AASLD November 13-16, 2020
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THE BEST OF THE LIVER MEETING® 2020

Basic and Translational Research

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About the program:

Best of The Liver Meeting 2020 was created by the Scientific Program Committee for the benefit of AASLD members, attendees of the annual conference, and other clinicians involved in the treatment of liver diseases. The program is intended to highlight some of the key oral and poster presentations from the meeting and to provide insights from the authors themselves regarding implications for patient care and ongoing research.

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Use of these slides:

Endothelin (ET)-A axis triggers biliary senescence, liver fibrosis, and angiogenesis by activation of transforming growth factor (TGF)-β1 signaling in primary sclerosing cholangitis (PSC)

Aim

Identify the coordinated role of ET signaling in cholangiocytes and vascular endothelial cells during PSC

Methods

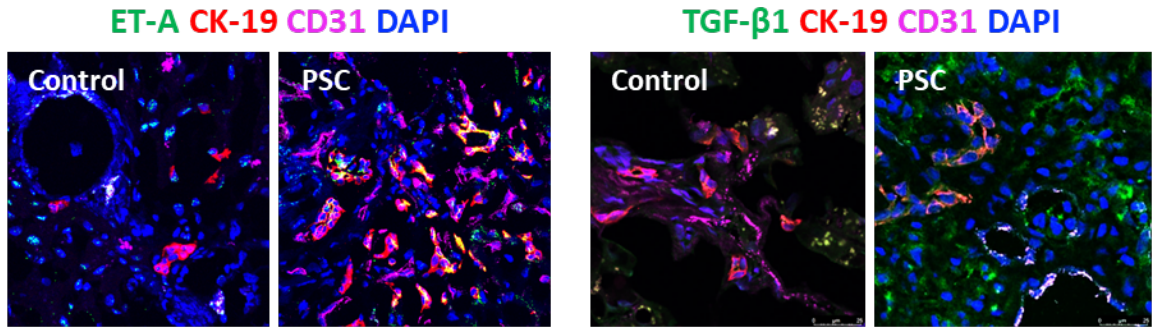
WT and Mdr2$^{-/-}$ mice (PSC model), and human control and PSC were analyzed for angiogenesis and ET expression, and Mdr2$^{-/-}$ mice were treated with an ET-A receptor antagonist (Ambrisentan) for 1 week.

Main Findings

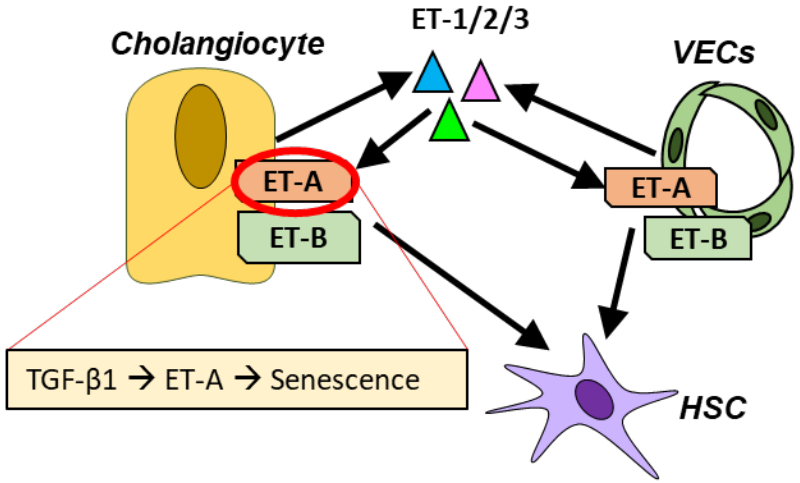
- ET-1/2/3 and ET-A/B expression, as well as angiogenesis are upregulated in human PSC and Mdr2$^{-/-}$ mice.
- TGF-β1 induces biliary senescence and liver angiogenesis by ET-A.

Conclusions

- Inhibition of ET-A reduces liver damage, ductular reaction, biliary senescence, and liver fibrosis in Mdr2$^{-/-}$ mice.
- Crosstalk between the bile ducts and vascular bed may occur via TGF-β1/ET-A signaling.



Working Model:



Kennedy LL, et al., Abstract 13

Microbiome changes induced by bariatric surgery protects against obesity and NAFLD by decreasing gastric inhibitory polypeptide (GIP) and increasing hepatic NKT cell expression

Objective

Determine if gut microbial changes induced by bariatric surgery is protective against the development of fatty liver disease and obesity

Methods

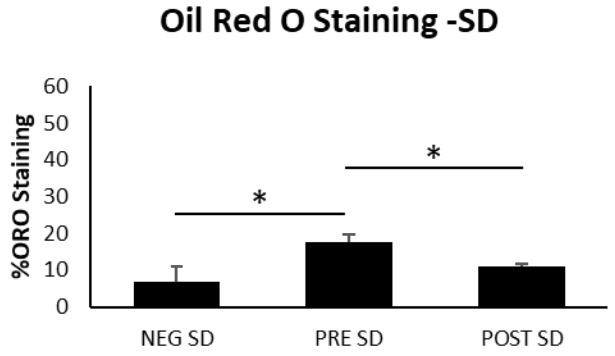
Transplantation of fecal microbiome of 4 patients who underwent laparoscopic sleeve gastrectomy before (PRE) and 6 months (POST) after surgery into antibiotic-treated mice while being fed on a standard diet (SD) or a high fat, high fructose, high cholesterol (HF) diet

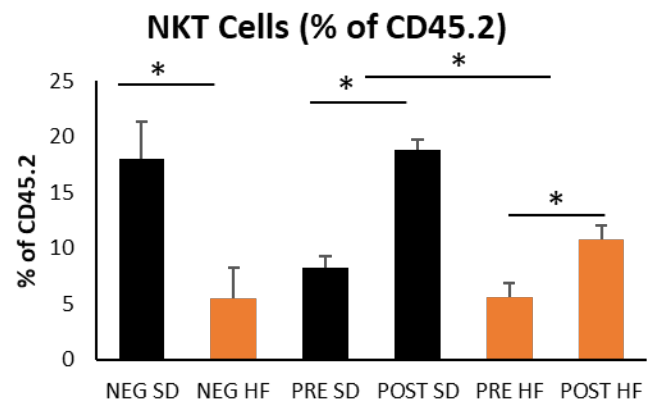
Main Findings

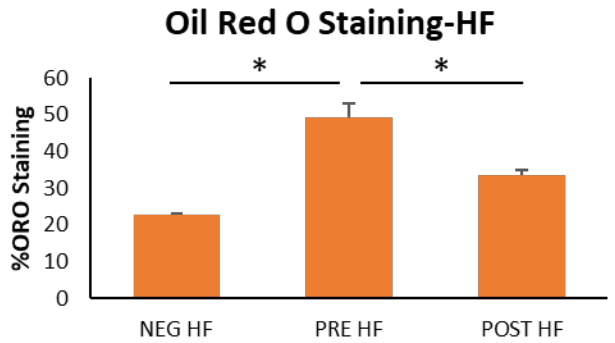
Post bariatric microbiome was protective against obesity and NAFLD by increasing NKT cell expression and decreasing GIP.

