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

Pediatric Liver Diseases

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AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

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:

Familial hemophagocytic lymphohistiocytosis hepatitis is mediated by IFN-γ intrinsically

Hypothesis

IFN-γ-mediated hepatocyte injury in murine familial hemophagocytic lymphohistiocytosis (FHL) model is caused by direct effect on hepatocytes.

Methods

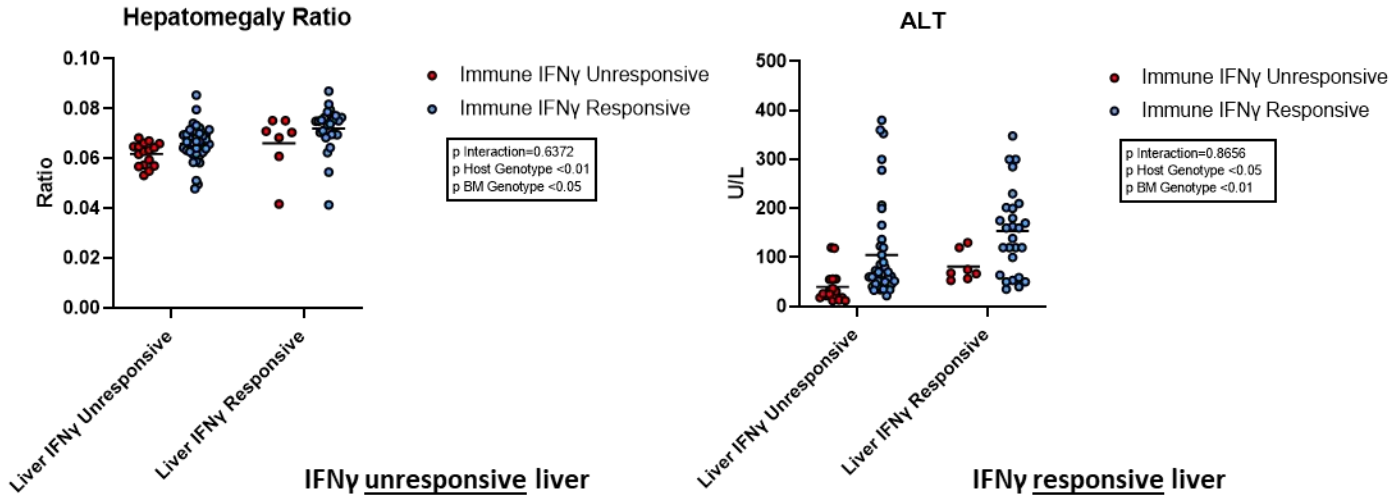
- Bone marrow chimeras of *IFNgR1* gene were created in the FHL mouse model (*Prf1−/−*) background to compartmentalize the IFN-γ response between marrow derived leukocytes and host hepatocytes.
- FHL physiology was induced by lymphocytic choriomeningitis virus infection. Degree of liver injury was assessed, as well as inflammatory milieu in the liver.

Conclusions

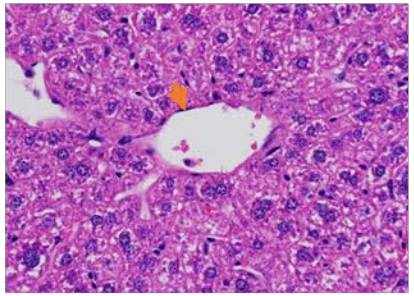
IFN-γ contributes to hepatitis in the murine model of FHL in a hepatic-intrinsic manner.

Diamond T, et al., Abstract 63

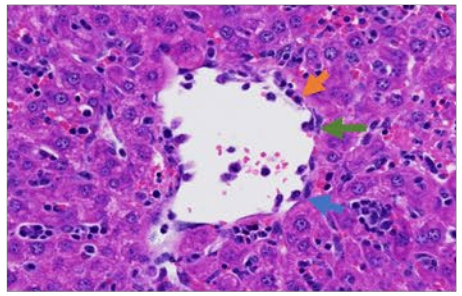
IFNγ contributed to liver injury in a hepatic-intrinsic manner independent of immune-mediated injury.



IFNγ unresponsive liver with no endotheliitis



IFNγ responsive liver with severe endotheliitis



Depletion of mannose phosphate isomerase activity leads to aberrant methylation in the liver

Aim

Identify the mechanisms by which MPI depletion leads to liver fibrosis

Methods

Livers were dissected from 1.5-year-old adult zebrafish and processed for histology and immunofluorescence.

Main Findings

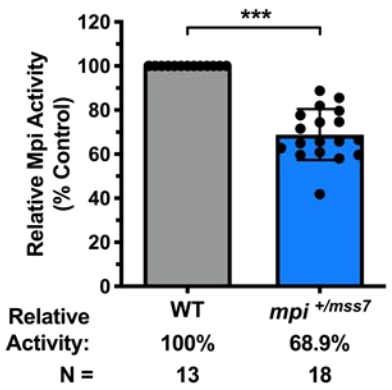
mpi $^{+/mss7}$ adult zebrafish livers **(A)** have decreased Mpi enzymatic activity and **(B)** demonstrate increased collagen deposition. Mpi depletion leads to increased levels of **(C)** O-GlcNAcylation and **(D)** 5-methylcytosine (5mC) immunofluorescence.

