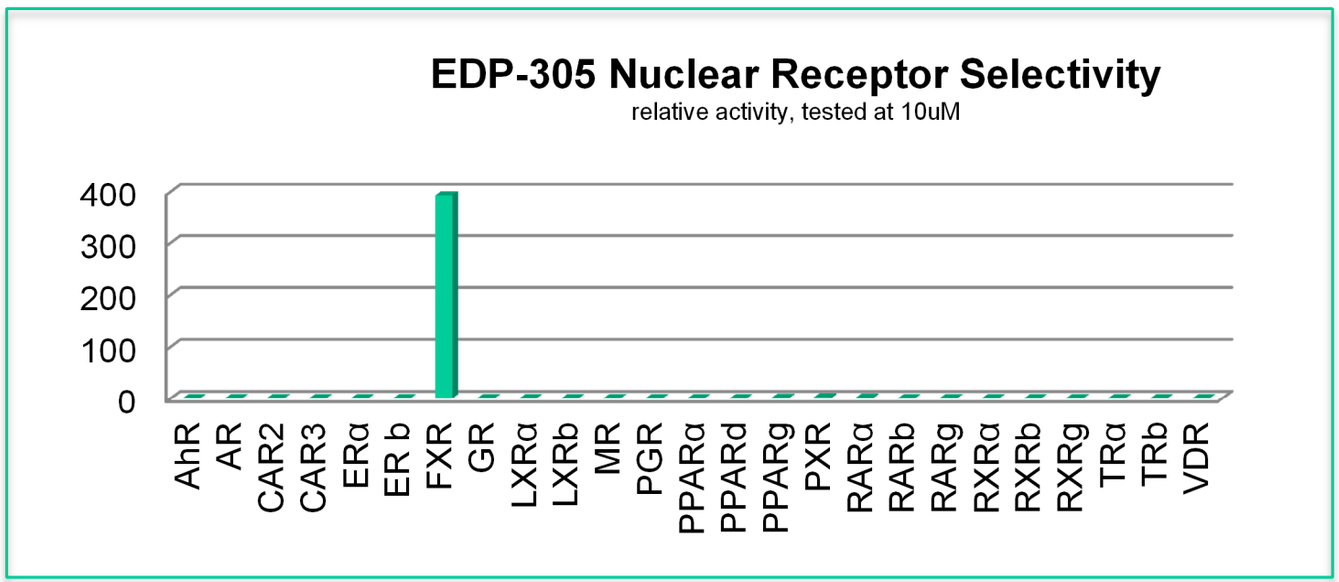
EDP-305 is a potent and selective FXR agonist

EDP-305 is >16-fold more potent than OCA and its major metabolites

Compound	FXR (HEK)	TGR5 (CHO)
	EC50 nM (% efficacy)*	
Obeticholic Acid (OCA)	130 (150)	380 (72)
Glyco-OCA	360 (155)	720 (157)
Tauro-OCA	250 (100)	540 (161)
EDP-305	**8 (152)**	**> 15,000 (NS)**

* Transporter inserted, FXR efficacy CDCA = 100%; TGR5 efficacy LCA = 100%





Y. Li, *et al*, AASLD 2016 poster 1540

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EDP-305 regulates key gene expression

In vitro

- **Bile acid metabolism**
  - SHP; FGF19; OST-α; BSEP; CYP7A1
- **Lipid metabolism**
  - LDLR; PCSK9;SREBP-1C; SCD1; CD36; DGAT2; APOB; APOC3; HL; SRB1
- **Inflammation**
  - NF-κB; TLR2; TLR9; TNFα; IL8; IL1α; IL1β; IL1R1; CCL2; CCR1; CCR4; CEBPB
- **Fibrosis**
  - α-SMA; TIMP1; TIMP2; PDGFα; PDGFβ; COL1A2; COL3A1; ITGB6
- **Glucose metabolism**
  - FGF21; IRS2; GLUT2; GLUT4; FOXO1

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Enanta AASLD 2016 posters 1540, 1568 & 1596

EDP-305 demonstrates its efficacy in eight (8) animal models

- Mouse model
  - FXR mechanism of action: SHP, CYP7A1 and FGF15 (Enanta Pharmaceuticals, Inc.)
- NASH models
  - STAM™ mouse NASH model (Stelic, Japan)
  - MCD-fed mouse steatohepatitis model with progressive fibrosis (Harvard/BIDMC)
  - Choline-deficient, L-amino acid-defined, high-fat-diet, mouse NASH model (Harvard/MGH)
  - Diet-induced NASH mouse model (Physiogenex, France)
- Biliary fibrosis models
  - Mdr2-/- mouse biliary fibrosis model (Harvard/BIDMC)
  - Rat bile duct ligation model (Harvard/MGH)
- Liver fibrosis/cirrhosis model
  - Thioacetamide-induced rat liver fibrosis/cirrhosis model (Icahn School of Medicine at Mt. Sinai)

