Update on Primary Sclerosing Cholangitis

TORONTO CENTRE FOR LIVER DISEASE

Gideon Hirschfield

Medicine
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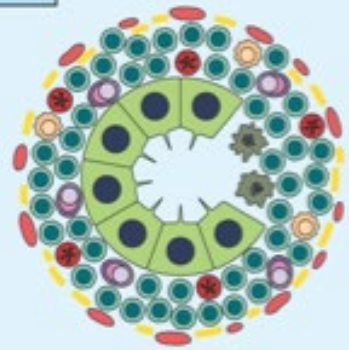
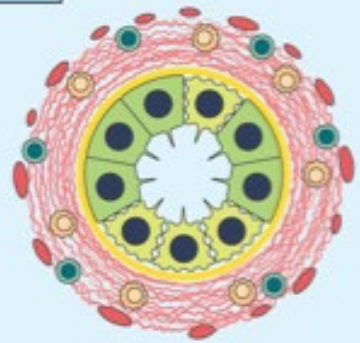
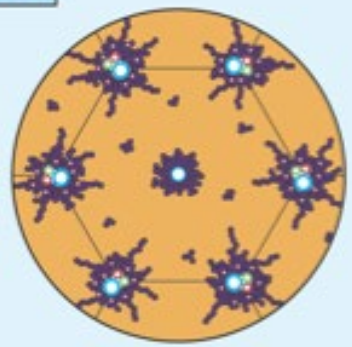
Initiation	Pre-Clinical	Early Clinical	Advanced Clinical
PBC 	**Histopathology:** • Lymphoplasmacytic Portal Infiltrates • Lymphocytic Cholangitis ± Florid Duct Lesions • Displaced BM and PCP • ± Granulomas **Autoantibodies:** • AMA, ANA (Non-specific or Specific gp210, sp100), SMA	**Laboratory Tests:** • Elevated ALP and ggt • Variable elevation ALT, AST • Elevated IgM **Signs or Symptoms:** • Asymptomatic or Fatigue • Cholestatic Pruritus • Other AI Diseases **SOC Therapy:** • UDCA • FXR and PPARα/δ Agonists	**Intolerance or Inadequate Response to UDCA:** • Progressive Ductopenia ↓ • Progressive Ductular Reaction ↓ • Biliary Fibrosis ↓ • Biliary Cirrhosis
PSC 	**Histopathology:** • Focal Fibrous Obliterative Cholangitis • Peribiliary Fibrosis • Lymphocyte-Macrophage Portal Infiltrates • Displaced PCP **Autoantibodies:** • pANCA (pANNA), ANA	**Laboratory Tests:** • Elevated ALP and ggt • ± Elevation ALT, AST **Signs or Symptoms:** • Asymptomatic or Fatigue • Associated IBD • Cholestatic Pruritus • Other AI Diseases **Cancer Risks:** CCA, CRC, GB **SOC Therapy:** None	• Progressive Biliary Strictures ↓ • Fibro-Obliterative Ductopenia ↓ • Progressive Biliary Obstruction ↓ • Progressive Ductular Reaction ↓ • Biliary Fibrosis ↓ • Biliary Cirrhosis
AIH 	**Histopathology:** • Lymphoplasmacytic Portal Infiltrates • Interface Hepatitis • ± Central Perivenulitis **Autoantibodies:** • ANA, SMA, LKM1, SLA	**Laboratory Tests:** • Elevated ALT, AST • Elevated IgG **Signs or Symptoms:** • Asymptomatic or Fatigue • Other AI Diseases **SOC Therapy:** • 1st Line Steroids + Thiopurine • 2nd Line CNI or MMF	**Intolerance or Inadequate Response to 1st or 2nd Line Immunosuppression:** • Progressive portal fibrosis ↓ • Bridging fibrosis ↓ • Post-necrotic cirrhosis

Trivedi, Hirschfield, Adams, Vierling Gastroenterology 2024 In Press

C COVERT

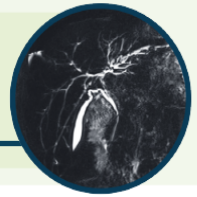
PSC affects both sexes and occurs at all ages; however, the majority of patients are male and the median age at onset is 30–40 years. Up to 80% of cases are associated with IBD. Approximately 50% of patients with PSC are asymptomatic at diagnosis.

PSC SYMPTOMS

When symptomatic, PSC is insidious. Patients most often complain of abdominal pain, pruritus, and fatigue.

PSC DIAGNOSIS

Diagnosis is usually based on: ❶ Serum ALP elevation, ❷ multi-focal biliary strictures with intervening dilatations on cholangiography (usually MRCP), ❸ exclusion of secondary sclerosing cholangitis, and ❹ liver biopsy when small-duct PSC or PSC-AIH is suspected.



Typical MRCP in PSC

HOLISTIC APPROACH

PSC care must integrate disease monitoring, treatment and research with psychosocial support that addresses the fear, uncertainty, and social isolation many patients experience. PSC support societies are an excellent resource.

C CHOLANGITIS

Genetic and environmental factors interact to establish the pathogenesis of PSC, which involves the gut microbiota, impaired bile acid composition and cholestatis, and autoimmunity.

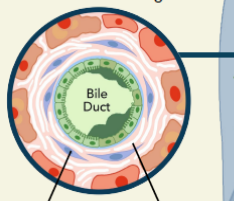
GENETICS
> 20 HLA and non-HLA loci have been linked to PSC, establishing it as an autoimmune disease.

MICROBIOTA
Altered gut and biliary microbiota may drive the immune response in PSC.

IMMUNE RESPONSE
The predominant cells identified in the vicinity of bile ducts are T cells, macrophages and neutrophils.

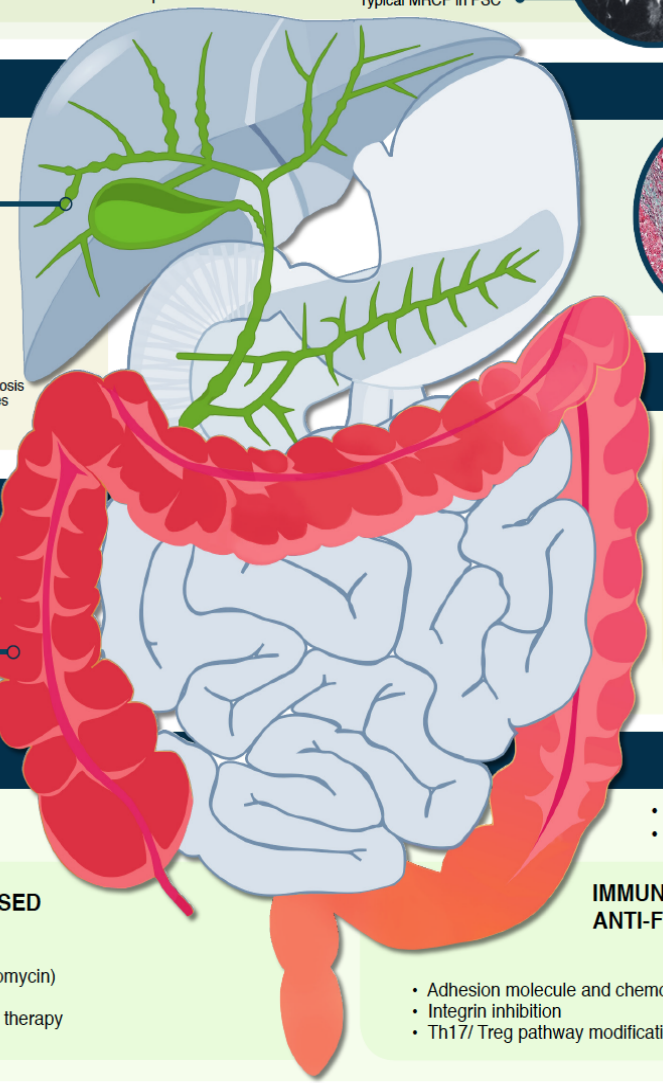
ENVIRONMENT
Multiple environmental exposures have been associated with PSC.

BILE ACIDS
Bile acid homeostasis is impaired and biliary epithelium is activated.

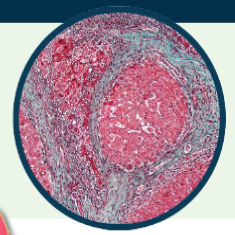


Activated fibroblasts and stellate cells (not shown) → Collagen deposition, fibrosis and strictures

"Onion-skinning" fibrosis



CIRRHOSIS C



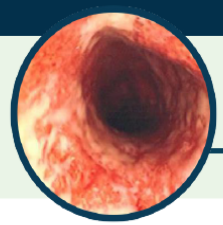
The end-point of PSC is cirrhosis.

The extent of inflammation and fibrosis observed does not necessarily correlate with the risk of biliary dysplasia or malignancy.

C COLITIS

PSC-IBD is phenotypically distinct from IBD without PSC.

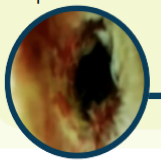
- Majority of IBD in PSC patients is UC and presents earlier than in those without PSC
- Frequently presents with pancolitis, predominantly right-sided, with "back-wash ileitis" and rectal sparing



CANCER C

CANCER RISK

PSC patients are at increased risk of **colorectal** and **hepatopancreatobiliary cancers**, including cholangiocarcinoma, hepatocellular carcinoma, pancreatic cancer, and gallbladder cancer.



Cholangiocarcinoma

PSC SURVEILLANCE

- Colonoscopy with screening biopsies at diagnosis and every 1-2 years
- Annual US
- Annual MRI/MRCP

Non-cancer screening:

- If cirrhosis: US and AFP every 6 months, screening for complications per guidelines
- Screening for osteoporosis and malnutrition

C CURE

Liver transplantation is indicated per regional guidelines, including for decompensated cirrhosis, intractable pruritus, recurrent bacterial cholangitis, and HCC.

- 5-year survival post-transplantation exceeds 80%
- PSC recurrs at a rate of approximately 20% post-transplantion

BILE ACID-BASED THERAPY

- UDCA and experimental analogues
- *Nor*UDCA
- FXR and FGF19 analogues
- PPAR agonists
- ASBT inhibitors

MICROBIOTA-BASED THERAPY

- Antibiotics (e.g. vancomycin)
- Fecal transplantation
- Bacteriophage-based therapy

IMMUNE-MODULATING & ANTI-FIBROTIC THERAPY

- Adhesion molecule and chemokine inhibition
- Integrin inhibition
- Th17/ Treg pathway modification

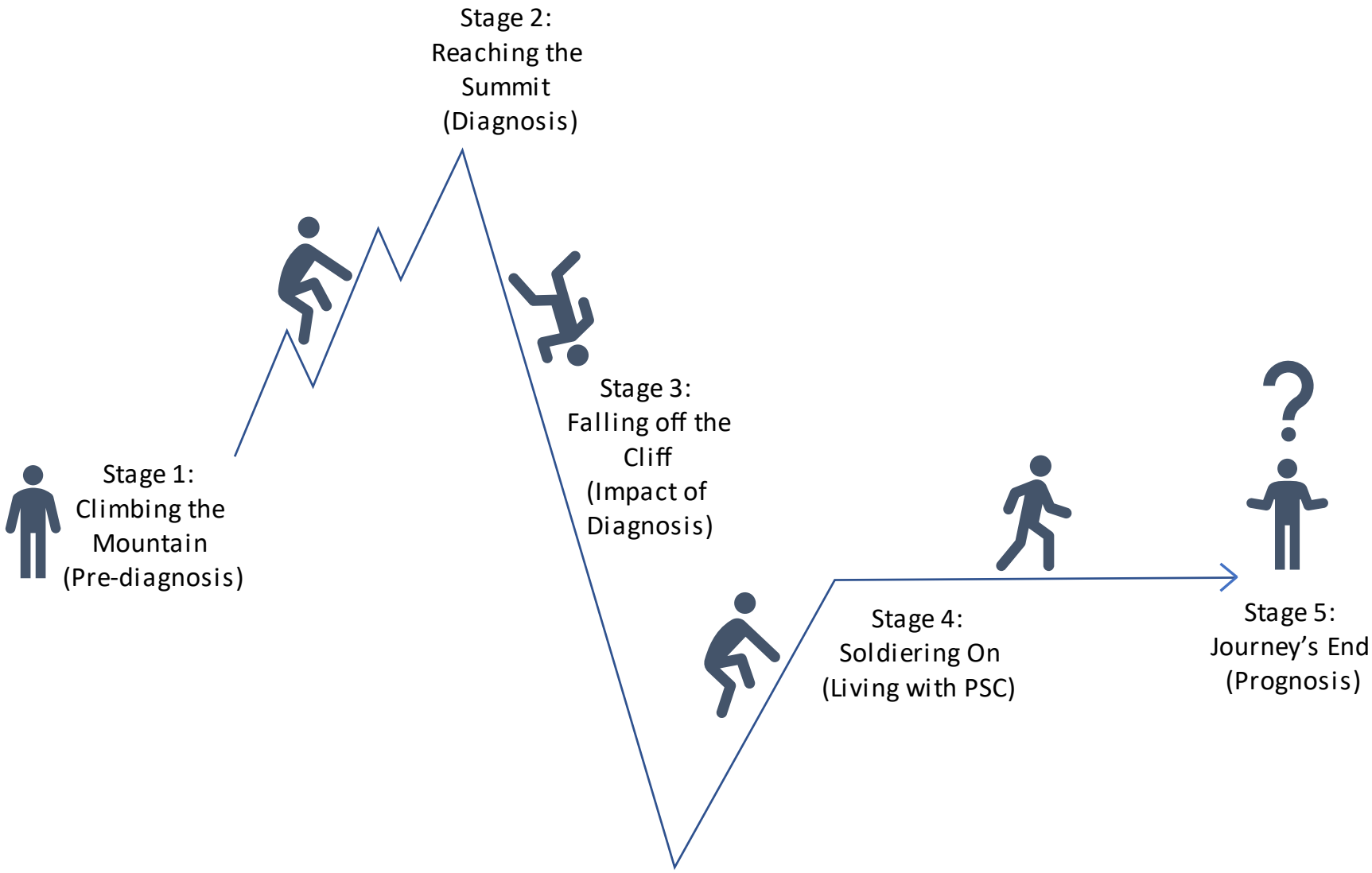
BIOMARKERS

Biomarkers are important for prognostication & evaluating treatment effect.