Conclusions

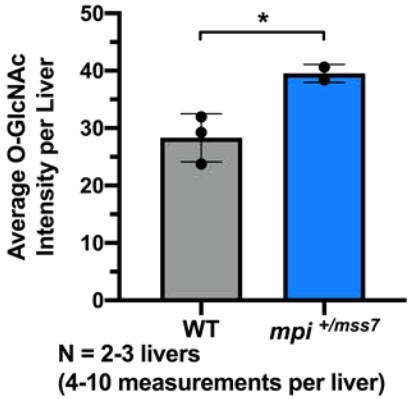
Depletion of MPI upregulates O-GlcNAcylation in the liver, which may lead to liver fibrosis through epigenetic alterations, such as methylation.

Morrison JK, et al., Abstract 64

A. Mpi enzyme activity

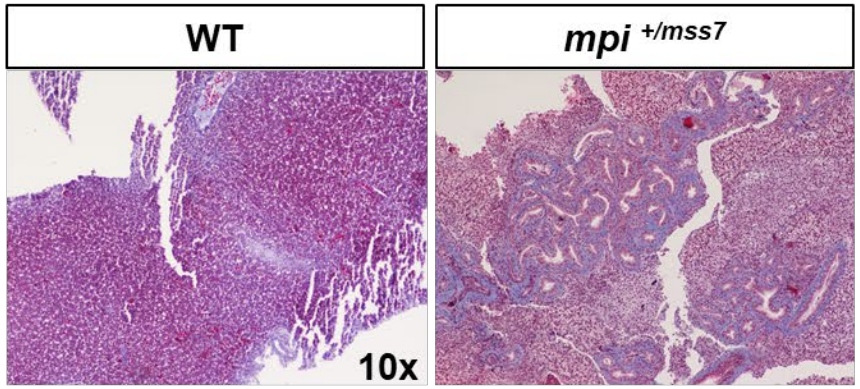


C. O-GlcNAc IF intensity

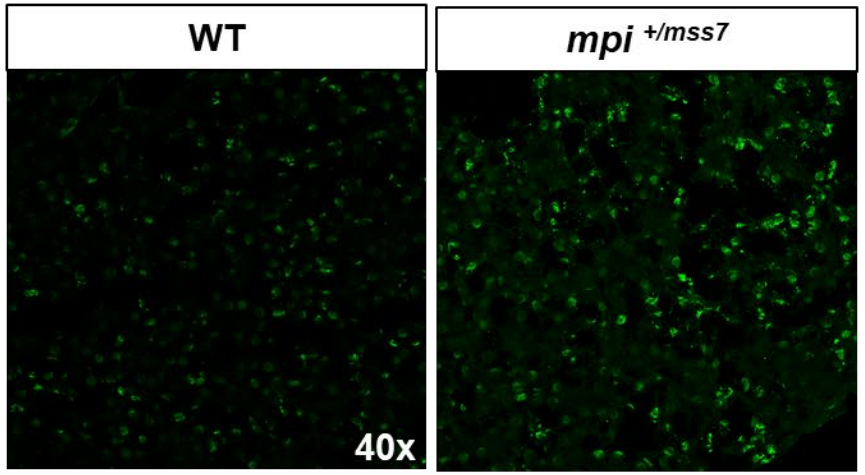


N = 2-3 livers
(4-10 measurements per liver)

B. Masson trichrome staining



D. 5mC immunofluorescence



STAT3 signaling may mediate protective effect of FXR agonist in parenteral nutrition associated cholestasis (PNAC)

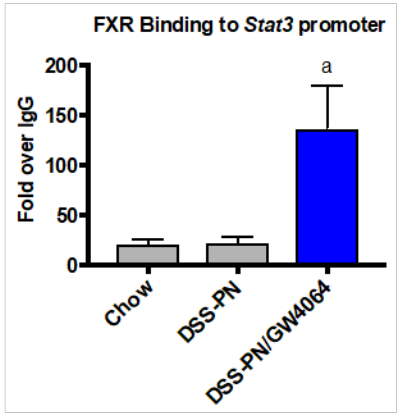
Objective

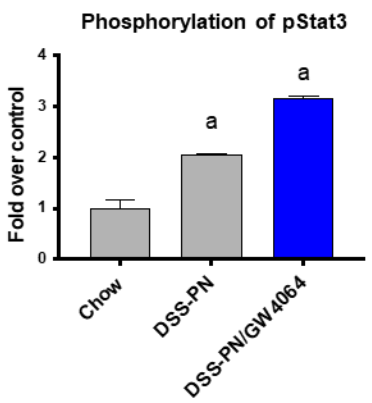
To determine role of Stat3 in hepatic protection through FXR signaling during PNAC.