EDP-305 protects rats and mice from liver steatosis and injury

- **Lowers liver and plasma lipid contents (including cholesterol, TG & FFA)**
- **Reduces ballooning & fibrosis progression, and reduces inflammation**
- **Lowers NAFLD Activity Score (NAS)**

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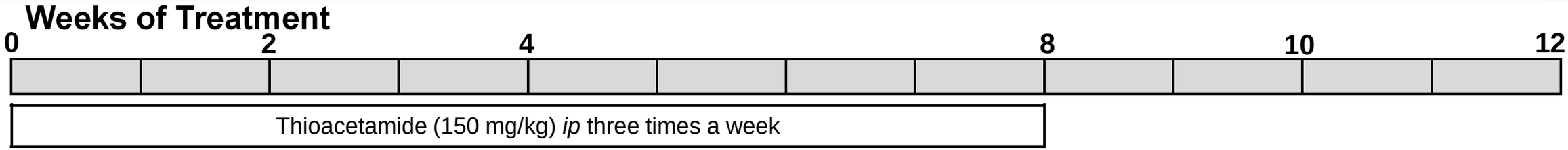
Rat model of thioacetamide(TAA)-induced liver fibrosis and cirrhosis

Study design



Weeks	Event
0 - 8	TAA *ip* injection three times per week
4	Rats develop fibrosis by week 4
4 - 8	Compound concurrently with TAA (Therapeutic Intervention)
8	Rats develop cirrhosis by week 8. Endpoint 1: fibrosis reduction
8 - 12	Compound w/o TAA (Cirrhosis Reversal)
12	Endpoint 2: cirrhosis reversal

- Endpoints:
  - Histopathologic analyses (including Sirius Red staining & pathology scores)
  - Serum clinical chemistry
  - Weight: body, liver & spleen
  - Key fibrogenic gene expression

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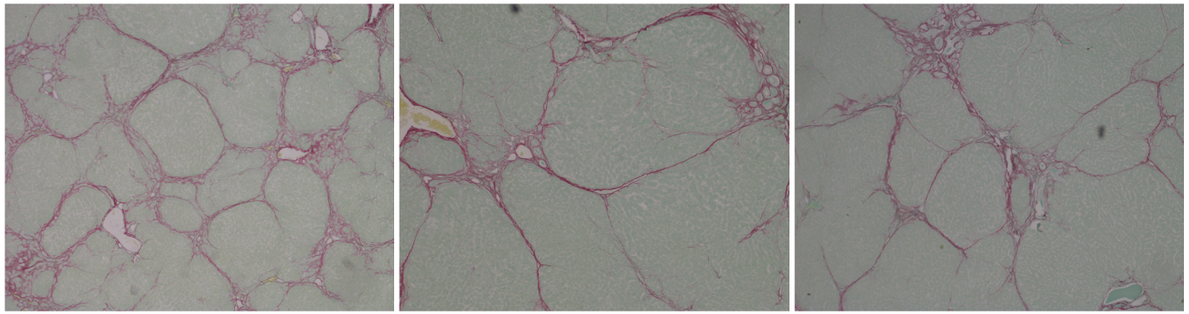
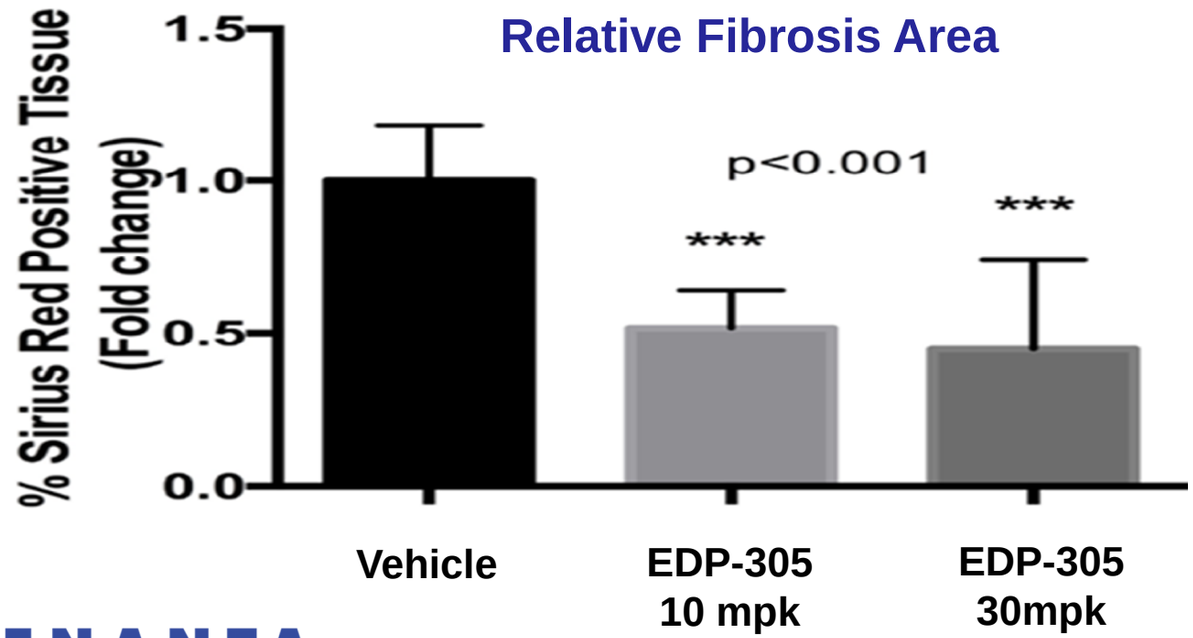
EDP-305 significantly reduced fibrosis progression in rats