- ?ALP
- ?ELF
- ?PRO-C3
- Liver biopsy
- Quantitative MRI
- Elastography

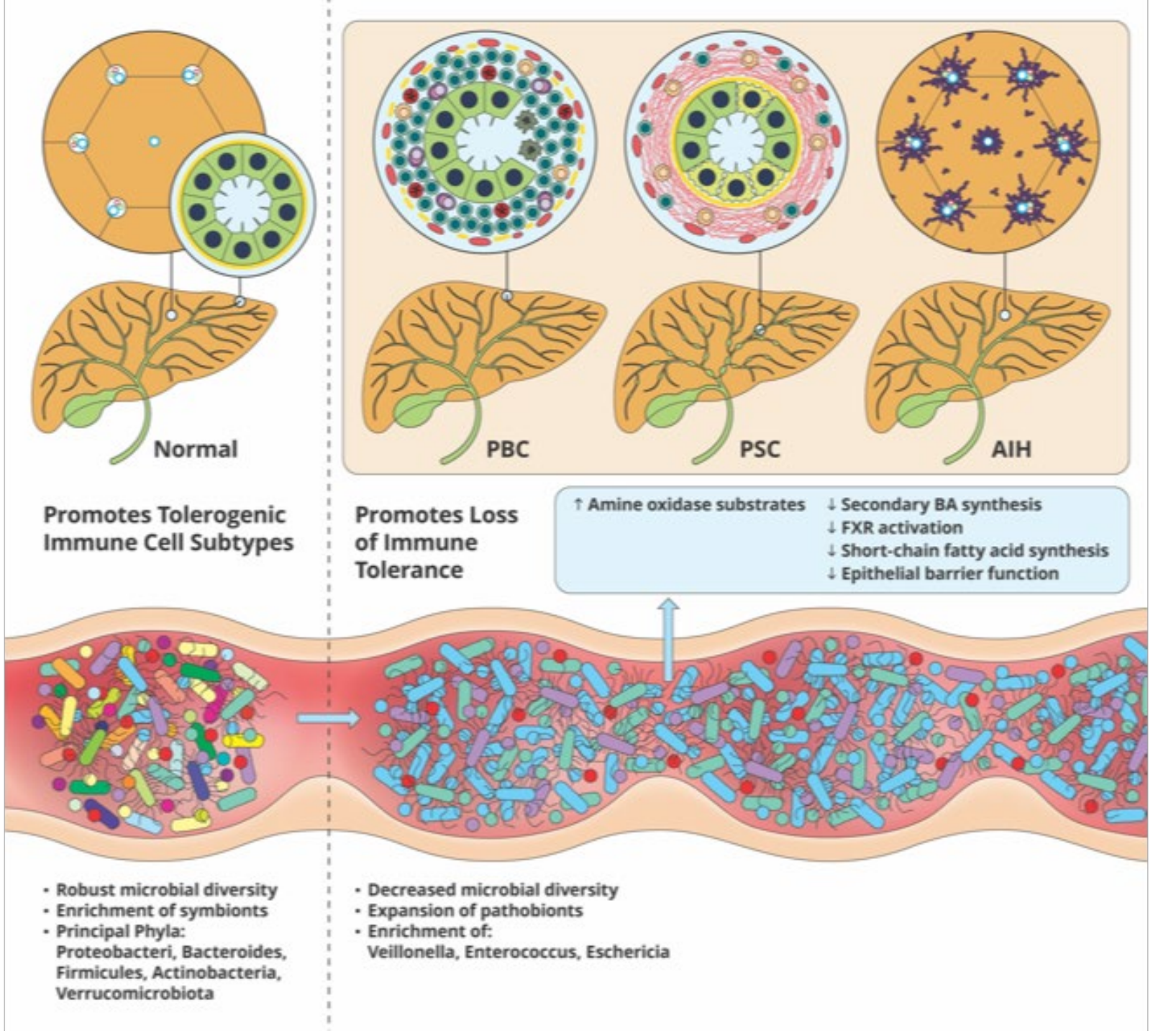
Deeb et al. J Hep 2020

Because our patients want a new journey



And speak for themselves

Symptom	***Quotes***
Abdominal pain	*"I just get like pain in my, my liver…like a knitting needle" (018) "I could barely walk, this pain was so bad" (026)*
Brain fog	*"It's sort of just slowly feels like knowledge is ebbing out…of my brain" (024)*
	"I do get this horrible brain fog and it's very negative…you're drunk but you haven't had any alcohol…I'm not a half full person when I'm in that state. I'm really half empty" (023)
Cholangitis	*"basically feeling terrible…aching everywhere, rigors (026)*
	"They pumped me full of antibiotics and pain relief and God knows what else to try and get the infection under control…I was constantly in and out with infections" (011)
Fatigue	*"it's like a blanket coming over you and I just can't keep my eyes open" (026)*
	"Tired all the time…someone had pulled the plug and energy was just going down the plughole" (023)
	"Felt like I was walking through treacle" (025)
Itch	*"Itching absolutely drove me insane…nothing really got on top of it…its unbearable" (026)*
	"I've ripped my skin to bits , I've got scars all over my body…I go to work and I've got scabs all over my face (016)
Weight loss	*"I'd stopped going on the scales after losing 30 pounds" (027)*
	"I'd lost loads of weight, I think I weighed 38 kilos" (011)
Multiple symptoms	*"jelly legs, wooliness in the head…extreme tiredness…lack of appetite…twinges in the side or back, pain in the top of my right shoulder…nausea" (013)*



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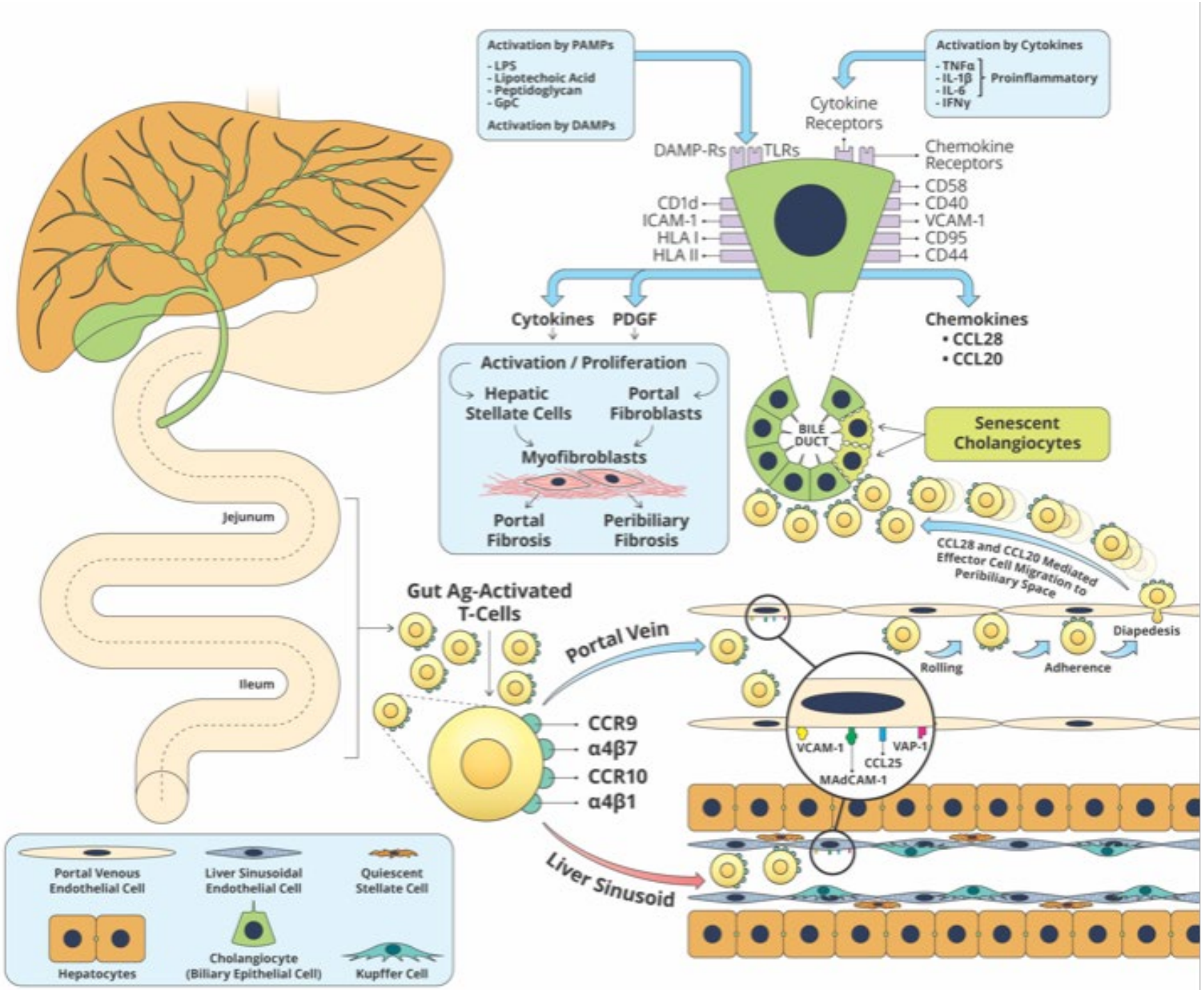

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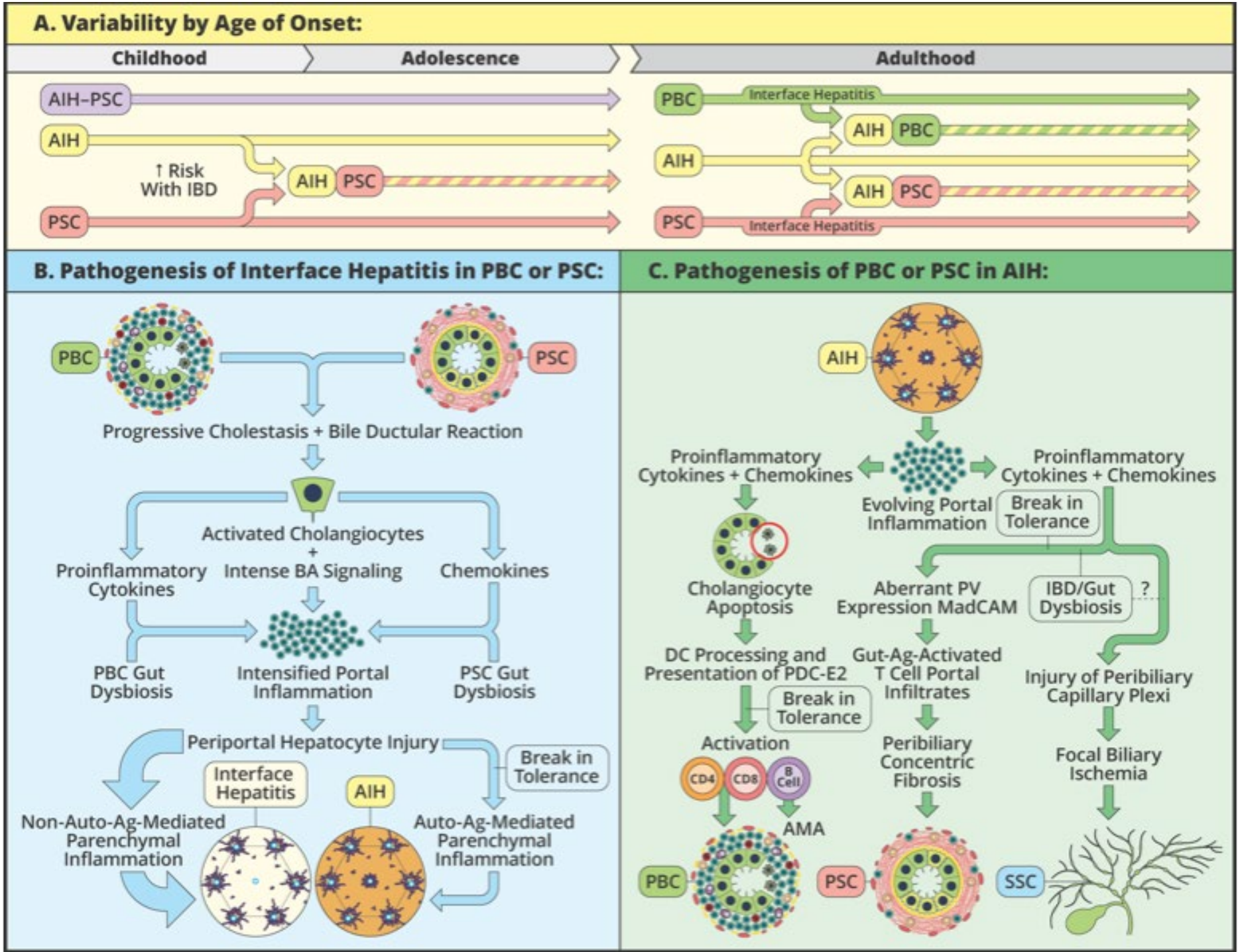