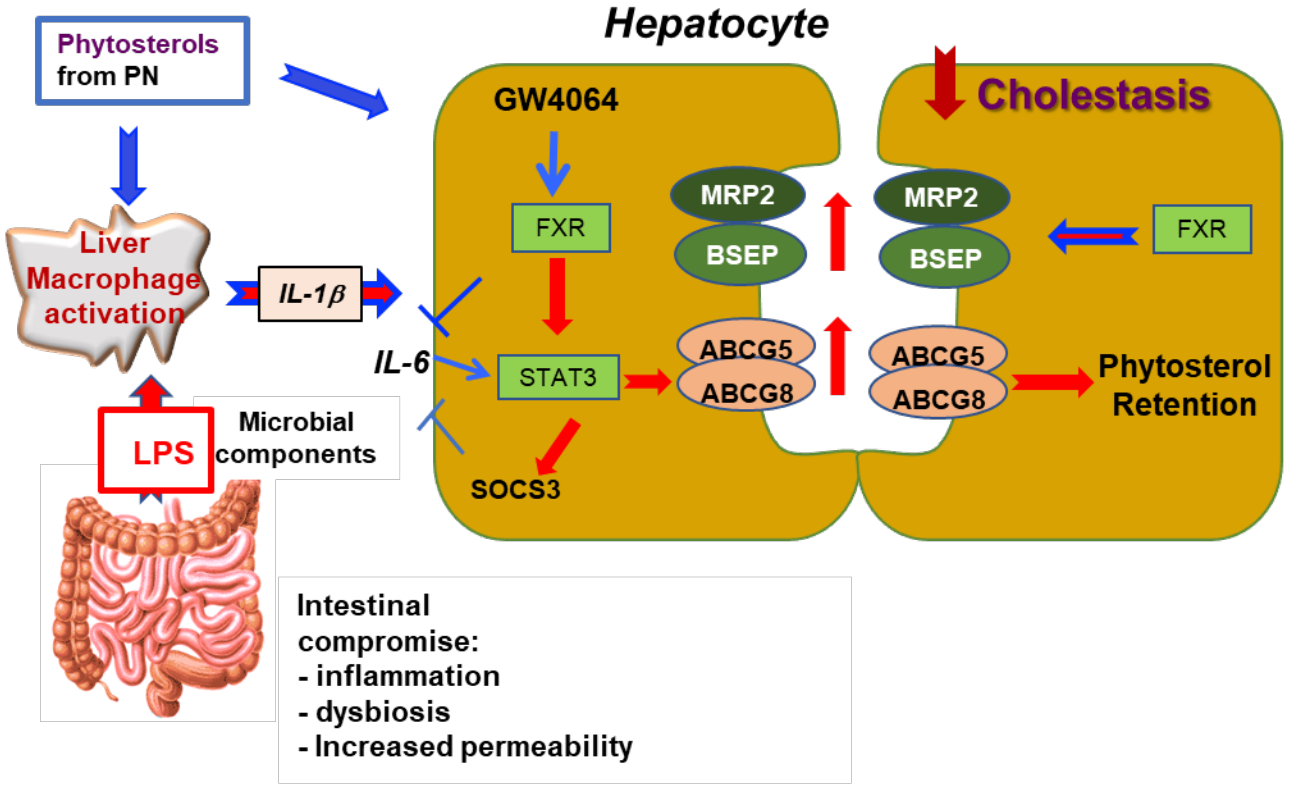
Methods

HepG2 cells and PNAC mouse model were used for qPCR, ChIP, and immunoblotting. FXR agonist GW4064 was used.

Main Finding







Conclusions

This study suggests that Stat3 signaling may play an important role in hepatic protection of FXR agonists in PNAC.

Ghosh S, et al., Abstract 65

Liver-specific deletion of XBP1, but not IRE1α, reduces liver injury and fibrosis in Mdr2(-/-) mice

Aim

To determine the effects of the hepatic IRE1α/XBP1 pathway on cholestatic liver disease progression using the Mdr2$^{-/-}$ mouse model

Methods

- Developed Mdr2$^{-/-}$ double knock out (DKO) mice with either Mdr2$^{-/-}$/liver-specific XBP1 knock out (LS-XBP1$^{-/-}$) or Mdr2$^{-/-}$/liver-specific IRE1α knockout (LS-IRE1α$^{-/-}$)
- Male 10 wk and 26 wk DKO and control single knock out (SKO) mice were analyzed using serum liver chemistries, qPCR, western blotting, liver histology, and RNAseq.

Main Findings

- XBP1-DKO mice which have increased hepatic IRE1α expression, have lower serum ALT and AlkPhos, and less portal fibrosis and ductular proliferation (see Figures 1 and 2) compared to SKO controls.
- In contrast, though IRE1α-DKO mice also lacked activated liver XBP1s, they were not protected against hepatic injury and fibrosis (see Figures 1and 2).

Conclusions

- Liver specific XBP1 deletion is protective in the Mdr2$^{-/-}$ mouse, which may be due to increased hepatic IRE1α signaling in these mice.
- IRE1α pathway is a potential therapeutic target for cholestatic liver diseases.

Kriegermeier A, et al., Abstract 171

Figure 1.