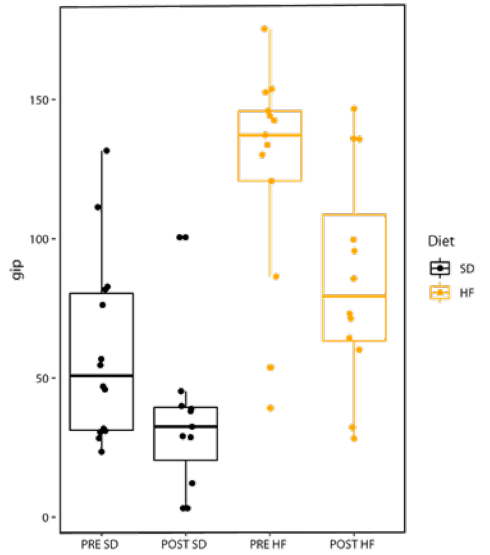
Conclusions

The protective effects of bariatric surgery is mediated by changes in the gut microbiome. Microbial-based targets may be potential therapies for obesity and NAFLD in the future.









Dong TS, et al., Abstract 17

Adenine base editing reduces liver burden and restores circulating alpha-1 antitrypsin in mice

Objective

Evaluate base editing as a treatment for both lung and liver manifestations of alpha-1 antitrypsin deficiency

Methods

Base editor mRNA and guide RNA were formulated in lipid nanoparticles and administered in the NSG-PiZ mouse model.

Main Findings

- Up to 30% correction of the PiZ mutation in total liver tissue by next generation sequencing
- Reduction in insoluble PAS-D stained aggregates in hepatocytes (see Figure 1)
- Increased serum levels of human alpha-1 antitrypsin (see Figure 2)

Conclusions

Base editing warrants further investigation as a treatment modality for alpha-1 antitrypsin deficiency lung and liver diseases.

Packer MS, et al., Abstract 32

Figure 1.

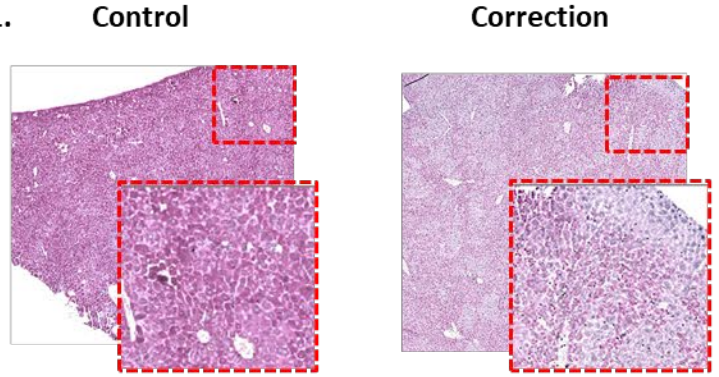
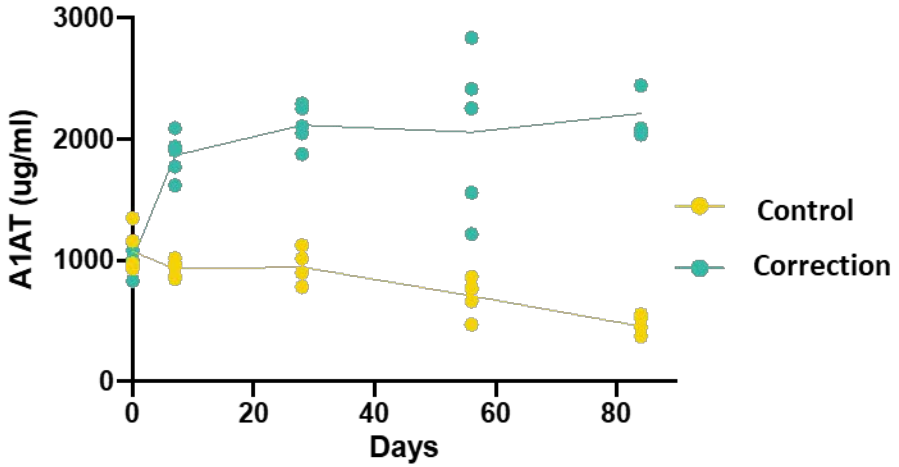


Figure 2.



Treatment of α-1 antitrypsin deficiency using hepatic-specified cells derived from human induced pluripotent stem cells

Hypothesis/Aim/Objective

Hepatic-specified cells may be repopulated in the livers of the transgenic mice.