Therapeutic Intervention Results

Vehicle | EDP-305, 10 mg/kg | EDP-305, 30 mg/kg



	Sirius red positive tissue (%)	Reduction in fibrosis (%)
Vehicle	100 %	--
EDP-305 10 mpk	50 %	50 % ↓
EDP-305 30 mpk	45 %	55 % ↓



- Pathology scores (including Scheuer score, Ishak score, Ductular reaction/Metaplasia scoring) also decreased in parallel with collagen morphometry

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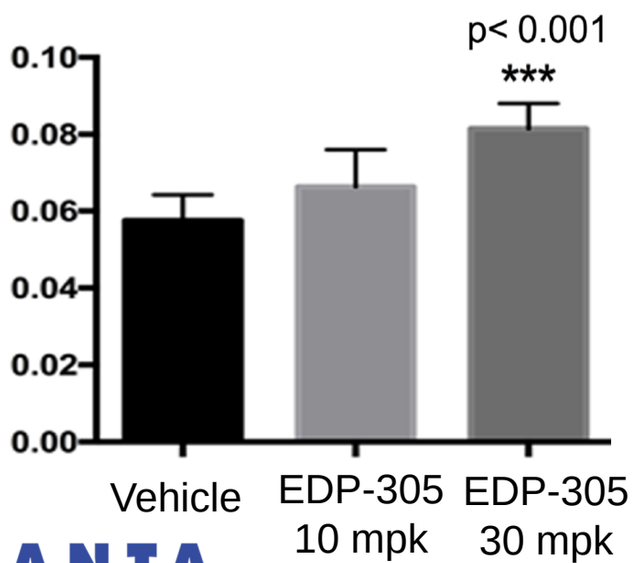
EDP-305 significantly improved liver/spleen weights & serum clinical chemistry

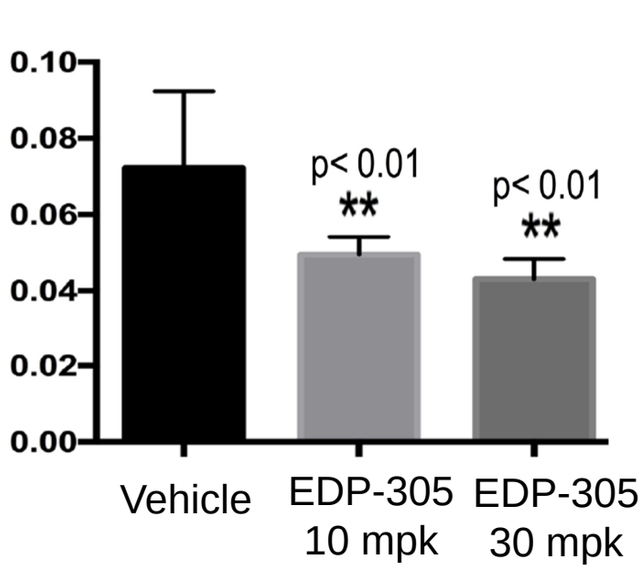
Therapeutic Intervention Results

- Progression of fibrosis/cirrhosis causes liver to body weight ratios to decrease, spleen to liver weight ratios to increase (Splenomegaly), and serum AST levels to increase
- EDP-305 significantly reduced the progression of fibrosis, which led to increased liver to body weight ratios and decreased spleen to liver weight ratios. EDP-305 also improved serum clinical chemistry (*e.g.*, AST) for liver function testing