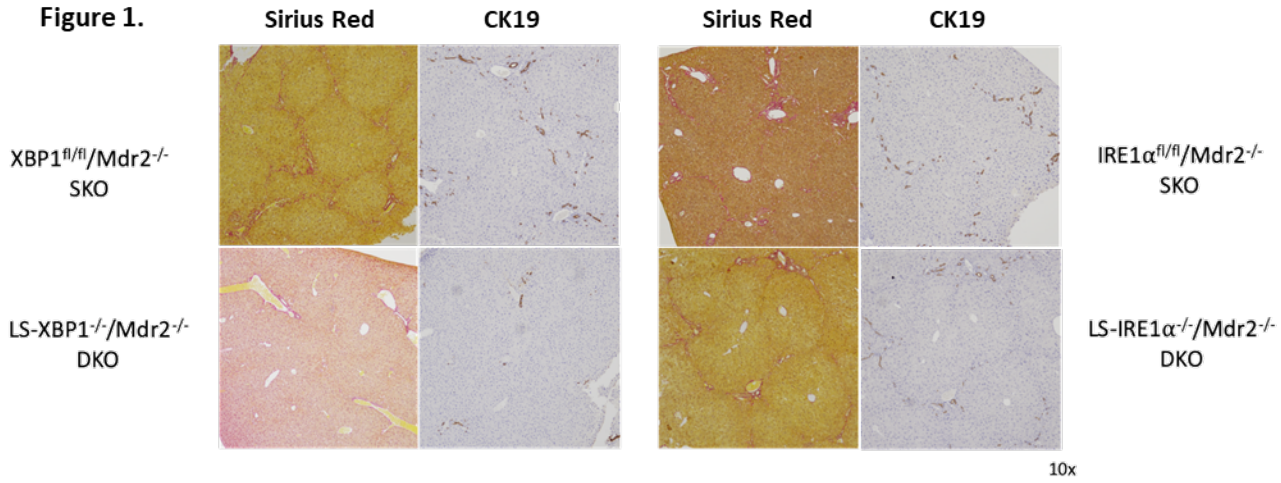
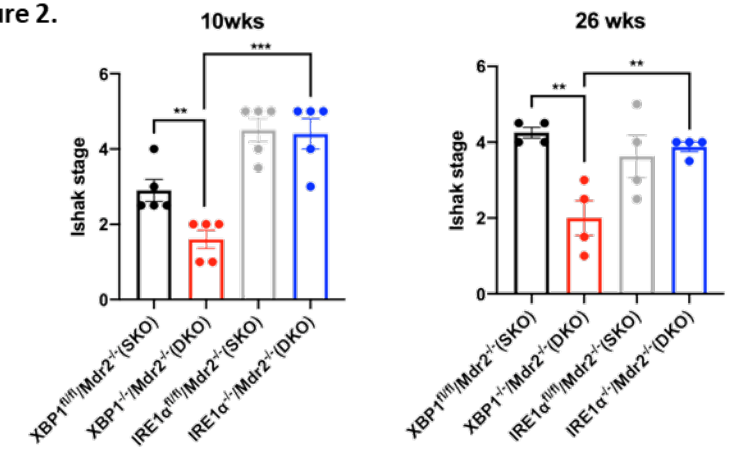


Figure 2.



Pediatric primary sclerosing cholangitis is associated with poor outcomes in racial/ethnic minorities

Objective

Identify racial/ethnic differences in disease presentation and progression in pediatric PSC

Methods

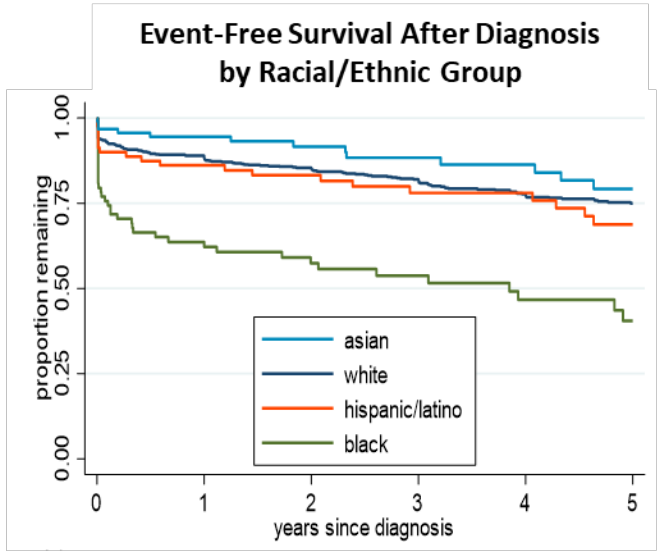
Retrospective study involving 54 centers globally from the Pediatric PSC consortium examining demographic, phenotypic, laboratory and histologic data at PSC diagnosis, as well as early hepatobiliary events and survival analysis, between the largest racial/ethnic groups

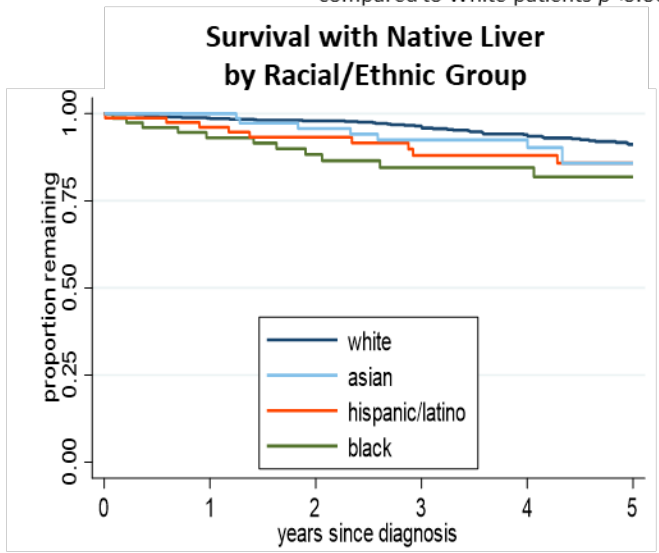
Conclusions

Pediatric PSC is not rare in minority populations and is associated with more advanced disease at presentation and more progressive disease overall, with Black and Hispanic patients having the worst clinical outcomes.

	White (n=808)	Black (n=88)	Hispanic (n=95)
Age at Diagnosis (median)	12.9 [9-13.4]	14.1 [11.3-16.1]*	10.5 [5.4-13.4]*
METAVIR Fibrosis Stage 4 (%)	13	26*	15
5-Year Survival Native Liver (%)	90 [87-92]	73 [60-83]*	79 [67-87]*
5-Year Event-Free Survival (%)	75 [71-78]	42 [30-55]*	62 [49-73]*
Early Hepatobiliary Events (%)	9	28*	12
Event Rate per Year (%/year)	3.5	7.8*	5.8*