Methods

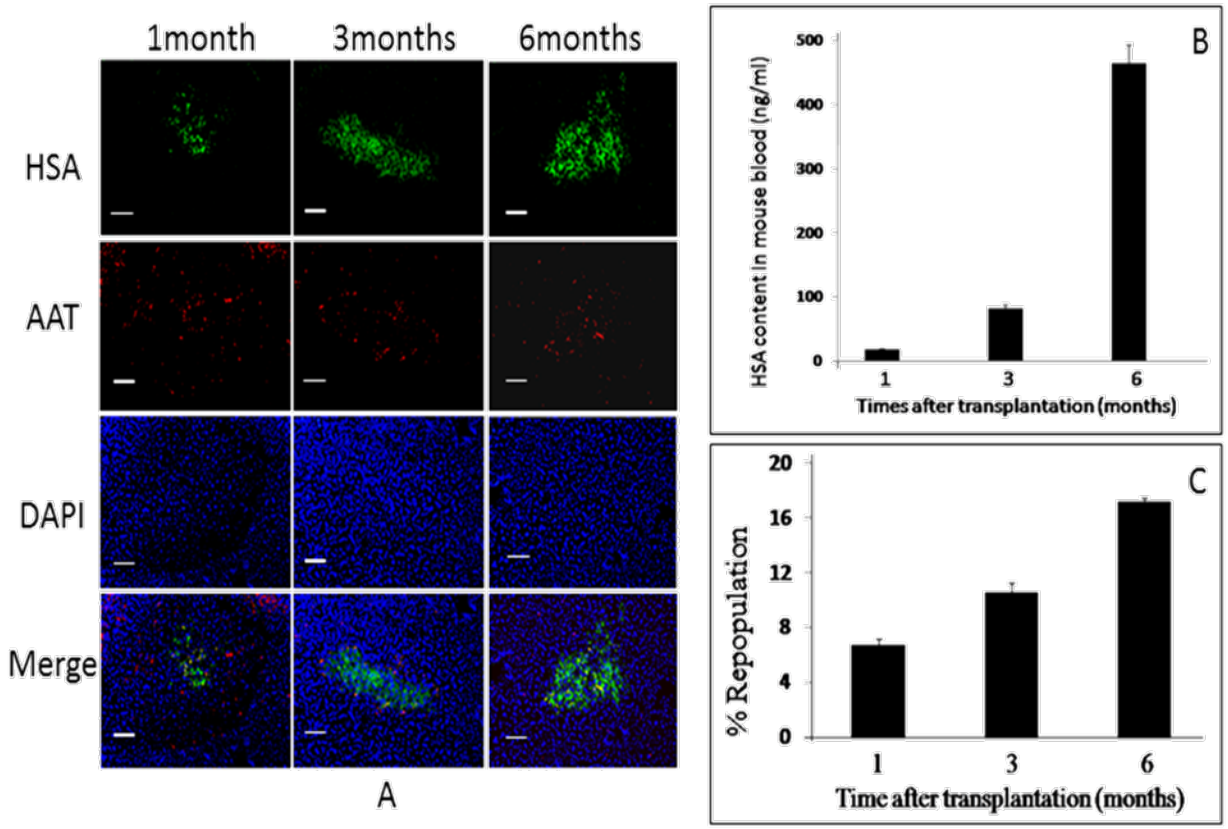
1 x 10^6 human hepatic-specified cells were transplanted into the livers of transgenic mice using intra-splenic injection.

Main Findings

Post transplantation, hepatic-specified cells were found to be successfully and progressively repopulated in the livers of the transgenic mice and secreted human serum albumin.

Conclusions

This study, therefore, highlights the potential of iPSC-derived hepatic specified cells, as novel cell replacement therapy for patients with α-1 antitrypsin deficiency.



Xu B, et al., Abstract 33

Outcomes of immune checkpoint inhibitor (ICI) rechallenge following high-grade ICI hepatitis

Aim

To characterize clinical outcomes following ICI rechallenge

Methods

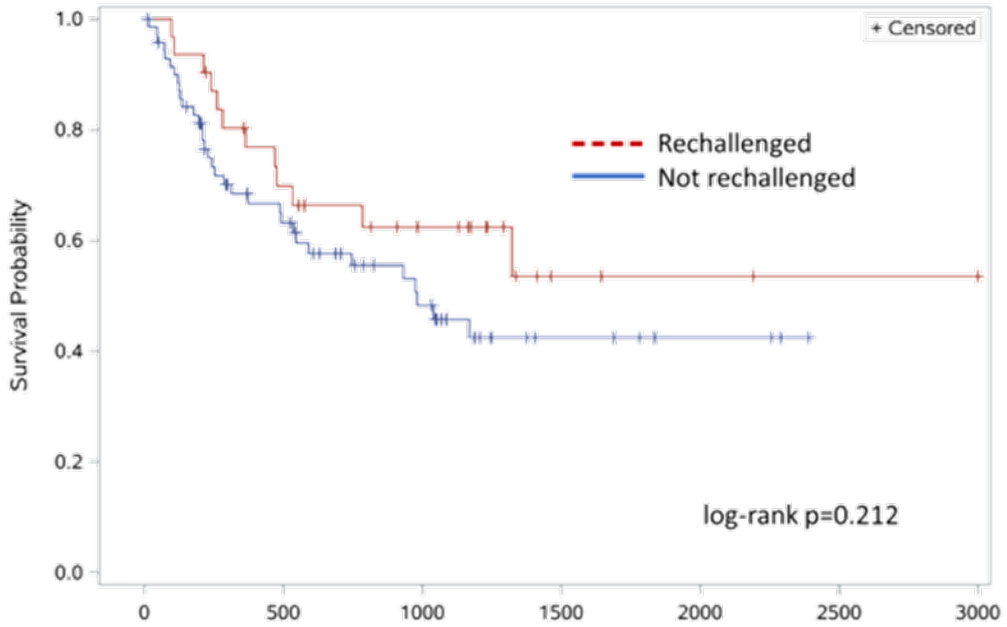
Multicenter, retrospective cohort study of 102 melanoma patients who developed grade ≥3 ICI hepatitis; 31/102 patients underwent ICI rechallenge

Main Findings

- ICI rechallenge did not change tumor response or time to all-cause death.
- 6/31 rechallenged patients developed immune-related toxicity that necessitated treatment discontinuation (4 patients with recurrent ICI hepatitis); patients receiving ipilimumab were less likely to tolerate rechallenge.

Conclusions

Melanoma patients who undergo ICI rechallenge following resolution of high-grade hepatitis have a relatively modest risk of hepatitis recurrence, although it remains unclear if ICI rechallenge improves clinical outcomes.



Time to All-Cause Death, Days

Li M, et al., Abstract 116

Mapping a HSC-macrophage physical interactome in normal and NASH mouse livers

Hypothesis

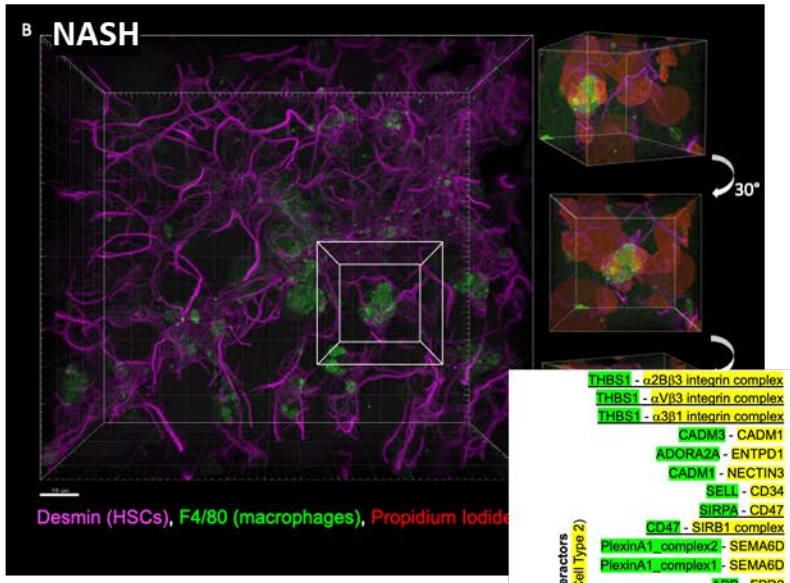
Physical associations between hepatic stellate cells (HSCs) and macrophages amplify disease activity in NASH; inhibition of these interactions will attenuate disease.