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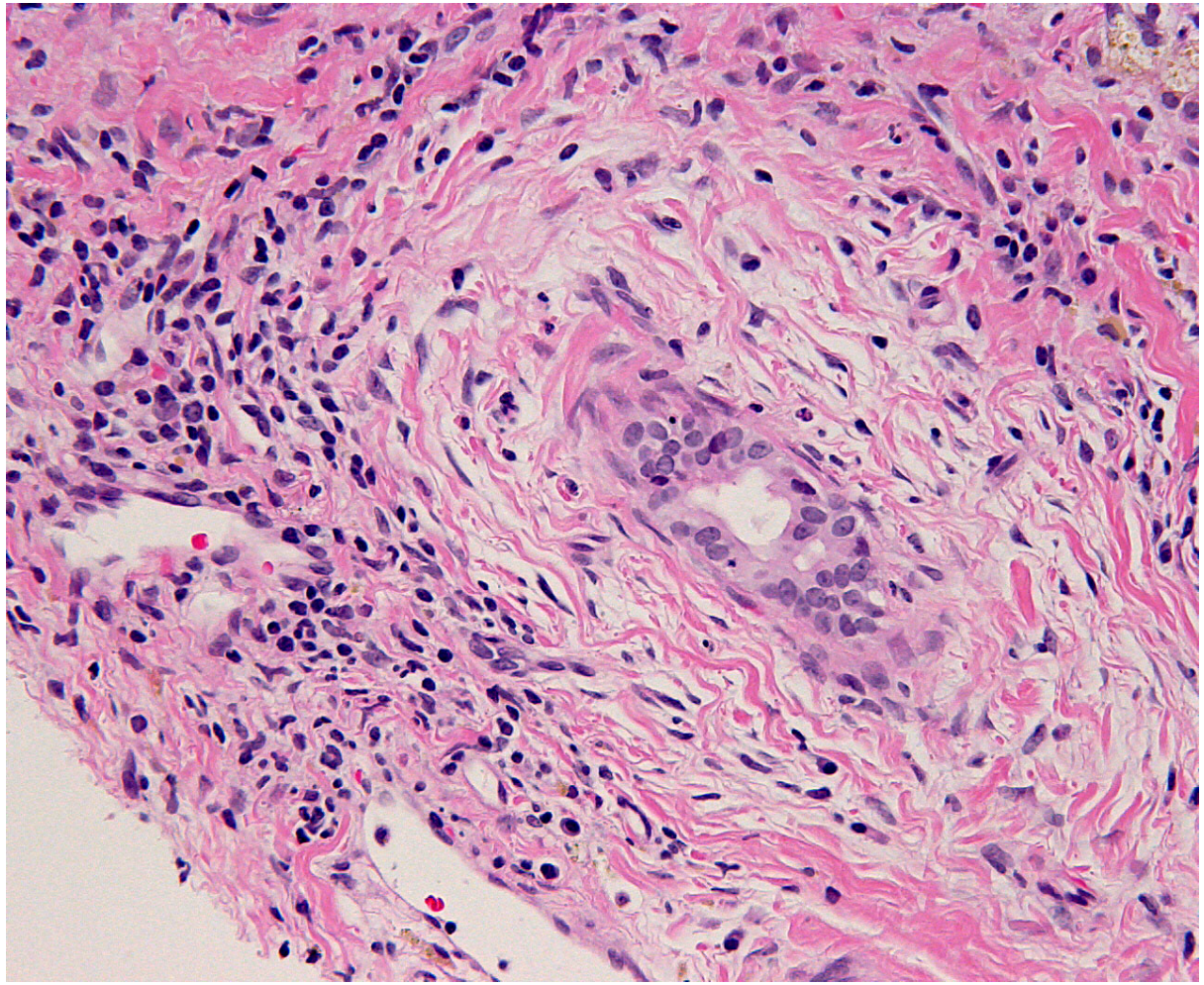
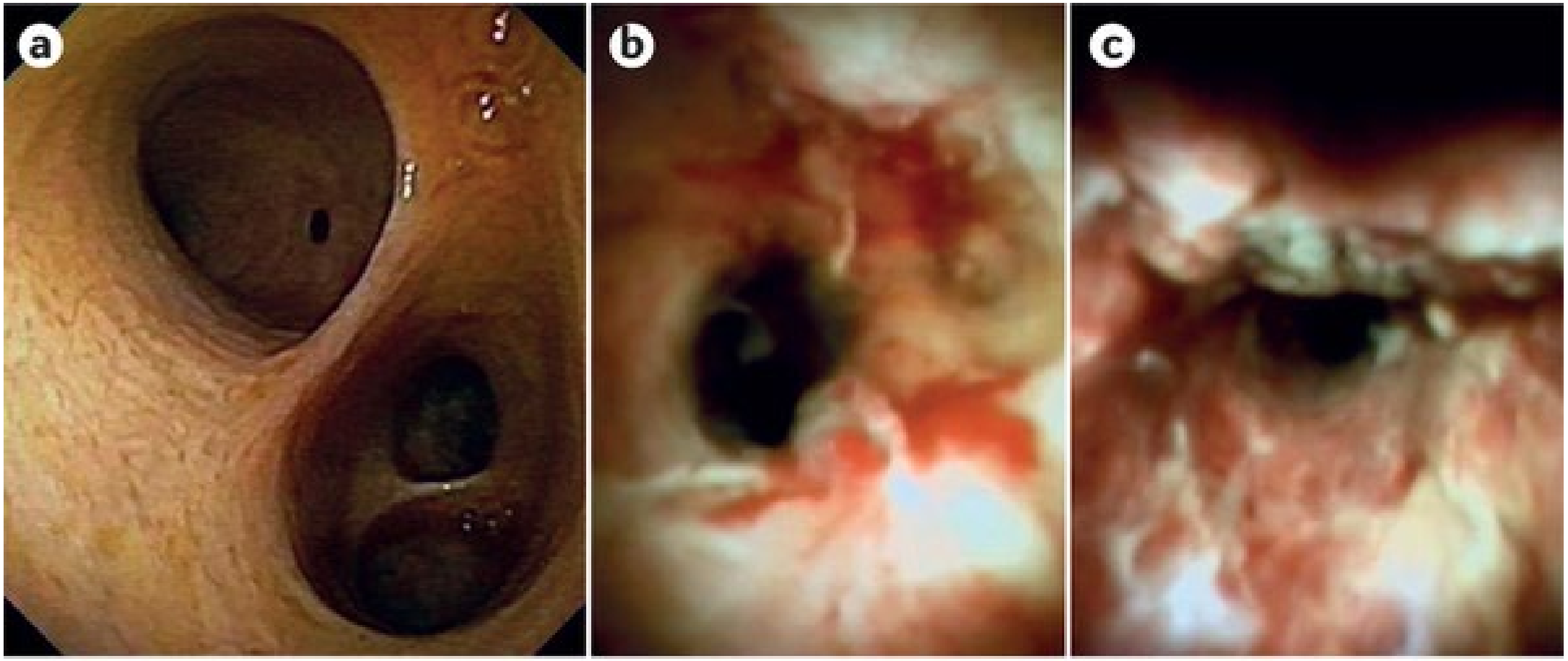


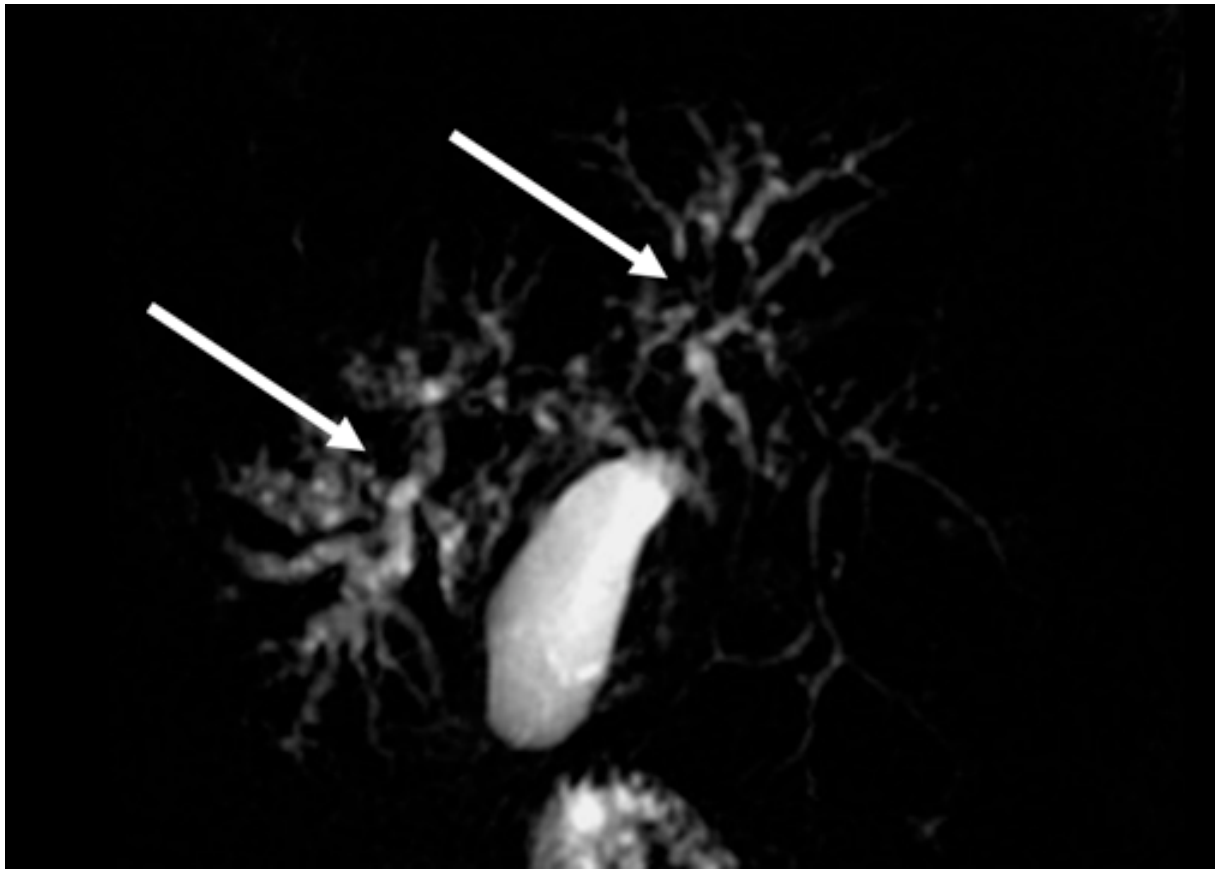
Chronic bile duct disease leading to fibrotic strictures and saccular dilatations of the intra- and extrahepatic bile ducts

Ulcerative C$_{(h)}$ol$_{(ang)}$itis



Nature Reviews Gastroenterology & Hepatology 14, 279–295 (2017)

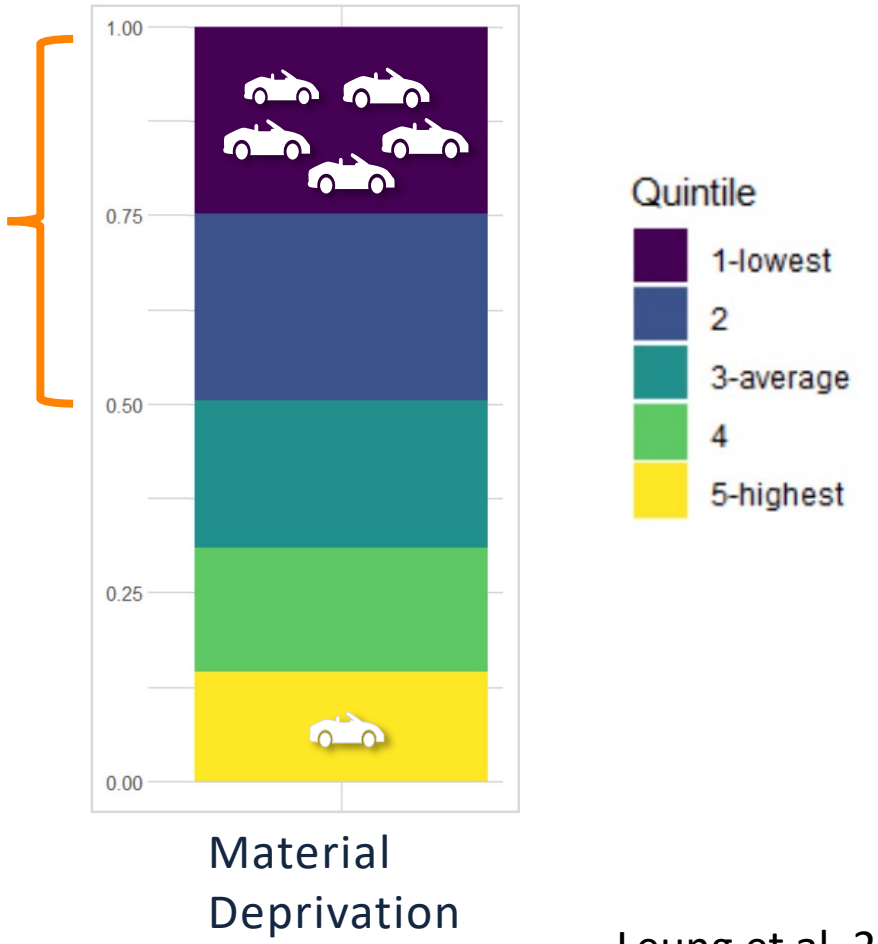
Sclerosing cholangitis



Data from Olmsted County (USA) in the year 2000 identified 20.9 cases of PSC per 100 000 of the population in men and 6.3 per 100 000 in women

