alpha diversity. Most genera separating PSC and HC were similar in PSC and UC. However, PSC patients exhibited a significantly increased abundance (2.8 fold) of the *Veillonella* genus compared to both HC and UC ($p < 0.02$).
Conclusions: The fecal microbial profile in PSC patients was different from HC and UC patients without PSC, while the profiles in PSC patients with and without IBD were similar. Compared with HC and UC, PSC patients exhibited a marked increase in abundance of the *Veillonella* genus, which has also been linked to other conditions of fibrosis.

O083
ABSENCE OF BSEP/ABCB11 PROTECTS FROM CHOLESTATIC LIVER AND BILE DUCT INJURY IN A MOUSE MODEL OF SCLEROSING CHOLANGITIS

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Background and Aims: Cholestasis, characterized by intrahepatic accumulation of potentially cytotoxic bile acids (BAs) leads to liver injury reflected by disruption of hepatocellular integrity, inflammation and fibrosis. Bile salt export pump (BSEP/ABCB11) is the main canalicular BA transporter and therefore rate limiting step for hepatobiliary BA secretion. Here we investigate the role of ABCB11 in development of cholestatic liver and bile duct injury in a model of sclerosing cholangitis.
Methods: Wildtype (WT) and ABCB11 knockout (KO) mice were subjected to common bile duct ligation (CBDL) (7 days) and DDC feeding (4 weeks) as models for acute and chronic cholestasis (sclerosing cholangitis), respectively. RNA profiling was performed by RT-PCR. BA transporter expression was assessed at protein level. Serum biochemistry, hepatic hydroxyproline (HP) levels, BA composition as well as liver histology were assessed.
Results: In contrast to WT, ABCB11 KO mice where protected from cholestatic liver injury after CBDL or DDC feeding, reflected by unchanged serum levels of ALT, AST, AP, total cholesterol and BA. ABCB11 KO mice where protected from inflammation (reflected by unchanged mRNA levels of F4/80 and MCP1) and fibrosis (reflected by unchanged mRNA levels of Col1a1, Col1a2 and aSMA protein levels) while WT mice display significant up-regulation of both inflammatory (F4/80 4-fold and Mcp1 60-fold) and fibrotic (Col1a1 2-fold, Col1a2 2.5-fold, HP levels 2-fold) markers. Polyhydroxylated BAs (PHBA) were increased 4-fold in ABCB11 KO CBDL mice compared to WT CBDL mice ($p < 0.01$). mRNA expression of Cyp2b10, downstream target of CAR, a nuclear receptor regulating BA detoxification, was increased (10-fold) in ABCB11 KO mice under cholestatic conditions. Protein levels of BA transporter such as NTCP, OATP (sinusoidal uptake) and MRP2 (canalicular export) were reduced in WT and increased in ABCB11 KO mice under cholestatic conditions. MRP3 and MRP4 (sinusoidal export) protein levels were increased in WT CBDL mice and not changed in ABCB11 KO mice. Notably, the phosphorylated form of STAT3 – essential for the differentiation of pro-inflammatory TH17 cells – was exclusively found in WT BDL mice.
Conclusions: Changes in BA metabolism favouring detoxification and efflux of potentially toxic BAs protects ABCB11 KO mice from development of acute and chronic cholestatic liver injury. Therefore PHBAs may open a new therapeutic avenue against cholestasis and subsequent progression toward fibrosis in cholangiopathies such as PBC and PSC.

O084
NOVEL TREATMENT OPTIONS TO IMPROVE ABERRANT PRE-MESSENGER RNA SPLICING AND PROTEIN FOLDING IN ATP8B1 DEFICIENCY

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Background and Aims: ATP8B1 deficiency is a severe autosomal recessive liver disease due to mutations in the *ATP8B1* gene and characterized by intrahepatic cholestasis. Many *ATP8B1* mutations are predicted to affect pre-messenger RNA splicing. The most common missense mutation (p.I661T) leads to protein misfolding and disturbed protein homeostasis (proteostasis). Current therapeutic options are insufficient. The aim of our study was to elucidate the molecular consequences of *ATP8B1* mutations at exon-intron boundaries and the development of mutation-specific therapies for ATP8B1 deficiency.
Methods: Fourteen *ATP8B1* mutations at exon-intron boundaries, associated with ATP8B1 deficiency, were analysed for their effect on pre-messenger RNA splicing using an *in vitro* minigene system. Modified versions of U1 small nuclear RNA (snRNA) matching donor splice sites were expressed and subsequent splice rescue was evaluated by reverse transcription PCR. The potential of 13 proteostasis regulators to restore ATP8B1 p.I661T plasma membrane expression was evaluated by cell surface biotinylation.
Results: Eleven mutations resulted in aberrant splicing and a complete absence of correctly spliced product. Three mutations led to partially incorrect splicing. Expression of modified U1 snRNA complementary to the mutated splice donor sites strongly improved or completely rescued splicing for several *ATP8B1* mutations located at donor, as well as acceptor, splice sites. Furthermore, six proteostasis regulators caused a significant upregulation of ATP8B1 p.I661T plasma membrane expression.
Conclusions: The majority of *ATP8B1* mutations at exon-intron boundaries resulted in total exon skipping and compensatory modified U1 snRNAs were able to improve exon definition very efficiently. In addition, proteostasis regulators were able to improve ATP8B1 p.I661T plasma membrane expression. Modified U1 snRNAs as well as proteostasis regulators could be a novel therapeutic strategy in ATP8B1 deficiency and other genetic diseases.

O085
LANREOTIDE REDUCES LIVER VOLUME YET ACCELERATES MUSCLE WASTING AND WEIGHT LOSS IN SYMPTOMATIC POLYCYSTIC LIVER DISEASE

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Background and Aims: Polycystic liver disease (PCLD) can induce malnutrition due to extensive hepatomegaly, forming an indication for liver transplantation (LTx). The somatostatin analogue (SA) lanreotide 120 mg (LAN) given for 6 months reduces liver volume (LV). We aimed to investigate the efficacy and long-term safety of LAN.