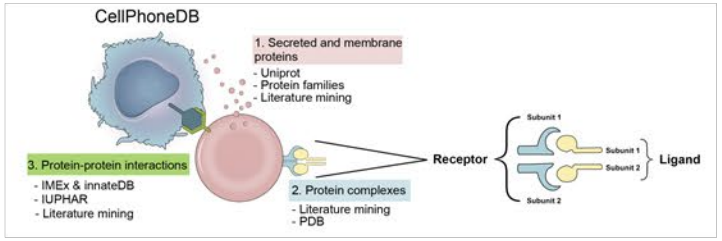
Methods

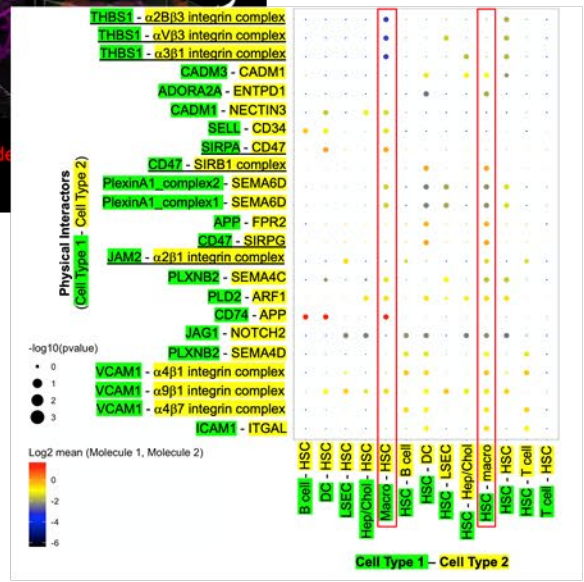
- Liver tissue clearing and confocal imaging to map hepatic stellate cells and macrophages in 3D
- Apply CellphoneDB algorithm to normal and NASH liver scRNAseq data (Xiong X, et al., 2019) to predict non-secreted ligand-receptor interactions

Main Findings/Conclusions

- Physical associations between HSCs and macrophages are prevalent in normal and NASH mouse livers.
- These associations are likely mediated by specific adhesion proteins, some unique to NASH that may serve as novel therapeutic targets.







Wang S, et al., Abstract 148

Serum ST6GAL1 is a novel biomarker for predicting efficacy of tyrosine kinase inhibitors in hepatocellular carcinoma

Hypothesis/Aim/Objective

We sought for HCC oncogenes involved in susceptibility of TKIs and aimed to develop their serum biomarkers.

Methods

- We created a novel HCC mouse model in which tumor diversity of genetic drivers was recapitulated by transposon-based intrahepatic delivery of a pooled barcode-tagged 10-oncogene cDNA library.
- Efficacy of biomarker candidates was assessed using pre-treated serum of 96 HCC patients who underwent TKI therapy.

Conclusions

ST6GAL1 is a tumor-derived secreted protein downstream of FGF19 that may be a useful serum biomarker for identification of patients with FGF19-driven HCC who may benefit from Lenvatinib therapy.

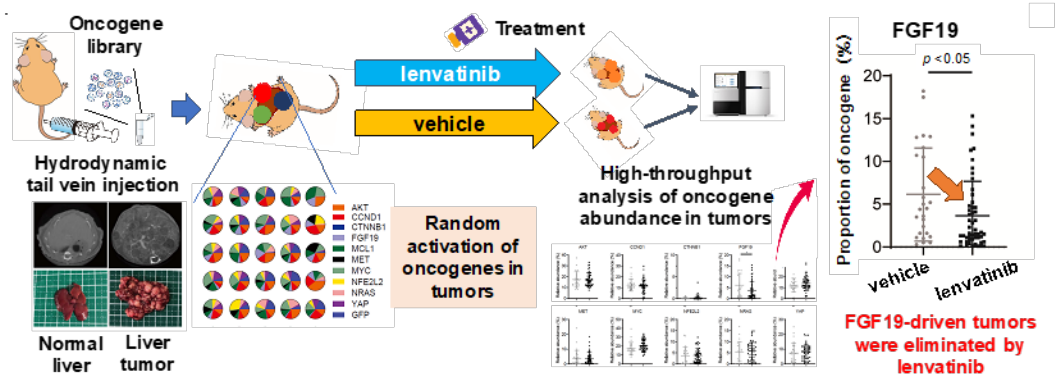


Figure 1. The novel mouse model that reproduces the inter-tumor oncogene heterogeneity of liver tumors and discovery of high susceptibility of FGF19-driven tumors to lenvatinib treatment

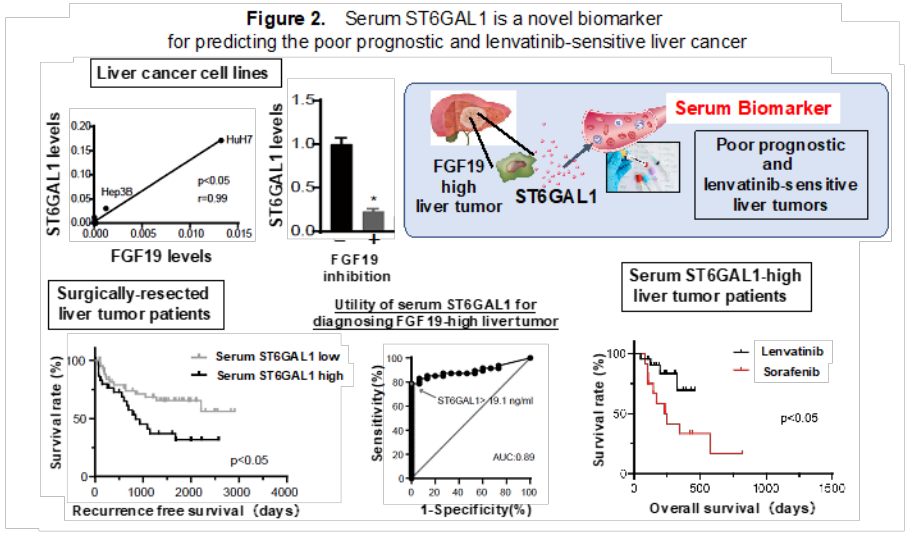


Figure 2. Serum ST6GAL1 is a novel biomarker for predicting the poor prognostic and lenvatinib-sensitive liver cancer