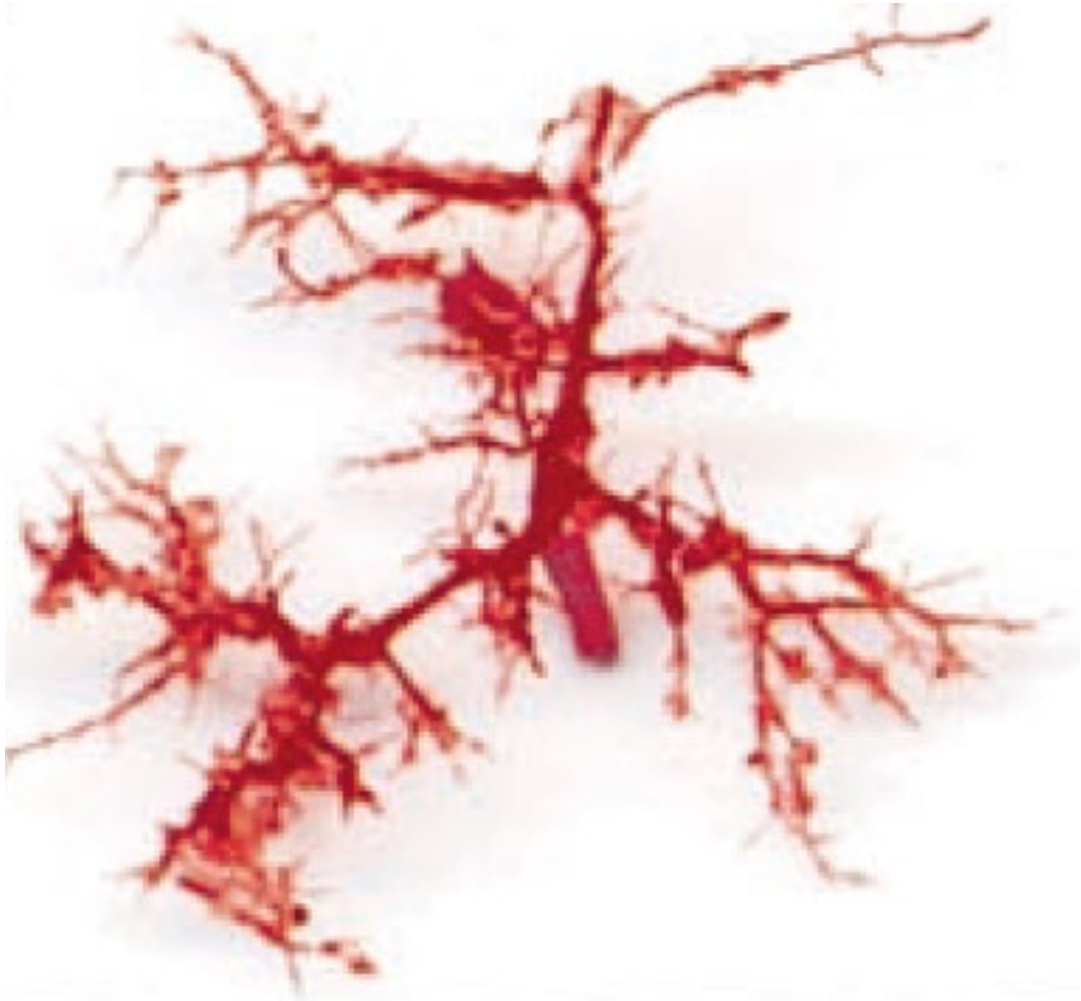
Gradient of wealth in those diagnosed with PSC-IBD favouring higher socioeconomic status

Larger proportions of PSC-IBD patients have higher income, and experience less material deprivation



Leung et al. 2023

Mdr2 deficient *mice develop* cholangiopathy



Gastroenterology 2002;123:1238–1251

Bile duct centric autoimmunity?

Article

Bile acid metabolites control T_H17 and T_{reg} cell differentiation

https://doi.org/10.1038/s41586-019-1785-z
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Saiyu Hang[1,12], Donggi Paik[1,12], Lina Yao[2], Eunha Kim[1], Trinath Jamma[3], Jingping Lu[4], Soyoung Ha[1], Brandon N. Nelson[5], Samantha P. Kelly[5], Lin Wu[6], Ye Zheng[7], Randy S. Longman[8], Fraydoon Rastinejad[4], A. Sloan Devlin[2], Michael R. Krout[5], Michael A. Fischbach[9]*, Dan R. Littman[6,10]* & Jun R. Huh[1,11]*

Bile acids are abundant in the mammalian gut, where they undergo bacteria-mediated transformation to generate a large pool of bioactive molecules. Although bile acids are known to affect host metabolism, cancer progression and innate immunity, it is unknown whether they affect adaptive immune cells such as T helper cells that express IL-17a (T_H17 cells) or regulatory T cells (T_{reg} cells). Here we screen a library of bile acid metabolites and identify two distinct derivatives of lithocholic acid (LCA), 3-oxoLCA and isoalloLCA, as T cell regulators in mice. 3-OxoLCA inhibited the differentiation of T_H17 cells by directly binding to the key transcription factor retinoid-related orphan receptor-γt (RORγt) and isoalloLCA increased the differentiation of T_{reg} cells through the production of mitochondrial reactive oxygen species (mitoROS), which led to increased expression of FOXP3. The isoalloLCA-mediated enhancement of T_{reg} cell differentiation required an intronic *Foxp3* enhancer, the conserved noncoding sequence (CNS) 3; this represents a mode of action distinct from that of previously identified metabolites that increase T_{reg} cell differentiation, which require CNS1. The administration of 3-oxoLCA and isoalloLCA to mice reduced T_H17 cell differentiation and increased T_{reg} cell differentiation, respectively, in the intestinal lamina propria. Our data suggest mechanisms through which bile acid metabolites control host immune responses, by directly modulating the balance of T_H17 and T_{reg} cells.

Article

Human gut bacteria produce T_H17-modulating bile acid metabolites

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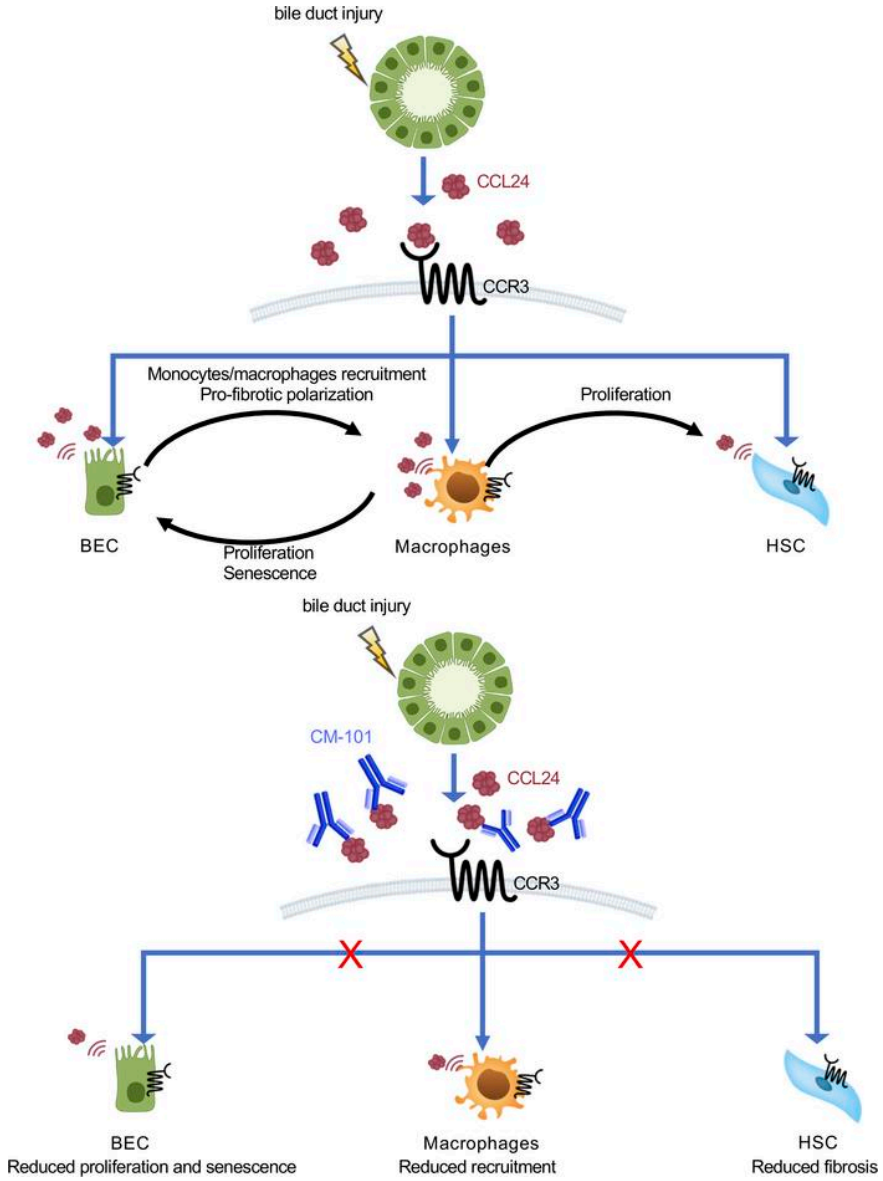
Donggi Paik[1,15], Lina Yao[2,15], Yancong Zhang[3,4], Sena Bae[4,5], Gabriel D. D'Agostino[2], Minghao Zhang[6], Eunha Kim[1], Eric A. Franzosa[4,5], Julian Avila-Pacheco[3], Jordan E. Bisanz[7], Christopher K. Rakowski[8], Hera Vlamakis[3,9], Ramnik J. Xavier[3,9,10,11], Peter J. Turnbaugh[7,12], Randy S. Longman[13], Michael R. Krout[8], Clary B. Clish[3], Fraydoon Rastinejad[6], Curtis Huttenhower[3,4,5], Jun R. Huh[1,14,15]* & A. Sloan Devlin[2,12]*

The microbiota modulates gut immune homeostasis. Bacteria influence the development and function of host immune cells, including T helper cells expressing interleukin-17A (T_H17 cells). We previously reported that the bile acid metabolite 3-oxolithocholic acid (3-oxoLCA) inhibits T_H17 cell differentiation[1]. Although it was suggested that gut-residing bacteria produce 3-oxoLCA, the identity of such bacteria was unknown, and it was unclear whether 3-oxoLCA and other immunomodulatory bile acids are associated with inflammatory pathologies in humans. Here we identify human gut bacteria and corresponding enzymes that convert the secondary bile acid lithocholic acid into 3-oxoLCA as well as the abundant gut metabolite isolithocholic acid (isoLCA). Similar to 3-oxoLCA, isoLCA suppressed T_H17 cell differentiation by inhibiting retinoic acid receptor-related orphan nuclear receptor-γt, a key T_H17-cell-promoting transcription factor. The levels of both 3-oxoLCA and isoLCA and the 3α-hydroxysteroid dehydrogenase genes that are required for their biosynthesis were significantly reduced in patients with inflammatory bowel disease. Moreover, the levels of these bile acids were inversely correlated with the expression of T_H17-cell-associated genes. Overall, our data suggest that bacterially produced bile acids inhibit T_H17 cell function, an activity that may be relevant to the pathophysiology of inflammatory disorders such as inflammatory bowel disease.

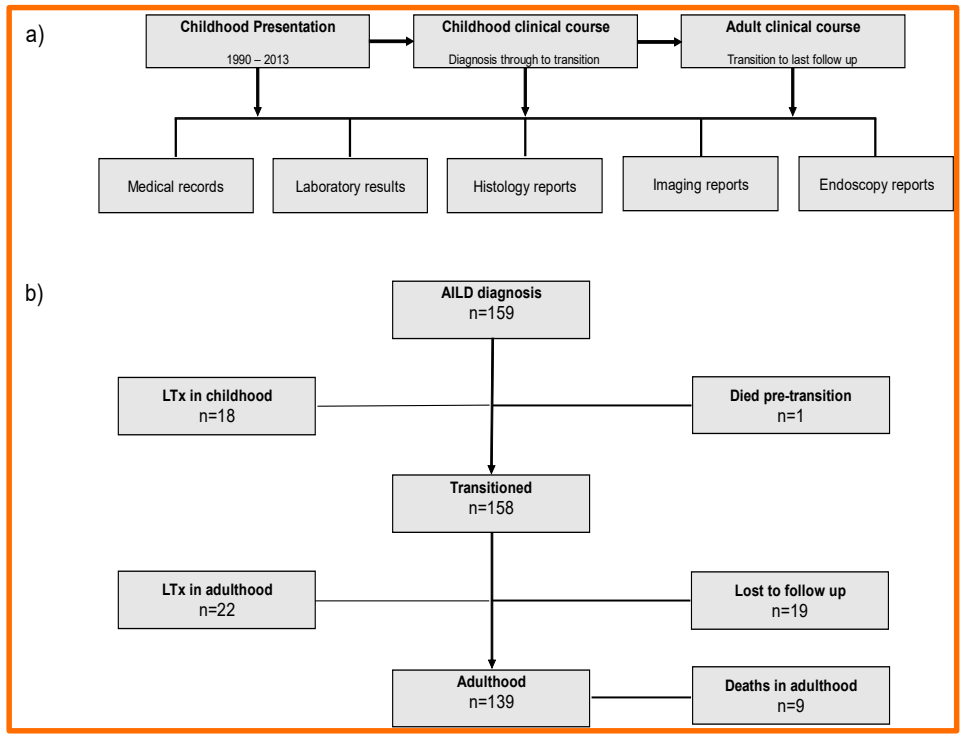
CCL24 regulates biliary inflammation and fibrosis in primary sclerosing cholangitis