* compared to White patients $p<0.001$





Hochberg JT, et al., Abstract 66

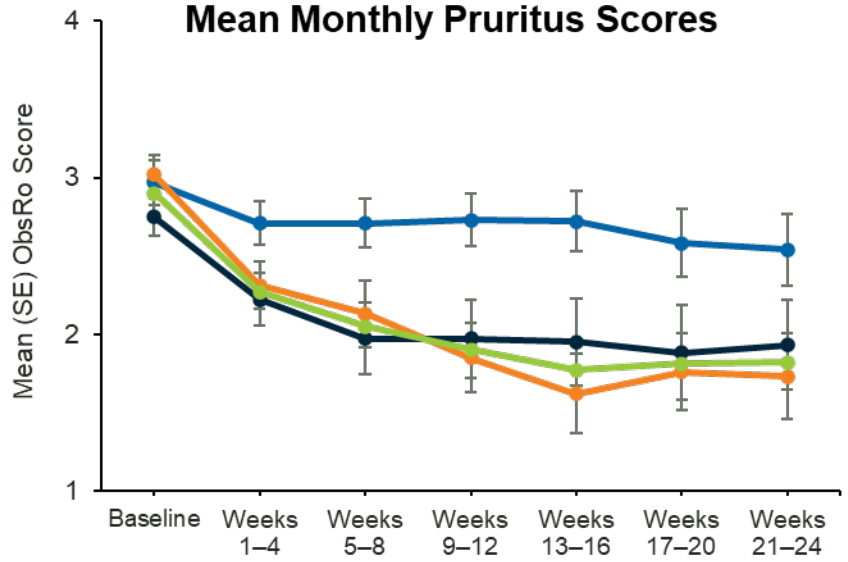
Efficacy and safety of odevixibat, an ileal bile acid transporter inhibitor, in children with progressive familial intrahepatic cholestasis types 1 and 2: results from PEDFIC 1, a randomized, double-blind, placebo-controlled phase 3 trial

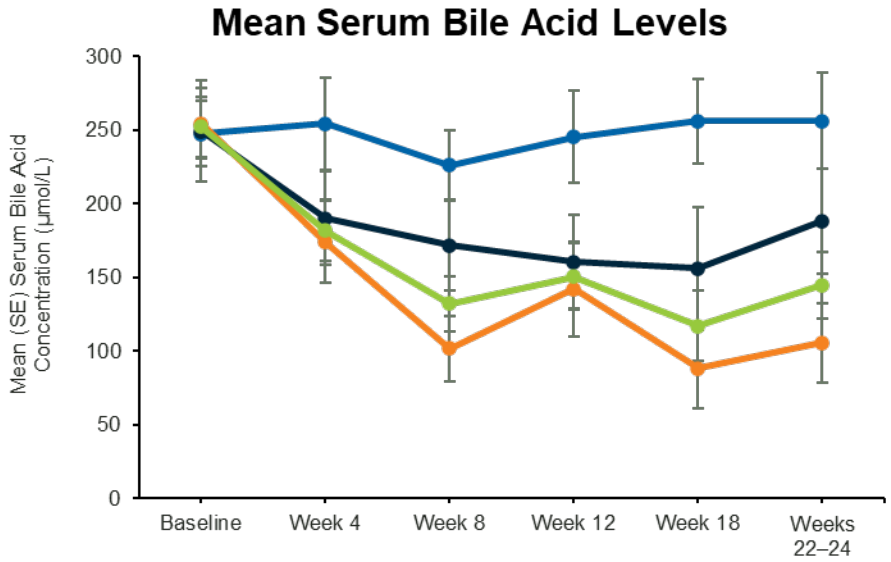
Main Findings

- Odevixibat, at both doses, led to significant reductions in pruritus and serum bile acids compared with placebo.
- Rapid onset of effects, sustained through week 24
- Well tolerated over 24 weeks, most TEAEs being mild to moderate in severity

Conclusions

- Both primary endpoints were met in this first, large, placebo-controlled phase 3 trial in PFIC.
- Odevixibat has potential to provide significant treatment benefits in a disease with high unmet medical need.





Thompson RJ, et al., Abstract LO4

Association of serum biomarkers with liver stiffness assessed by transient elastography in 330 children with cholestatic liver disease

Hypothesis

Serum biomarkers from a targeted panel will be associated with LSM in children with biliary atresia (BA), Alagille syndrome (ALGS), and alpha-1 antitrypsin deficiency (A1AT).

Methods

Spearman correlation coefficients and multiple linear regression (adjustment covariates: age, TB, albumin, GGT, AST) examined associations between LSM (Fibroscan™) and 9 biomarkers (ELISA) and clinical parameters.

Main Findings

After multi-variable adjustment, IL-8 and MMP-7 remained significantly associated with LSM in BA and CTGF with LSM in A1AT.

Conclusions

Significant biomarker correlation with LSM and clinical variables exist in BA and A1AT and may depend on disease.

Leung DH, et al., Abstract 62

Multiple Linear Regression Models

	LOX	MMP-3	Endoglin	TIMP-1	Mac2	Periostin	IL-8	CTGF	MMP-7
BA LSM			1.6%* p=0.02			1.1%* p=0.05	1.9%* p<0.001		7.6%** p<0.001
A1AT LSM								-2.3%* p=0.004	5.0%** p=0.10
ALGS LSM			1.7%* p=0.06				1.2%* p=0.09		

* The given estimate represents the relative change in LSM for a 10% increase in the biomarker concentration.
** The given estimate represents the relative change in LSM for a 1 unit increase in the biomarker concentration.