Myojin Y, et al., Abstract 164

Activation of the bile acid receptor TGR5 on macrophages induces TGFβ signaling and promotes fibrosis in murine sclerosing cholangitis

Hypothesis

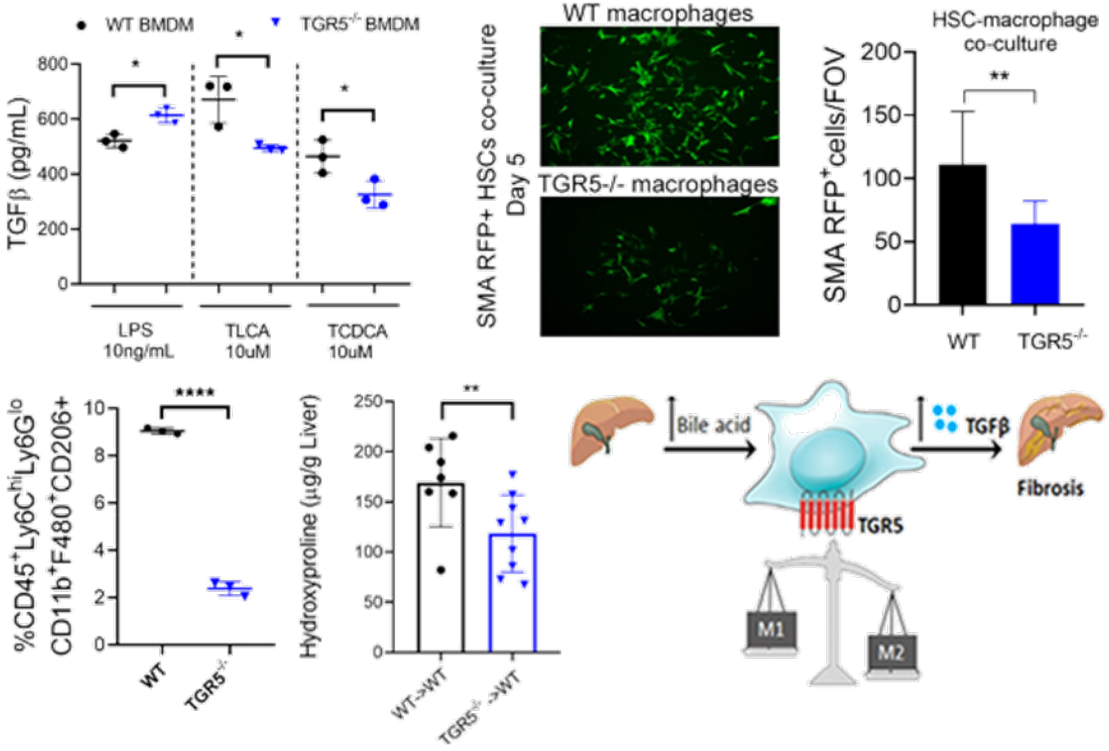
TGR5 promotes pro-fibrogenic responses under cholestatic conditions.

Methods

Bone marrow derived macrophages (BMDMs) were stimulated and TGFβ release was assayed by ELISA. Co-cultures were performed with hepatic stellate cells (HSCs) from αSMA:RFP reporter mice. Bone marrow chimeras from TGR5KO and WT mice were subjected to bile duct ligation and subsequent fibrosis was measured by quantifying the hydroxyproline content. Polarization of CD206+, M2, macrophages was determined by flow cytometry.

Main Findings

Genetic deletion of TGR5 on macrophages results in reduction of TGFβ secretion and stellate cell activation in response to hydrophobic bile acids. Loss of TGR5 signaling leads to reduction of alternatively polarized macrophages and protects against biliary fibrosis.



Conclusions

TGR5 regulates macrophage polarization and fibrotic responses in murine models of PSC.

Malik A, et al., Abstract 174

Fecal microbiota transplant reduces antibiotic resistance genes (ARG) in gut microbiota in decompensated cirrhosis: analysis of two randomized clinical trials

Aim

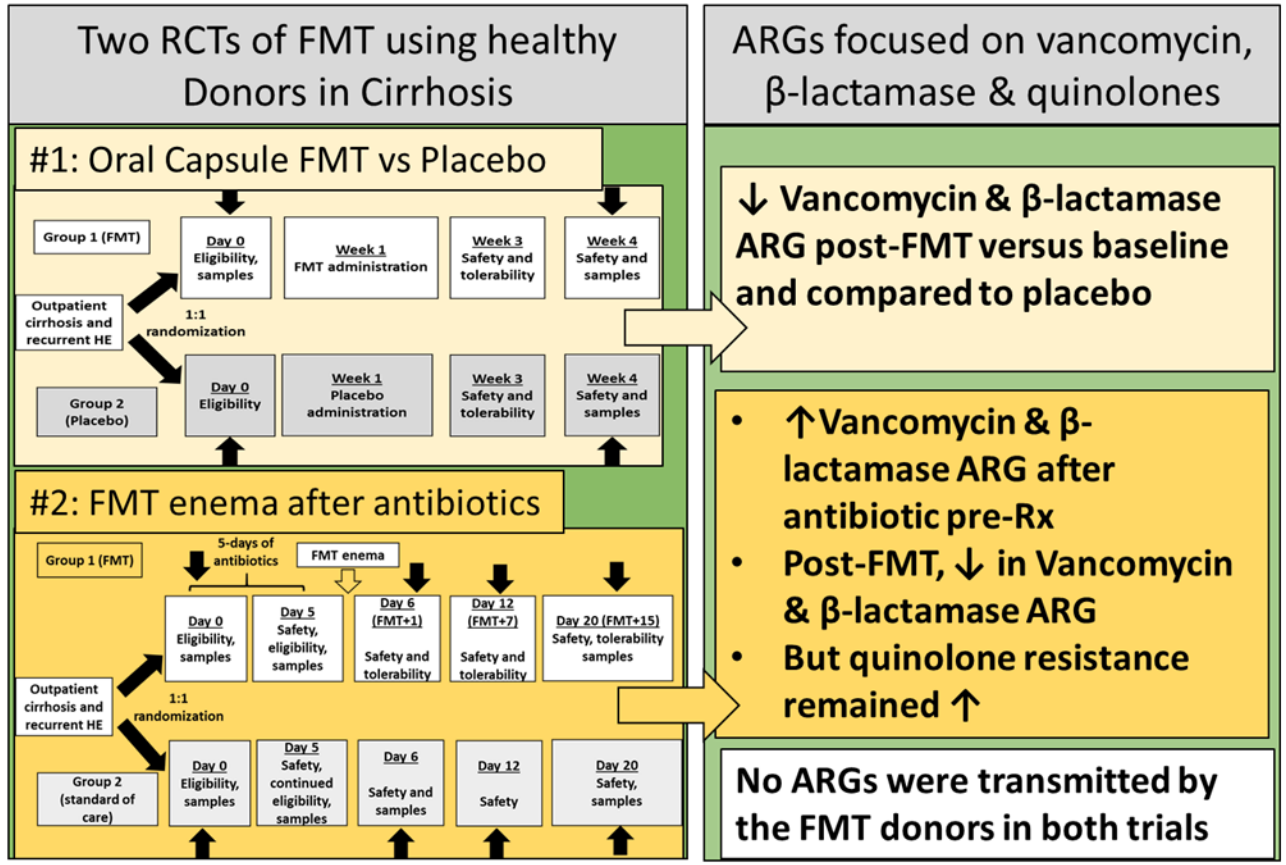
Determine the impact of healthy donor FMT on ARG expression in patients with decompensated cirrhosis through metagenomic analysis of the two published trials