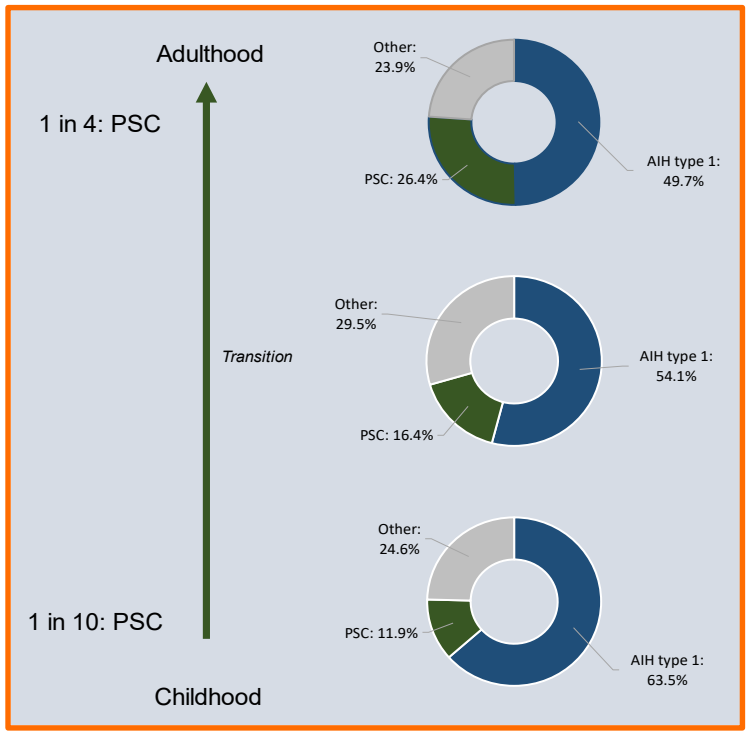


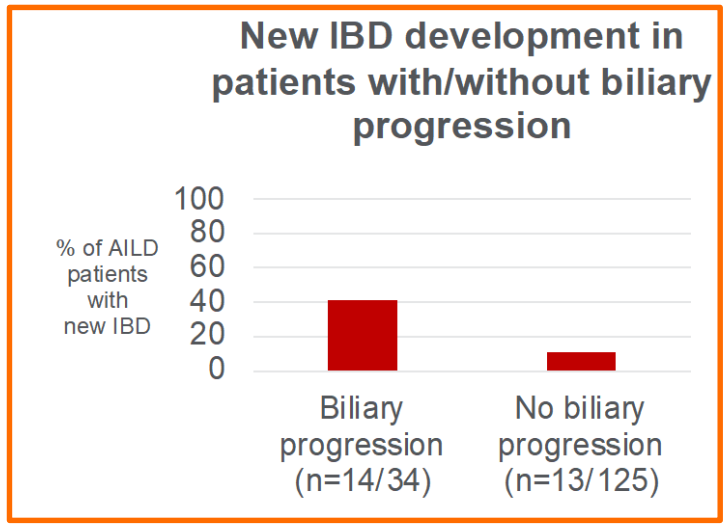
10.1172/jci.insight.162270

Biliary disease progression in childhood onset autoimmune liver disease – a 30 year follow up into adulthood

Long term follow-up studies of paediatric onset autoimmune liver disease (AILD) are invaluable in helping better understand the clinical course of disease.





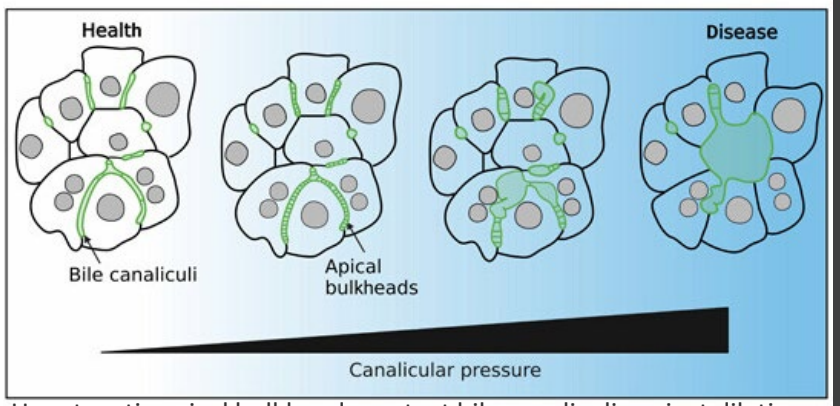


Three decades of follow-up demonstrates how children presenting with AILD have a significant risk of clinical transformation to PSC. Biliary progression was associated with the development of inflammatory bowel disease.

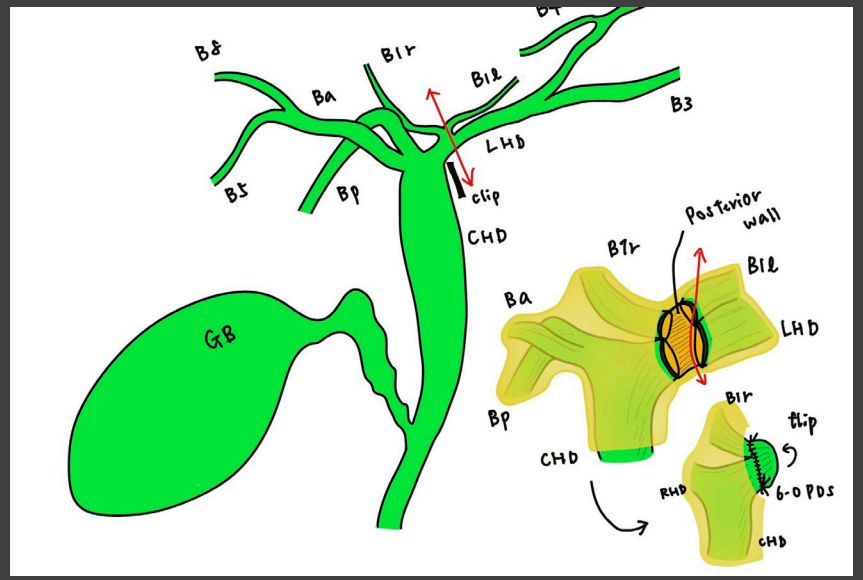
J Hep Reports

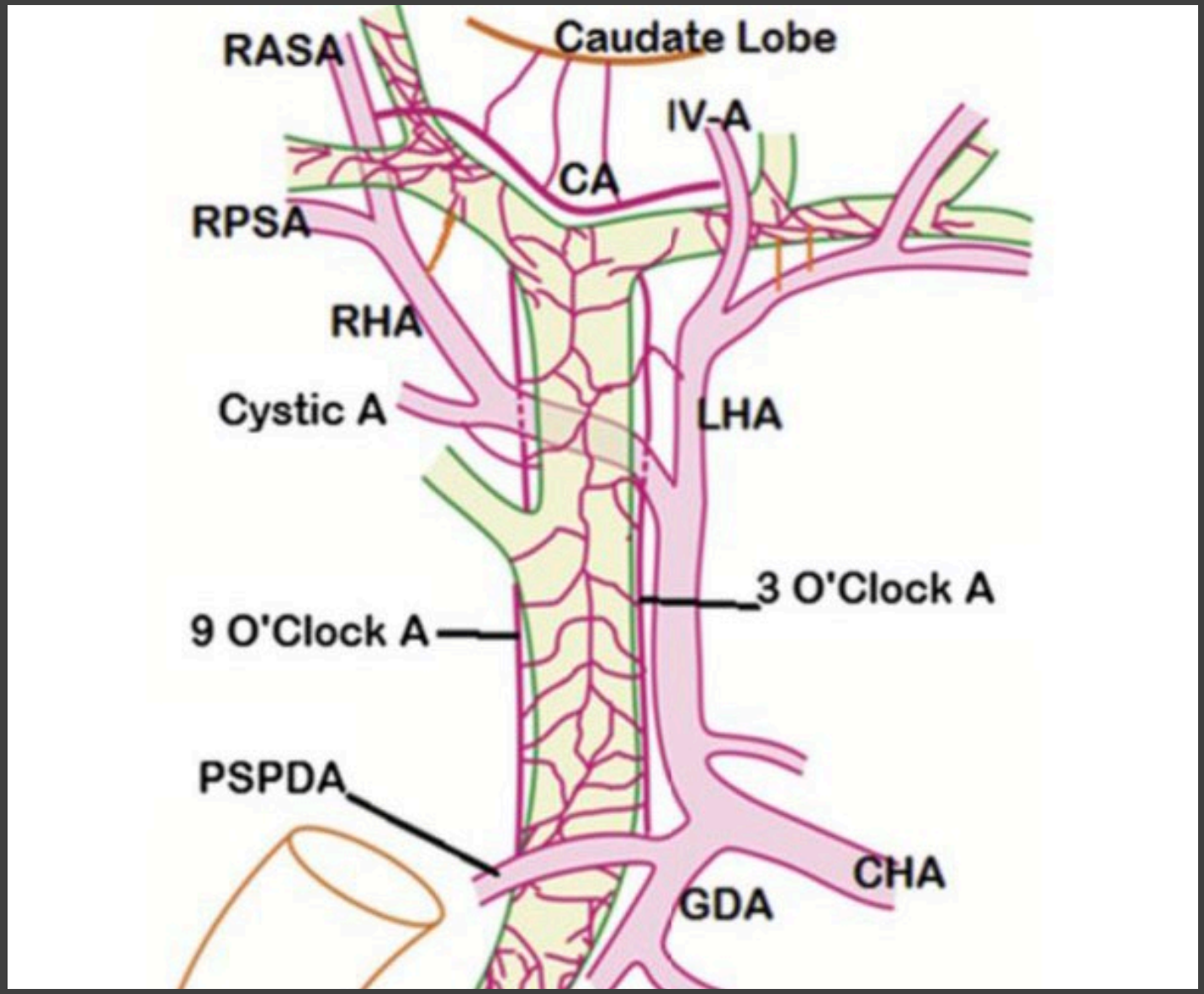
Warner S, Rajanayagam J, Russell E, Lloyd C, Ferguson J, Kelly D A, Hirschfield GM

Warner et al. J Hep Reports 2023



Hepatocytic apical bulkheads protect bile canaliculi against dilation and hepatocyte rosette formation upon elevated canalicular pressure.





Toru Goto MD via Twitter

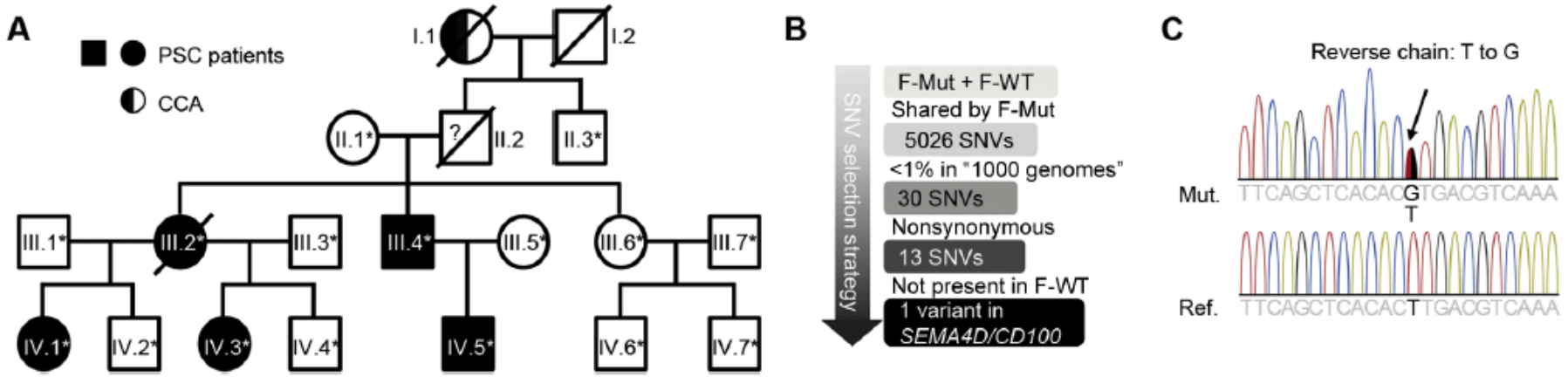
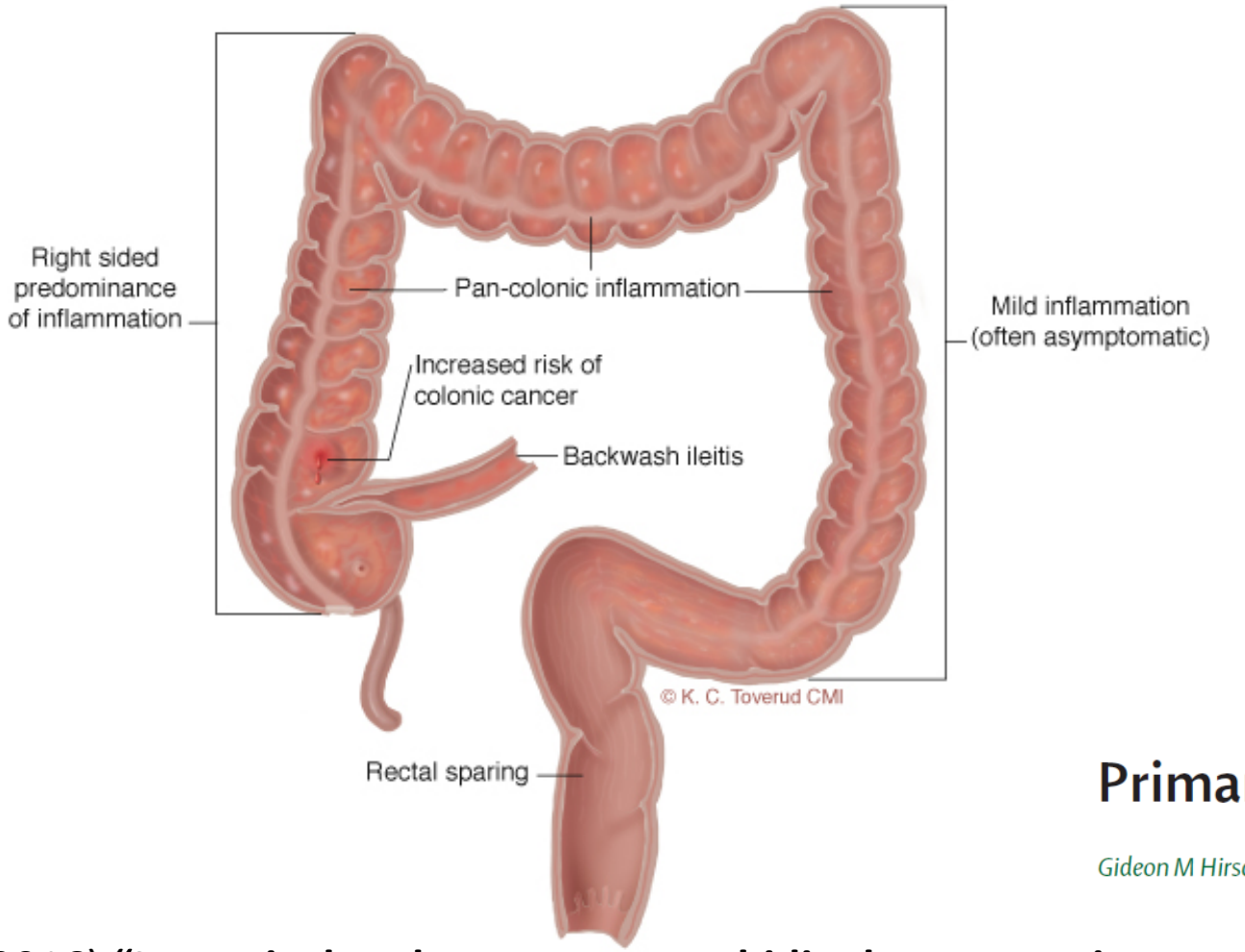


Fig. 1. Identification of a missense mutation in *SEMA4D/CD100* in a family with PSC. (**A**) Pedigree of a family with PSC. Squares, male participants; circles, female participants; black filled symbols, patients with PSC; half-filled symbol, patient with cholangiocarcinoma (CCA) but without a confirmed diagnosis of PSC; crossed-out symbols, deceased participants. Whole-exome sequencing was carried out on participants with an asterisk. (**B**) Single-nucleotide variant (SNV) selection strategy. (**C**) Confirmation of the $CD100^{K849T}$ mutation by Sanger sequencing. F-Mut, family members with PSC; F-WT, healthy family members.