BA: Spearman Correlations Between Biomarkers and Labs

	LOX	MMP-3	Endoglin	TIMP-1	Mac-2	Periostin	IL-8	CTGF	MMP-7
Bilirubin		0.30**				0.21*	0.28**	-0.21*	
GGTP				0.41**			0.40**		0.38**
AST			0.28**	0.42**			0.53**		0.44**
ALT				0.36**			0.42**		0.32**
Albumin				-0.25*			-0.29**		-0.28**
INR						0.28**			
Platelets			-0.19*	0.32**					

* $p<0.01$
** $p<0.001$

3-Dimensional architecture of multilineage biliary organoids from children with biliary atresia exhibit structural deficits in epithelium and peribiliary glands

Aims

- To build a multi-lineage biliary organoid (MOB)
- To investigate the development of the biliary epithelium and peribiliary glands (PBGs) in biliary atresia (BA)

Methods

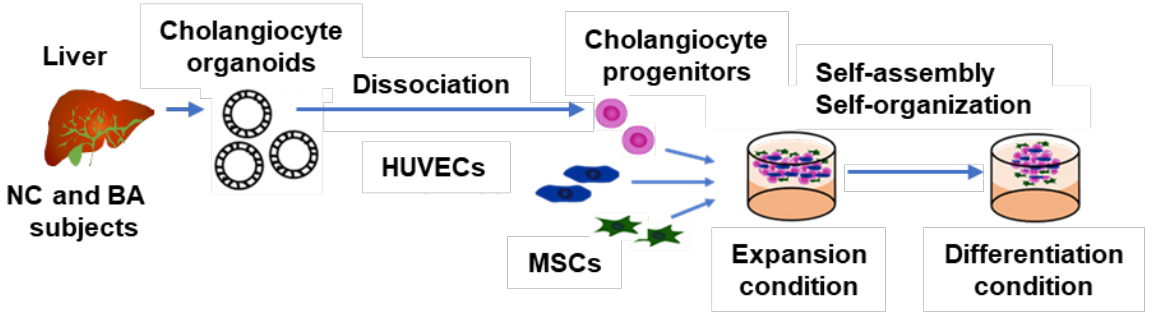
Cholangiocyte organoids from biopsies of normal control (NC; N=3) and BA (N=3) subjects were dissociated and re-cultured in combination with human endothelial and mesenchymal cells (HUVECs and MSCs) to generate MBOs.

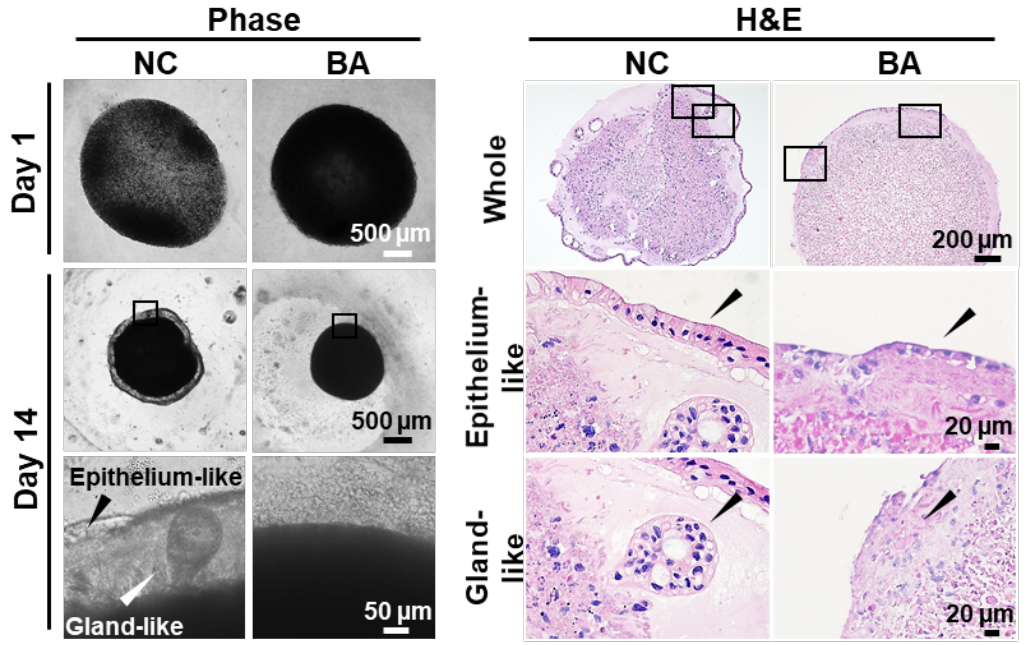
Main Findings

- Co-cultured cells self-assemble into 3-dimentional MBOs . They form epithelium- and PBG-like biliary structures in NC.
- MBOs from BA have epithelial fragments (NC: 49,301 ± 60,383 μm^2 vs BA: 10,746 ± 19,214 μm^2; $P<0.05$).
- MBOs from BA have small PBG-like structures (NC: 1372 ± 438 μm^2 vs BA: 932 ± 216 μm^2; $P<0.05$).

Conclusions

The MBO recapitulates structural features of bile duct formation and identifies defects in the epithelial lining and PBGs linked to pathogenesis of BA.





Ayabe H, et al., Abstract 172

Prognostic value of serum bile acids after achieving bile flow with the Kasai portoenterostomy in biliary atresia

Hypothesis

In infants achieving normal bilirubin levels, serum bile acids measured 6 months after KP (6mSBAs) may predict outcomes.