Methods

Prior HE (on lactulose, rifaximin) were the population for both trials; *Trial #1*: Oral capsule vs placebo and *Trial #2*: Antibiotics+Enema FMT vs standard of care (SOC) with metagenomic analysis of ARGs at baseline/post-therapy.

Main Findings

FMT was associated with reduction in beta-lactamase and vancomycin resistance gene abundance compared to baseline and non-FMT groups and none of the ARGs were donor-transmitted.



Conclusions

There is a relative reduction in antibiotic resistance gene expression after capsule or enema FMT in patients with decompensated cirrhosis.

Bajaj JS, et al., Abstract 175

Single session fecal microbiota transplantation in decompensated cirrhosis: an initial experience of clinical endpoints

Objectives

1⁰ Objective: To assess the difference in 180-day mortality between the FMT group and the SOC group

2⁰ Objectives

- To compare the changes in prognostic scores (CTP/MELD/MELD Na)
- To compare the complications in both groups
- Changes in ammonia levels and inflammatory markers (IL-1b, IL-6,) in both groups at 28 days

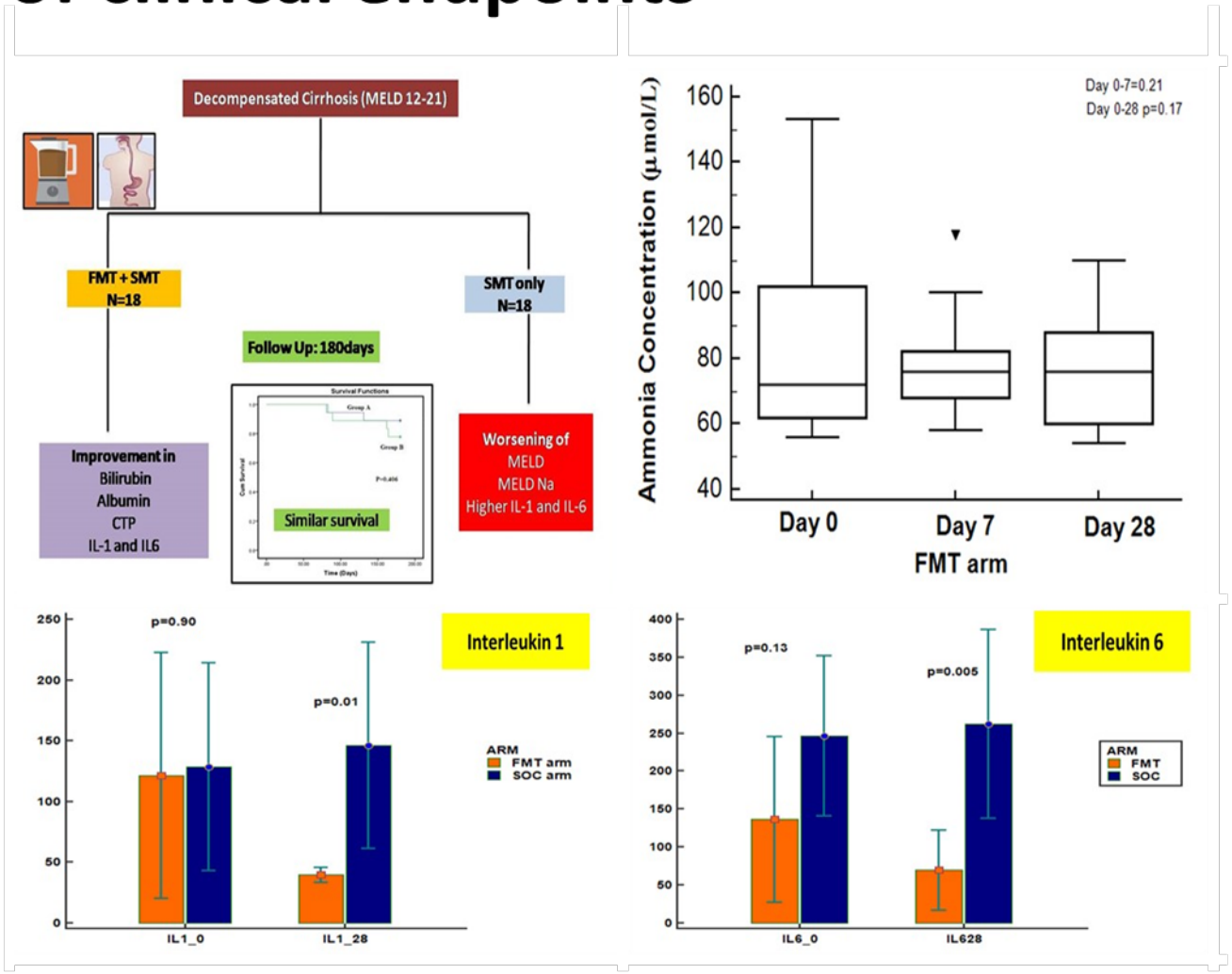
Methods

Open-label randomized control trial single session FMT (nasojejunal) using stool from family donors on patients with decompensated cirrhosis (DC) with MELD 12-21

Conclusions

FMT in advanced but stable DC leads to selective improvement of prognostic scores, reduces inflammatory cytokines, and is associated with non-significant reduction in ammonia. However, there are no differences in complications (HE, SBP, VH) or 180-day mortality.