"However, this mutation is not a common risk factor for PSC in general because our examination of 3178 patients did not identify any other carriers, and, to the best of our knowledge, it has not been reported in PSC elsewhere."

Jiang et al., Sci. Transl. Med.13, eabb0036 (2021)



Primary sclerosing cholangitis

Gideon M Hirschfield, Tom H Karlsen, Keith D Lindor, David H Adams

Nature Genetics 48, 510–518 (2016) **“In particular, the strong comorbidity between primary sclerosing cholangitis and inflammatory bowel disease is likely the result of a unique disease, which is genetically distinct from classical inflammatory bowel disease phenotypes.”**

Table 1 | Estimate of genetic correlation among autoimmune-related diseases

	PSC	CD	UC	IBD	Lupus	PBC*
Primary sclerosing cholangitis (PSC)	1	0.24 (se = 0.07)	0.62 (0.08)	0.46 (0.06)	0.20 (0.10)	0.31 (0.09)
Crohn's disease (CD)		1	0.62 (0.03)	0.92 (0.02)	0.13 (0.055)	0.18 (0.05)
Ulcerative colitis (UC)			1	0.90 (0.01)	0.22 (0.07)	0.23 (0.05)
Inflammatory bowel disease (IBD)				1	0.19 (0.05)	0.23 (0.04)
Lupus					1	0.49 (0.06)
Primary biliary cirrhosis (PBC)*						1

The asterisk "*" indicates that imputed summary statistics were used to estimate the SNP-heritability and pairwise genetic correlation using the SSimp package. "se" stands for the standard error of the pairwise genetic correlation between PSC and each trait.

Nature Communications volume 14, Article number: 1069 (2023)

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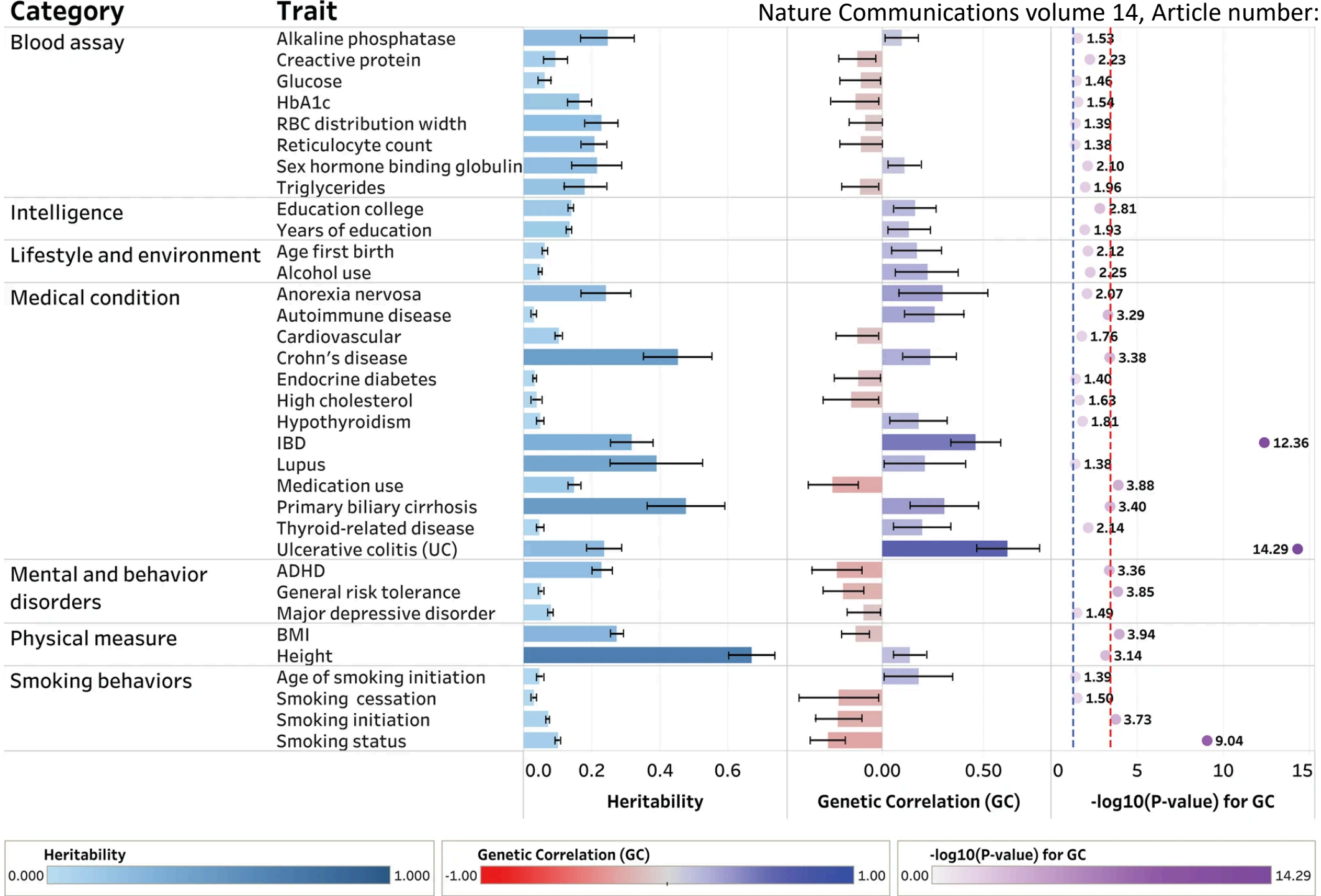
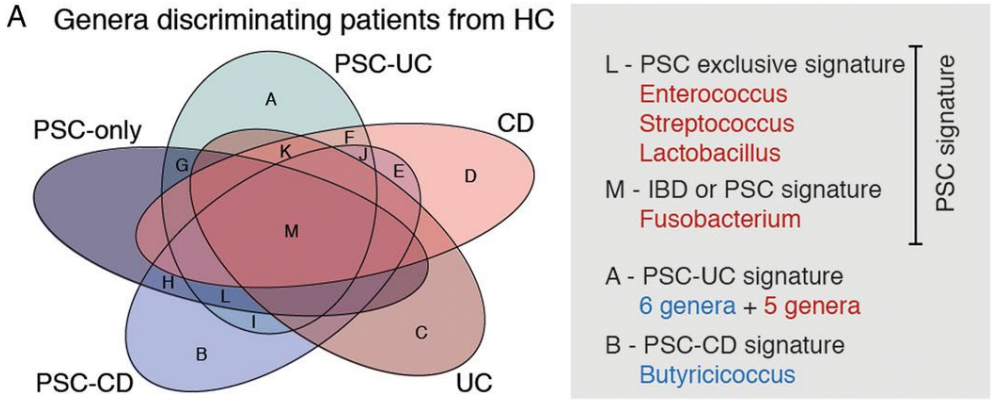
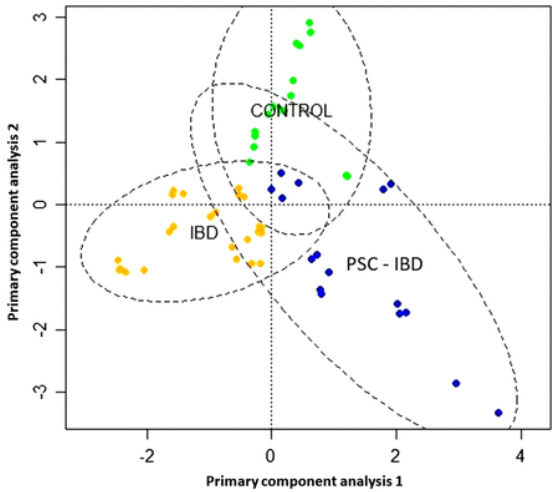