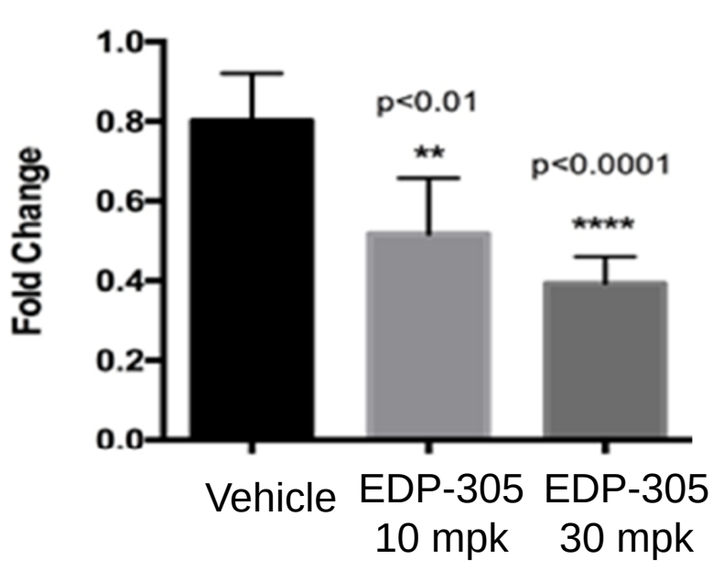
Liver to body weight ratio



Spleen to liver weight ratio



Serum AST



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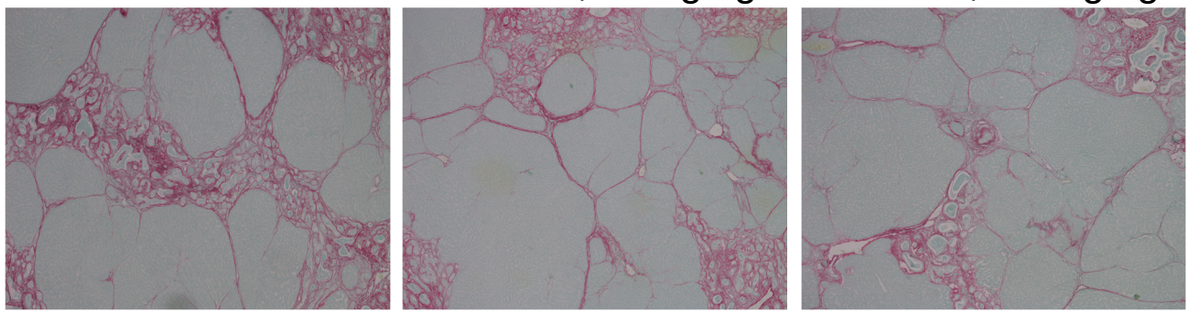
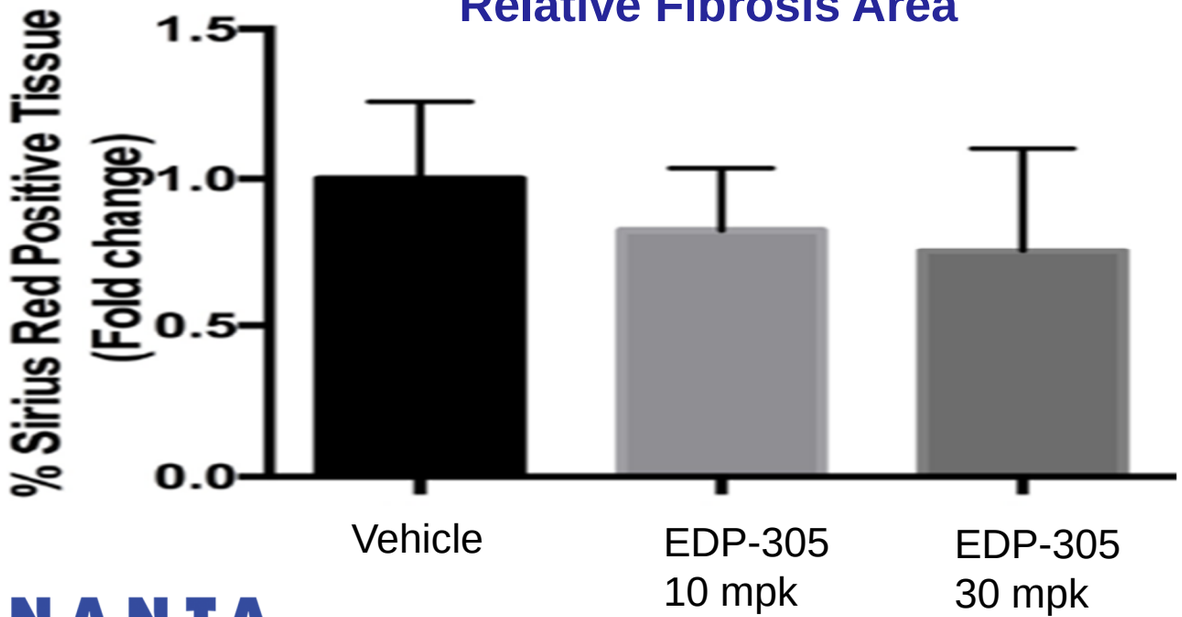
EDP-305 decreases collagen deposition in rats with established cirrhosis