Roy A, et al., Abstract 176



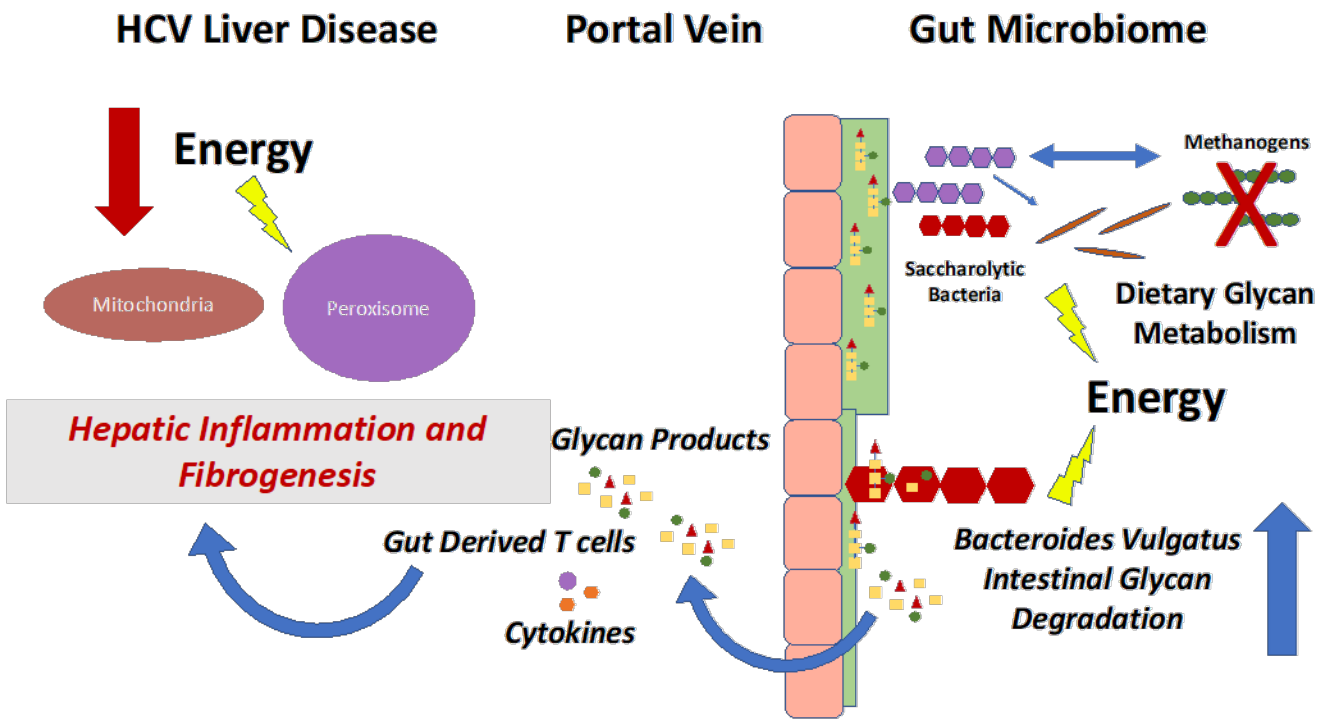
Exploring the portal vein to understand the alterations in hepatic and microbial gene expression in chronic HCV-associated cirrhosis

Aim

To understand the interplay between the liver and the gut microbiome and identify alterations from HCV infection and changes after treatment

Methods

Evaluation of the liver transcriptome, the gut microbiome composition and transcriptome, and a comprehensive panel of immunological and metabolic parameters in both portal and systemic circulation. Comparison of these data sets based on HCV status and cirrhosis.



Conclusions

By evaluating the liver, portal vein, and microbial function, we have identified energy homeostasis as a major liver-gut axis disturbance. Notable was hepatic peroxisome dysfunction with subsequent maladaptation in gut microbial function and ecology in cirrhosis, independent of HCV.

Ali RO, et al., Abstract 177

Suppression of intestinal microRNA194 reduces alcohol-induced liver injury in mice

Aim

To test the hypothesis that ethanol-induced upregulation of miR194 in the intestine contributes to the ethanol-induced hepatic BA synthesis through down regulation of intestinal Fxr expression

Methods

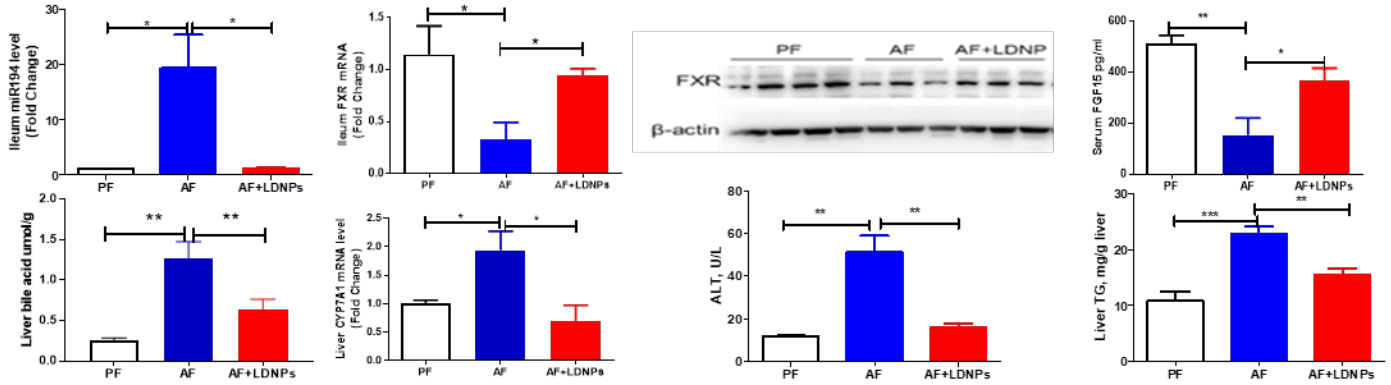
C57BL/6 and intestinal epithelial cell-specific Fxr knockout (*Fxr*$^{\Delta IEC}$) mice were subjected to NIAAA binge-on-chronic alcohol exposure. Control mice were pair-fed maltose-dextrin in substitution of ethanol.