Methods

Retrospective study measuring serum bile acids from stored samples (n=139) and comparing levels to long term outcomes

Main Findings

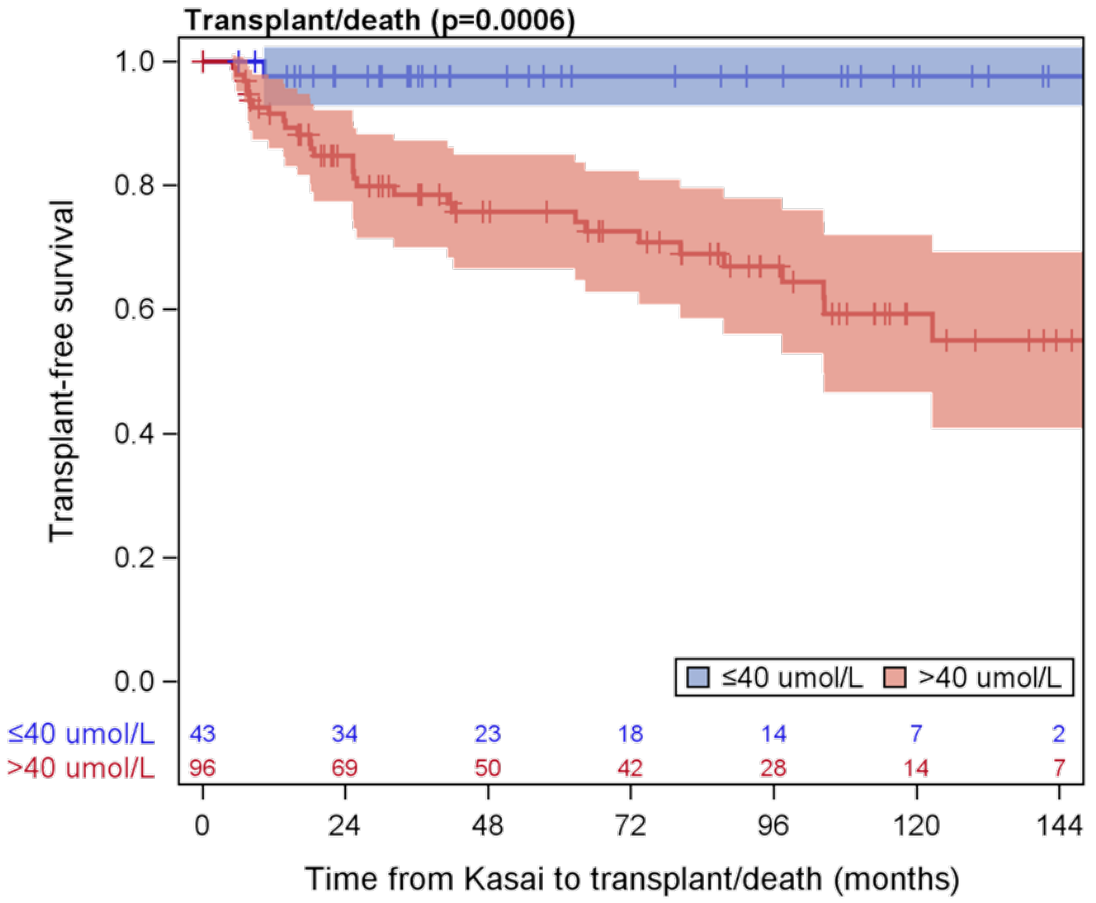
In patients achieving normal bilirubin levels, 6mSBAs:

- Vary widely and are frequently markedly abnormal
- Predict 2-year outcomes and the development of sentinel events
- Driven by differences in conjugated (rather than unconjugated) bile acids.

Conclusions

In patients achieving normal bilirubin levels, serum bile acid measured 6 months after KP can predict long-term outcomes.

Harpavat S, et al., Abstract 339



Novel serum biomarkers of portal hypertension in children with biliary atresia

Aim

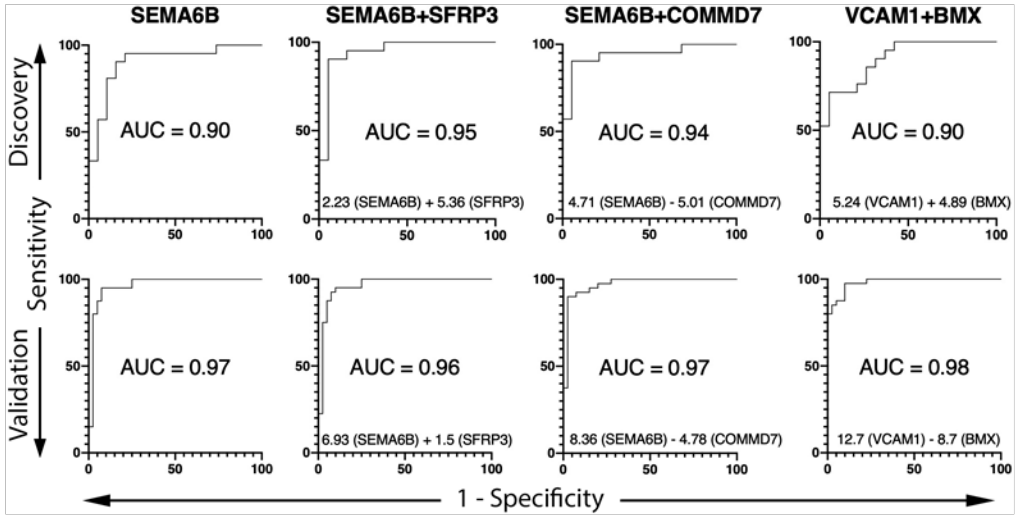
Identify serum biomarkers of portal hypertension (PHT) in patients with biliary atresia using large-scale proteomics

Methods

- Serum samples obtained from the Childhood Liver Disease Research Network. Cohorts: 1) Definite PHT and 2) No PHT
- SOMAScan® proteomics assay and multivariate logistic regression analysis performed to identify biomarkers that distinguished those with PHT with an AUC ≥0.90 in *discovery* (N= 40) and *validation* (N=80) cohorts.