Cirrhosis Reversal Results

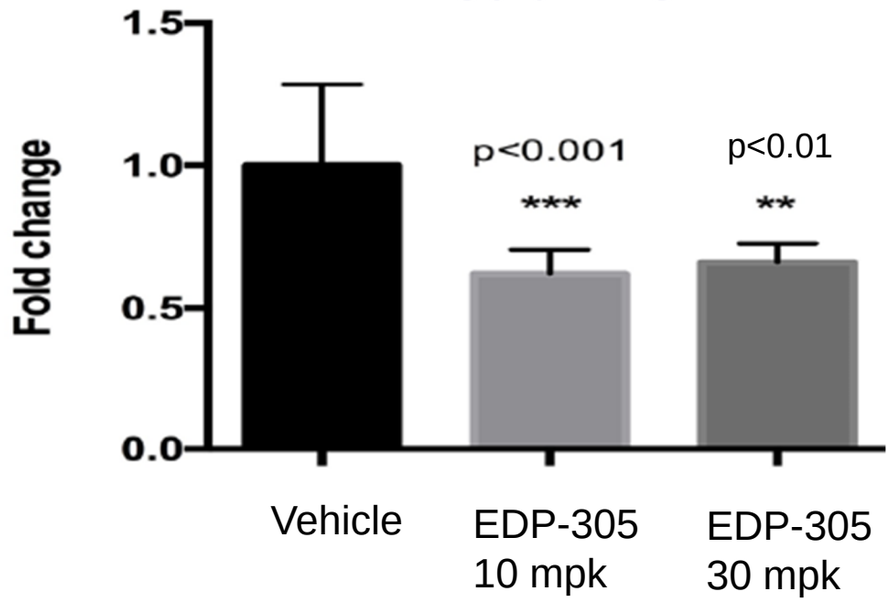


	Sirius red positive tissue (%)	Reduction in fibrosis (%)
Vehicle	100 %	--
EDP-305 10 mpk	89 %	11 % ↓
EDP-305 30 mpk	75 %	25 % ↓