Conclusions

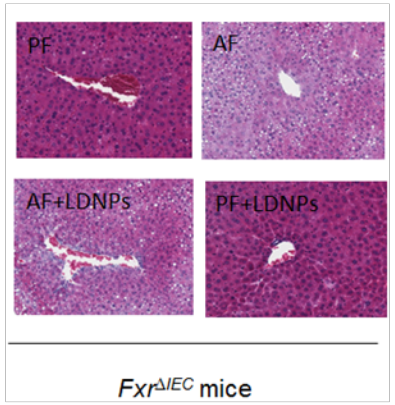
Alcohol consumption upregulates miR194, leading to downregulation of Fxr and Fgf15 in the intestine, which contributes to increased hepatic BA synthesis and liver injury. Suppression of miR194 by probiotic LGG-derived nanoparticles (LDNPs) prevents ALD through intestinal miR194-FXR-FGF15 axis.

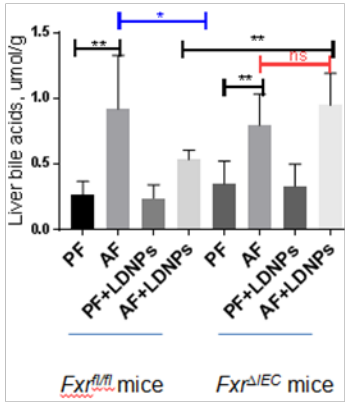
Jiang M, et al., Abstract 179

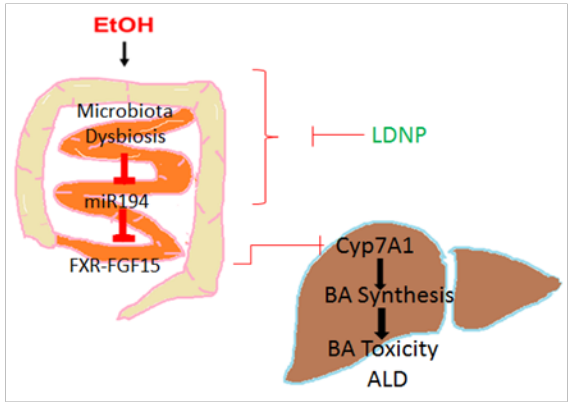
Alcohol disrupted intestinal miR194-FXR-FGF15 signaling and increased liver BA synthesis and injury, which was suppressed by LDNPs.



The beneficial effect of LDNPs is abolished in *Fxr*$^{\Delta IEC}$ mice.







Microfibril associate protein 4 (MFAP4) as a potential regulator of liver regeneration and disease

Hypothesis

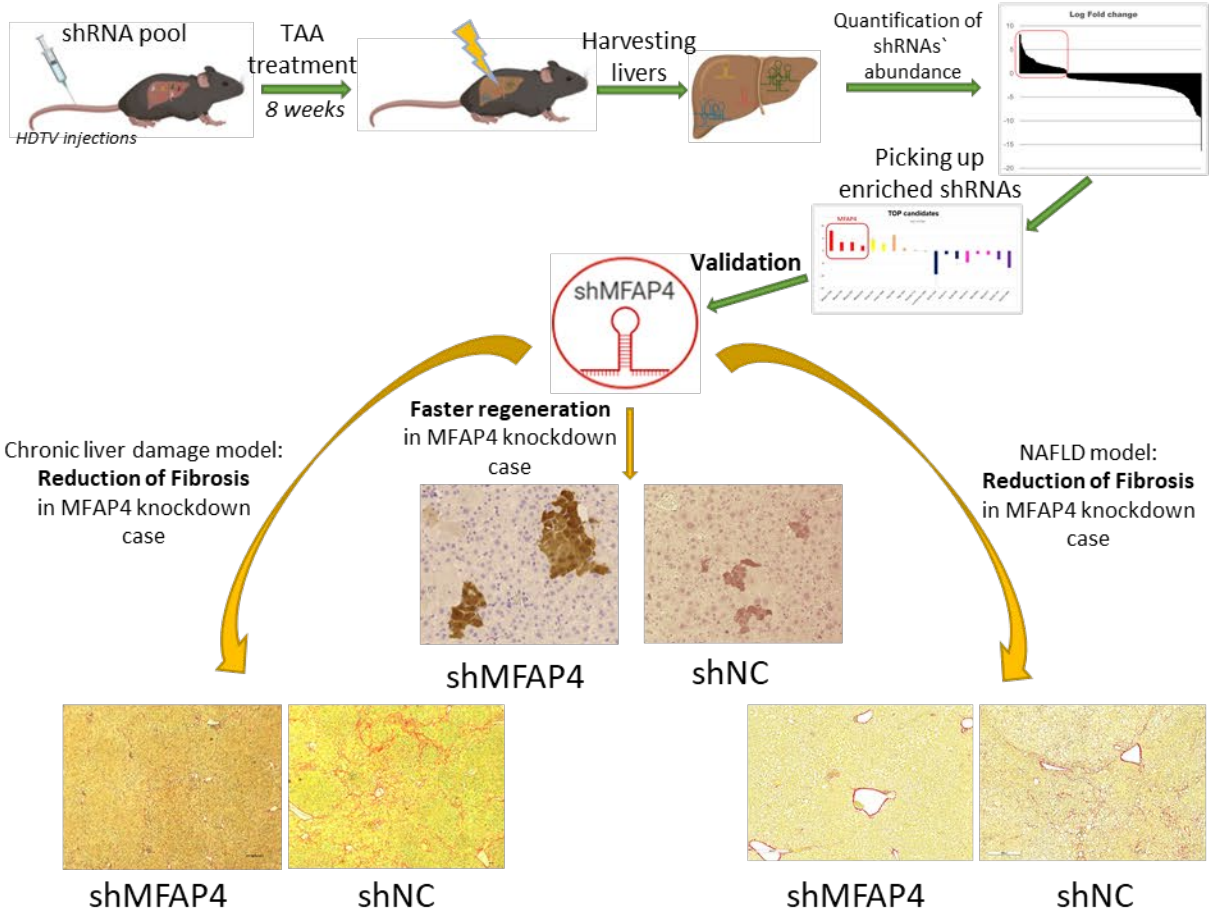
In vivo functional genomics can be applied to identify novel therapeutic targets for liver regeneration and disease.

Methods

- A pool of shRNAs (250 shRNAs targeting 89 genes) was delivered into C57Bl6 mice.
- Chronic liver damage protocol (TAA) was used in order to perform *in vivo* functional genetic screen.
- *In vivo* validation of potential candidates by using different models: regeneration model (repopulation & partial hepatectomy), chronic liver damage model (TAA), "Western Diet" NAFLD model

Conclusions

MFAP4 knockdown accelerates regeneration and attenuates chronic liver disease.



Iakovleva V, et al., Abstract LO6

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