Dysbiosis in PSC and PSC-IBD

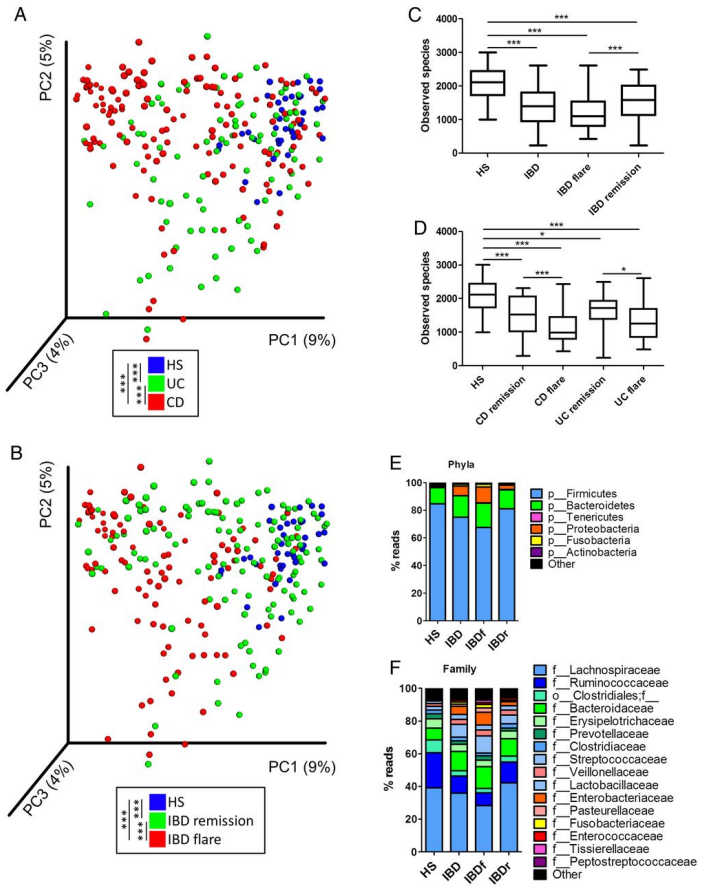
PSC-IBD



Sabino et al. Gut. 2015



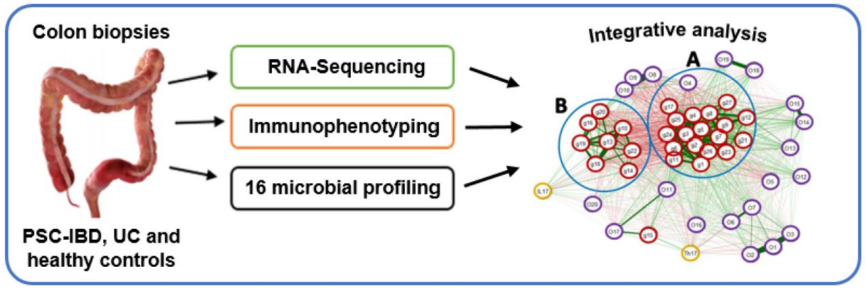
Quraishi MN et al. Gut. 2017

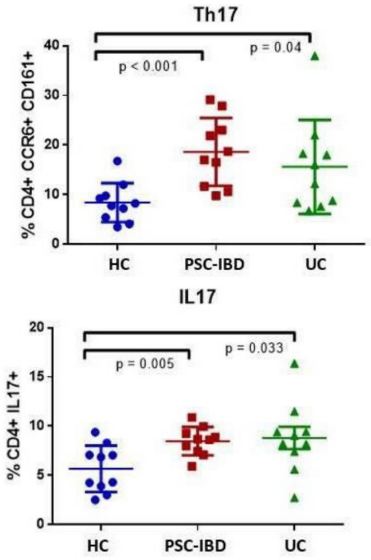


Sokol et al. Gut. 2015

Slides courtesy of Nabil Quraishi and Palak Trivedi

PSC-IBD disease mechanisms appear to be different to UC at a mucosal level

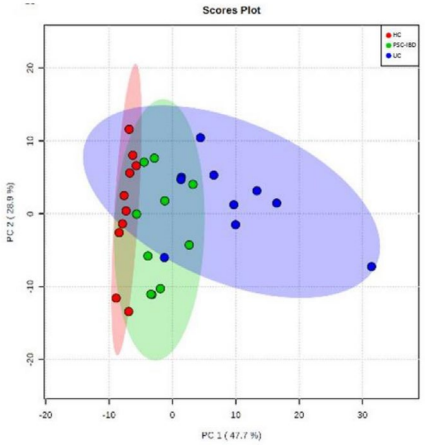


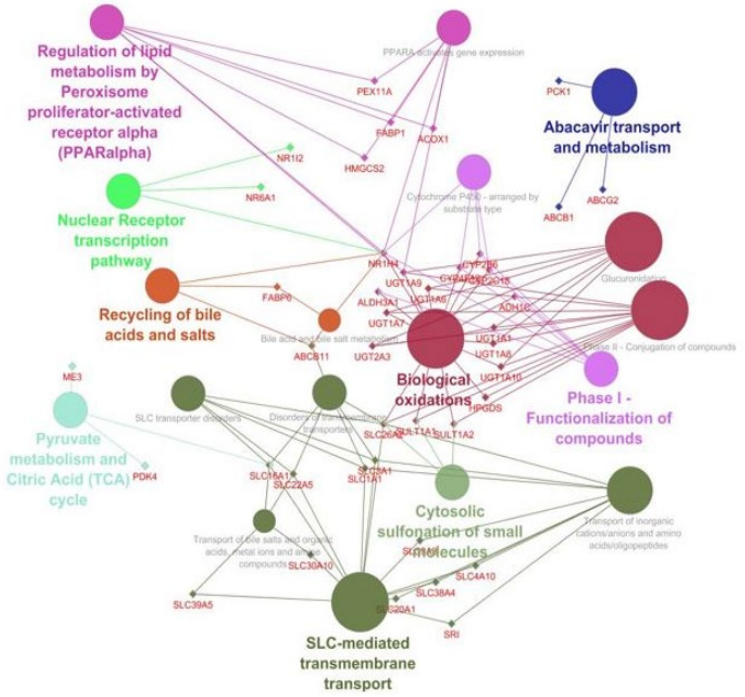


PSC-IBD and UC have similar immune mediated pro-inflammatory signals

Different triggers for this immune response

Large differences in colonic mucosal gene expression versus UC





Bile acid homeostatic pathways significantly aberrant in PSC-IBD compared to UC

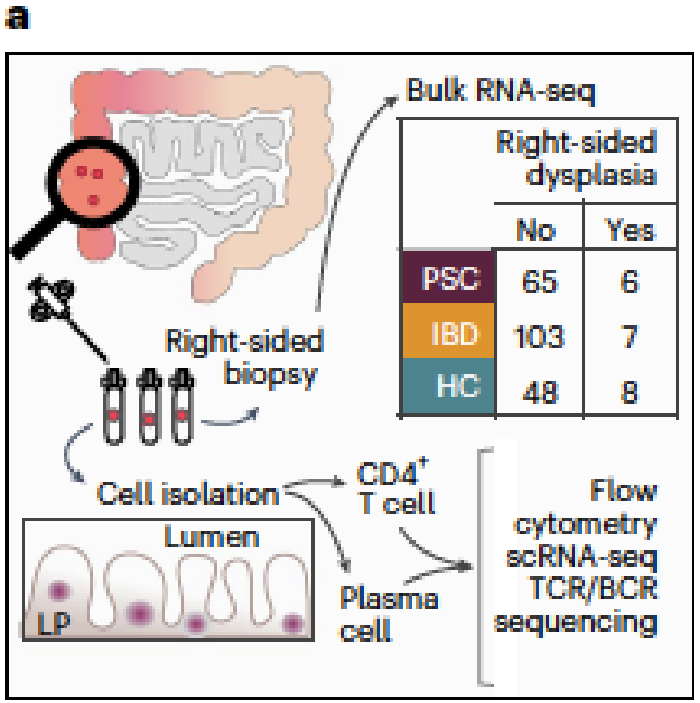
? Bile acid mediated inflammation

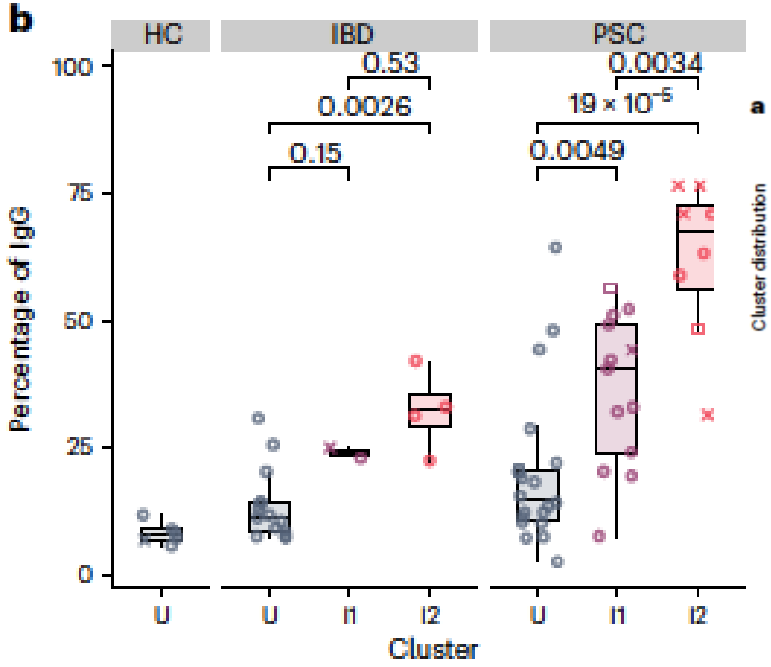
Quraishi MN, et al. J Crohns Colitis. 2020

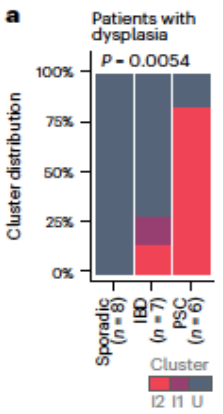
Slides courtesy of Nabil Quraishi and Palak Trivedi

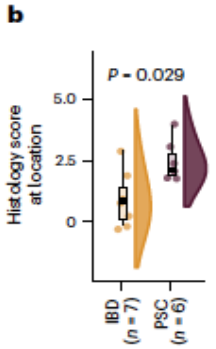
https://doi.org/10.1038/s41591-023-02372-x

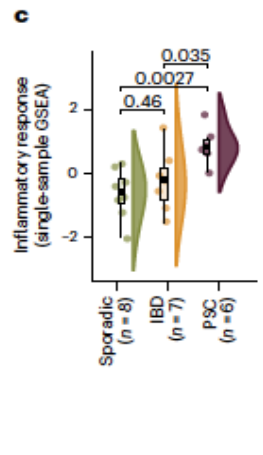
Antigen-driven colonic inflammation is associated with development of dysplasia in primary sclerosing cholangitis

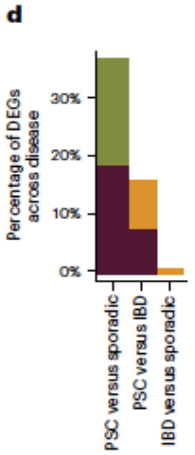






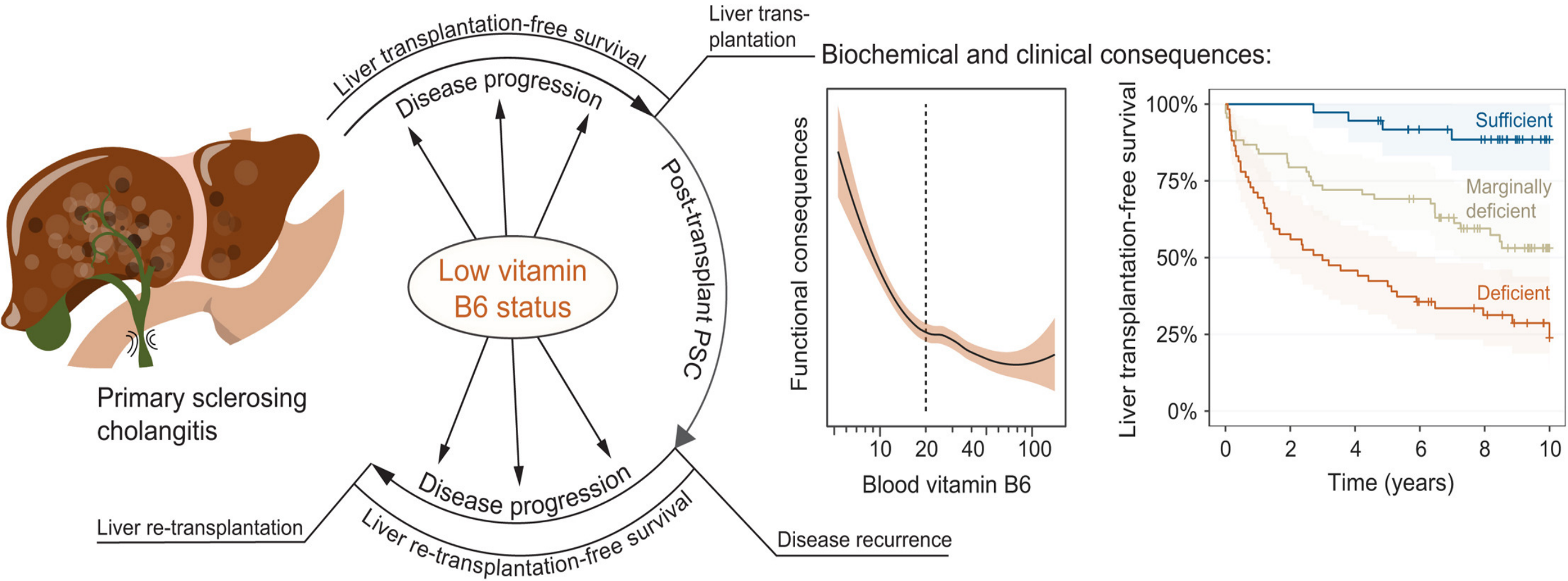






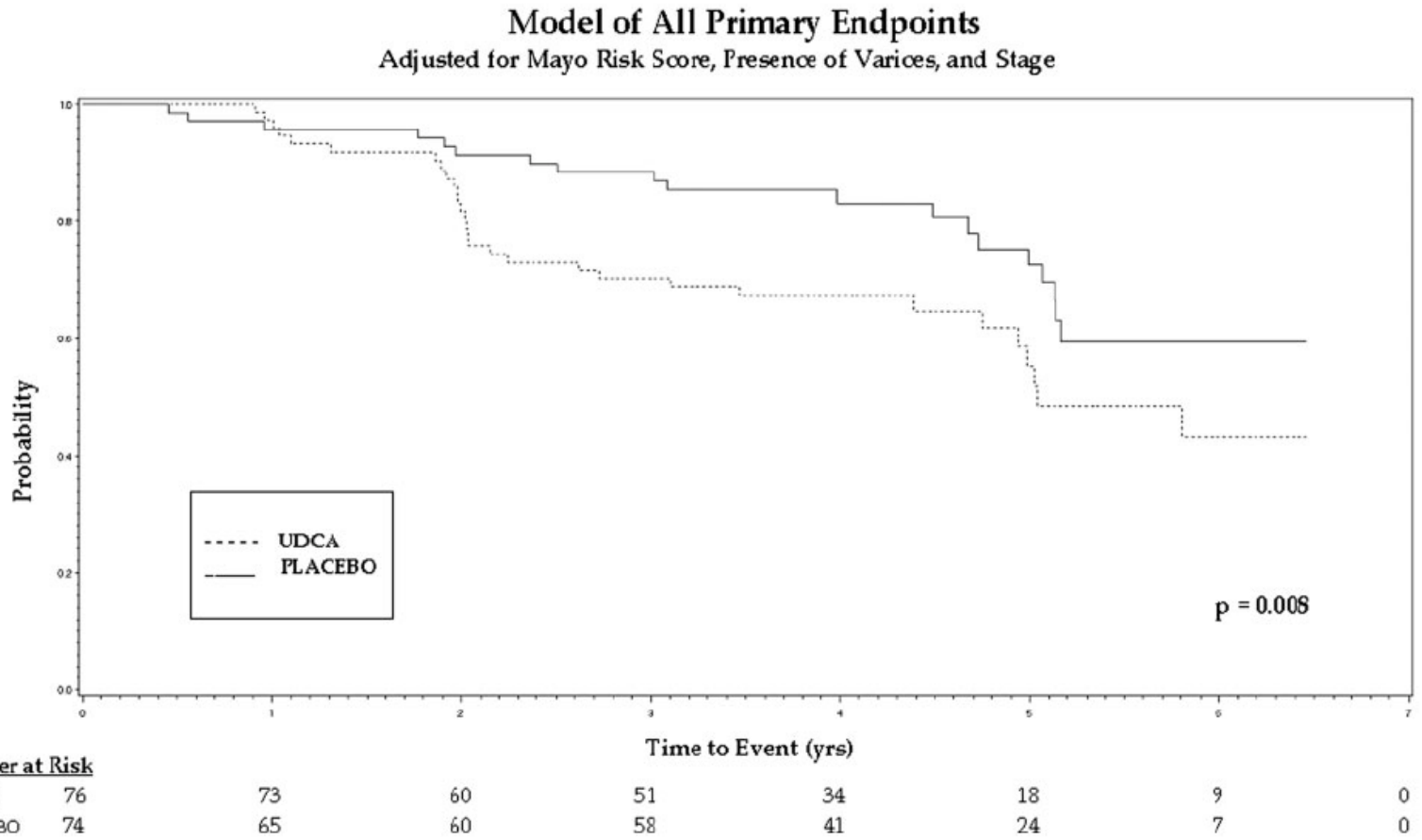
Clinical and biochemical impact of vitamin B6 deficiency in primary sclerosing cholangitis before and after liver transplantation

Peder Rustøen Braadland et. al Journal of Hepatol 10.1016/j.jhep.2023.05.038



The genetic potential of the gut microbiota to synthesize the coenzyme form of vitamin B6, pyridoxal 5'-phosphate (PLP), was reduced in people with PSC compared to healthy controls. Accordingly, people with PSC had lower circulating levels of PLP than healthy controls, and low PLP was associated with adverse outcomes.