Relative Fibrosis Area



Serum AST



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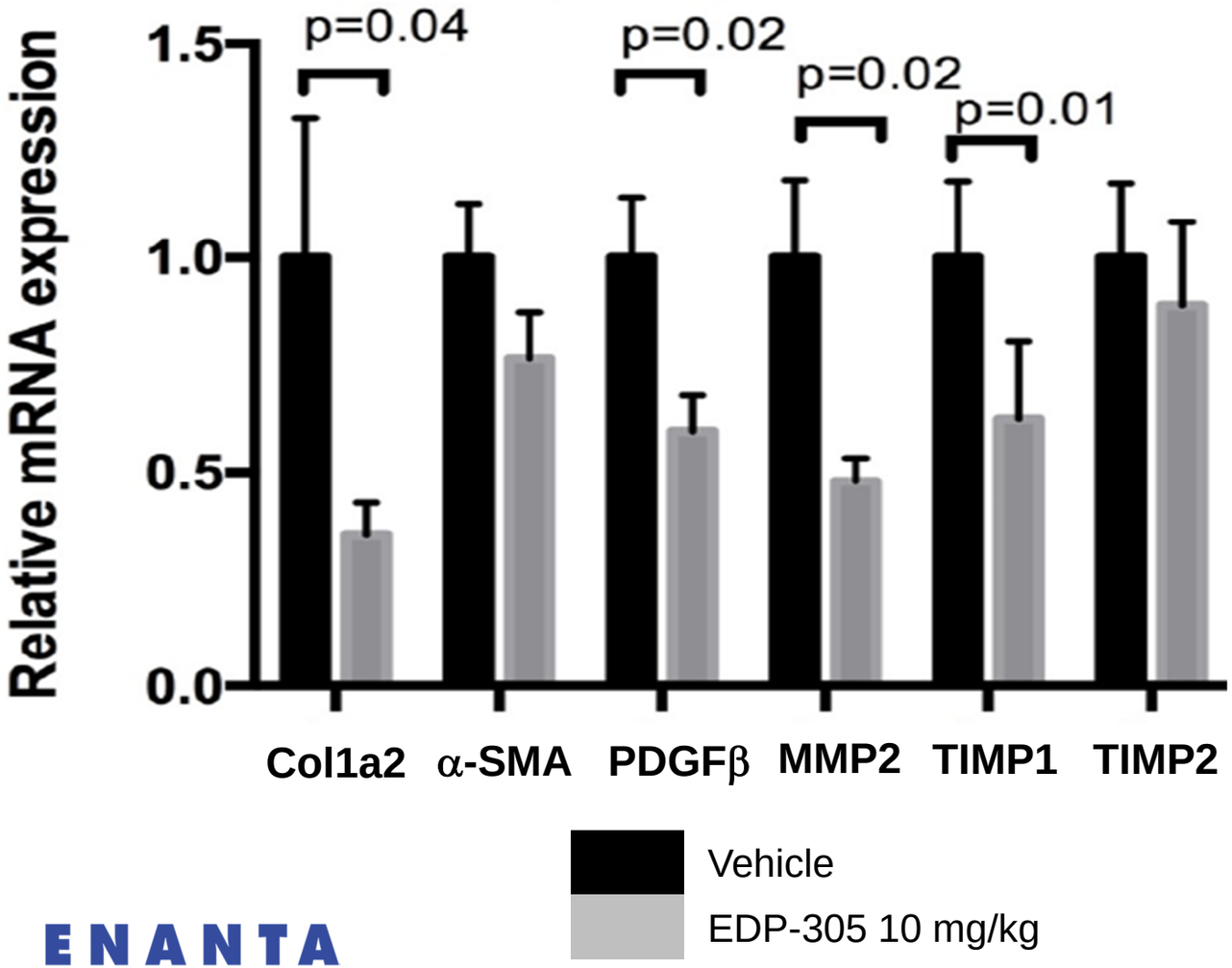
EDP-305 down-regulated key fibrogenic genes

Cirrhosis Reversal Results



	% Reduction compared to vehicle
Collagen type1 alpha 2 (Col1a2)	65% ↓
Alpha smooth muscle actin (α-SMA)	23% ↓
Platelet derived growth factor β (PDGFβ)	40% ↓
Matrix metallopeptidase 2 (MMP2)	52% ↓
Tissue inhibitor of metalloproteinase-1 (TIMP1)	37% ↓
Tissue inhibitor of metalloproteinase-2 (TIMP2)	11% ↓

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Conclusions & EDP-305 development

- EDP-305 is a potent FXR receptor agonist with no/minimal activity against other nuclear receptors and TGR5
- EDP-305 exhibits excellent anti-fibrotic efficacy in rats with ongoing TAA-induced fibrosis
- It also decreases collagen deposition in rats with established cirrhosis
- These results warrant further clinical study of EDP-305 for the treatment of NASH and PBC
- Phase 1 study in healthy subjects and subjects with presumed NAFLD has recently been completed
- Fast Track Designation has been granted by FDA

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EDP-305 posters in this meeting

- "A novel FXR agonist EDP-305 potently suppresses hepatic stellate cell activation and hepatic fibrosis in chronic mouse models of biliary and metabolic liver disease" (#367)
  - Presented from 8 am – 5:30 pm on Oct 20

- "EDP-305 favorably regulates lipoprotein mechanism *in vitro*" (#1988)
  - Selected as "Presidential Poster of Distinction"
  - To be presented from 8 am – 5:30 pm today (Oct 23)

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THANKS FOR YOUR ATTENTION

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