Main Findings

Large-scale proteomics in discovery and validation cohorts uncovered SEMA6B, sFRP3, COMMD7, VCAM1, and BMX as potential biomarkers of PHT individually or in combination.



	Discovery Cohort			Validation Cohort		
Prediction models	AUC (95% CI)	Sens (%)	Spec (%)	AUC (95% CI)	Sens (%)	Spec (%)
SFRP3	0.93 (0.85 to 1.00)	90	84	0.73 (0.62 to 0.84)	70	65
SEMA6B	**0.90 (0.80 to 1.00)**	**90**	**84**	**0.96 (0.92 to 1.00)**	**95**	**93**
β2-microglobulin + IGFBP2	0.93 (0.86 to 1.00)	86	84	0.88 (0.80 to 0.96)	85	80
SEMA6B + SFRP3	**0.95 (0.87 to 1.00)**	**90**	**95**	**0.96 (0.92 to 1.00)**	**93**	**93**
SFRP3 + COMMD7	0.97 (0.93 to 1.00)	90	95	0.72 (0.61 to 0.84)	70	75
SEMA6B + COMMD7	**0.94 (0.87 to 1.00)**	**90**	**95**	**0.97 (0.94 to 1.00)**	**93**	**95**
REG4 + NK-p44	0.97 (0.93 to 1.00)	100	89	0.87 (0.78 to 0.96)	88	85
VCAM1 + BMX	**0.90 (0.81 to 0.99)**	**71**	**95**	**0.98 (0.96 to 1.00)**	**95**	**93**
VCAM1 + Galectin4 + Angiotensinogen	0.86 (0.75 to 0.98)	86	79	0.99 (0.99 to 1.00)	98	95

Osborn JB, et al., Abstract 338

Center-level variation in long-term outcomes for children undergoing liver transplantation—Does a child's home neighborhood matter?

Aim

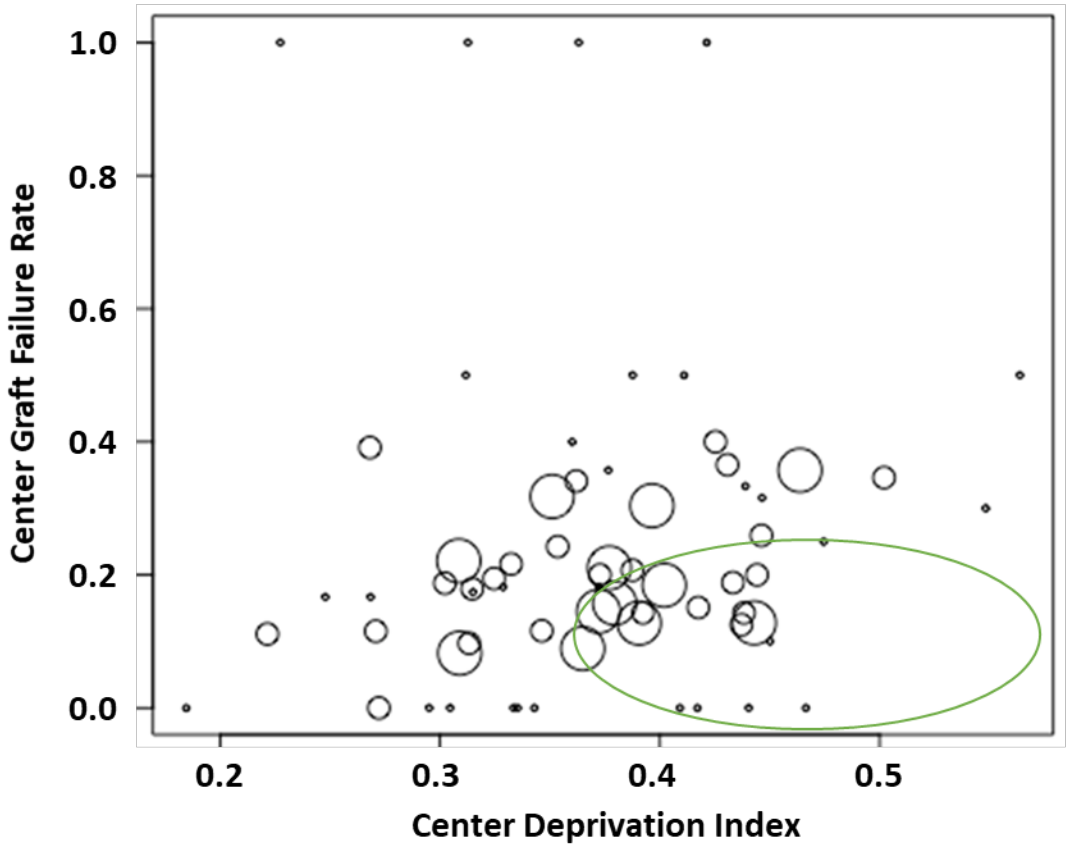
Neighborhood socioeconomic deprivation is associated with graft failure and death following liver transplantation in children. We evaluated whether the effect of deprivation on transplant outcomes varies by center.

Methods

Using SRTR data, we matched children to a neighborhood socioeconomic deprivation index and aggregated this index by transplant center to evaluate center-level patient-mix deprivation on outcomes.

Conclusions

Center-specific practices can mitigate the effects of neighborhood socioeconomic deprivation; future work should characterize these practices.



Wadhwani S, et al., Abstract 151

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