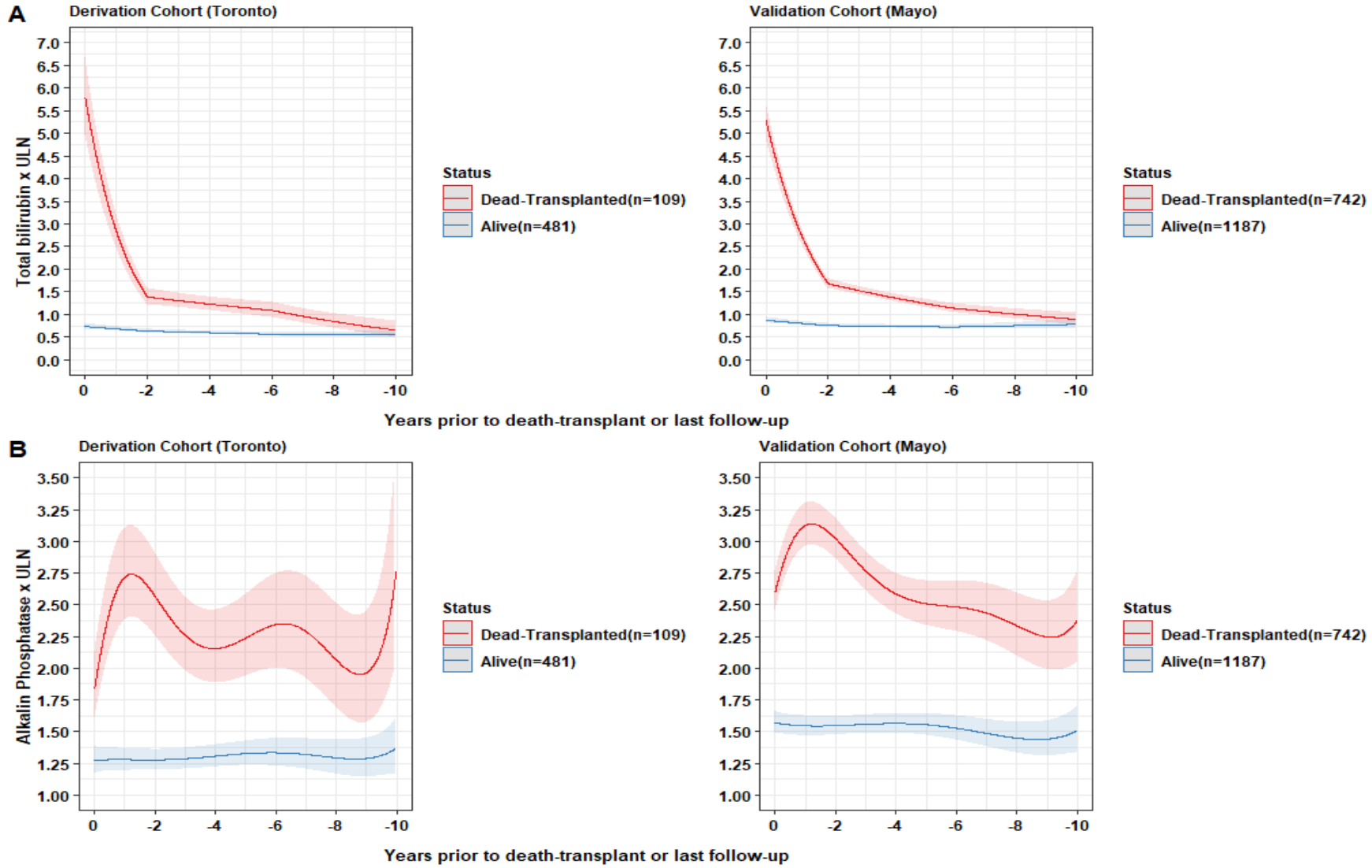
And nothing is obvious: High dose UDCA vs Placebo



Number at Risk								
UDCA	76	73	60	51	34	18	9	0
PLACEBO	74	65	60	58	41	24	7	0

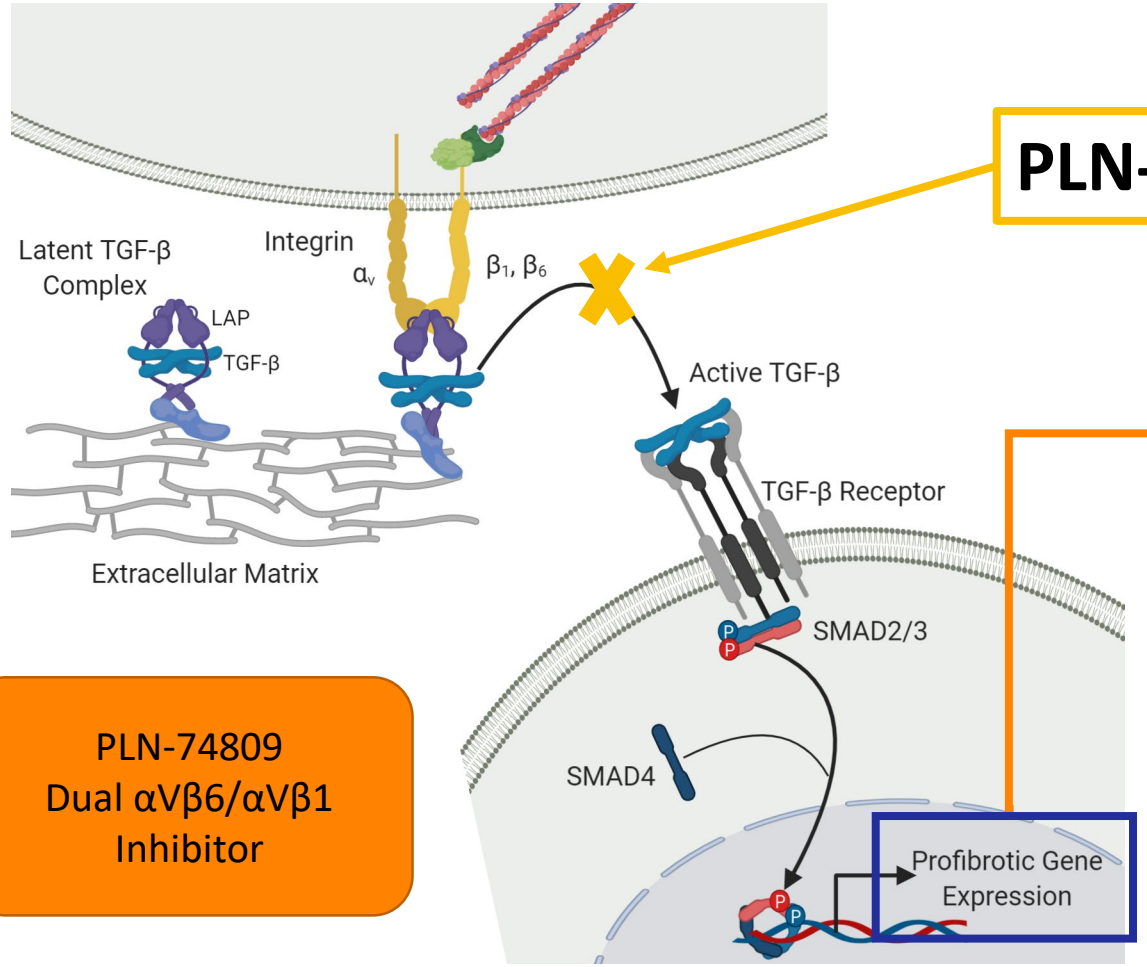
HEPATOLOGY, Vol. 50, No. 3, 2009

Progressive disease phenotypes



Ismail et al. In Prep./EASL 2022

PLN-74809: Antifibrotic Activity through Upstream Inhibition of TGF-beta Activation

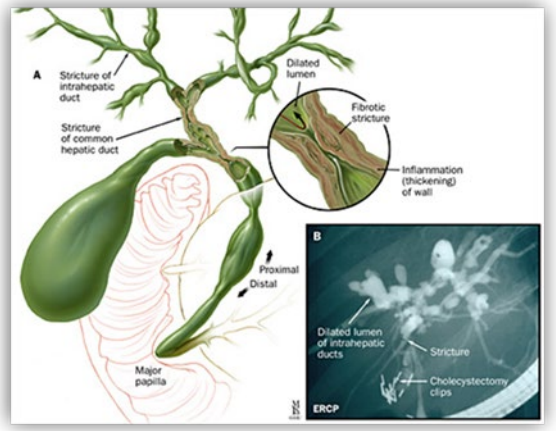


PLN-74809

PLN-74809
Dual αVβ6/αVβ1
Inhibitor

Col1a1
Col3a1
Timp1
CTGF
ATX
…

Hepatobiliary Fibrosis

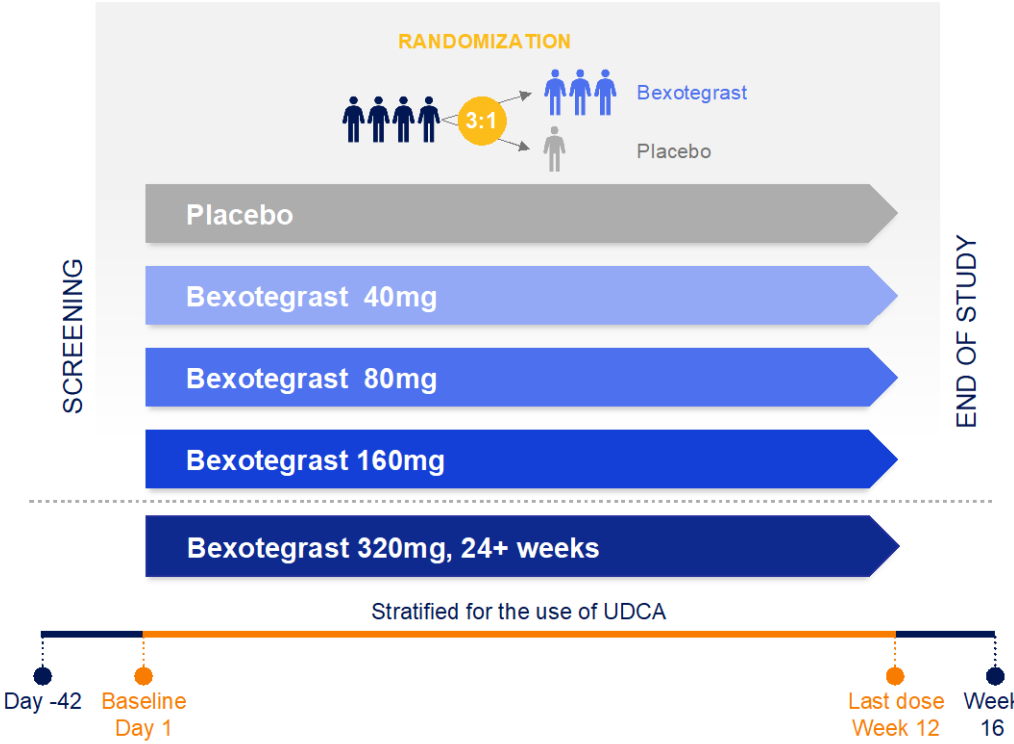


Upstream inhibition of TGF-β leads to reduction of multiple profibrotic genes

Slide based on PLIANT figure

Oral $\alpha_v\beta_6/\alpha_v\beta_1$ Integrin Inhibition in Primary Sclerosing Cholangitis: 12-week Interim Safety and Efficacy Analysis of INTEGRIS-PSC, A Phase 2a Trial of Bexotegrast

INTEGRIS-PSC: Study Design and Objectives



PRIMARY AND SECONDARY ENDPOINTS

- Safety and tolerability
- Pharmacokinetics[a]

EXPLORATORY ENDPOINTS

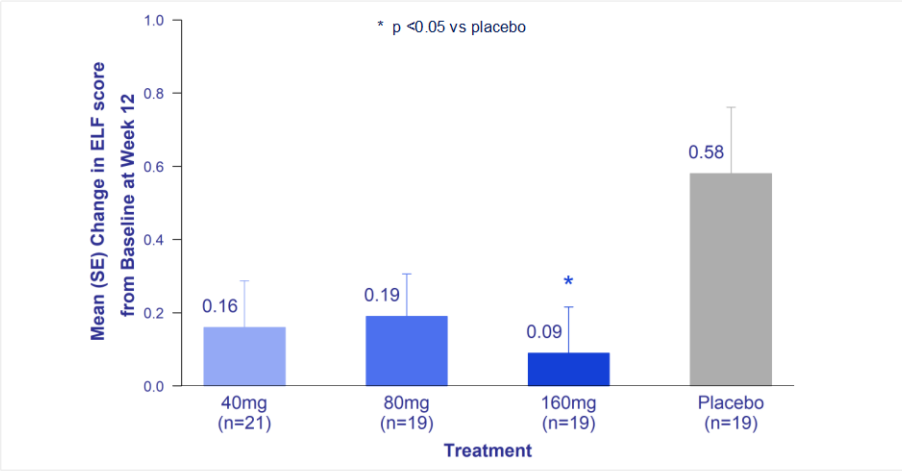
- Change in liver fibrosis markers: ELF score and PRO-C3
- Change in gadoxetate-enhanced MR parameters (voluntary sub-study)
- Change in ALP
- Change in Itch NRS

[a]Pharmacokinetics results are not presented but are available in the ePoster
ALP, alkaline phosphatase; ELF, enhanced liver fibrosis; MR, magnetic resonance; NRS, numerical rating scale; PRO-C3, neo-epitope pro-peptide of type III collagen formation

Hirschfield et al. LB Session 2 With Permission

ELF Score

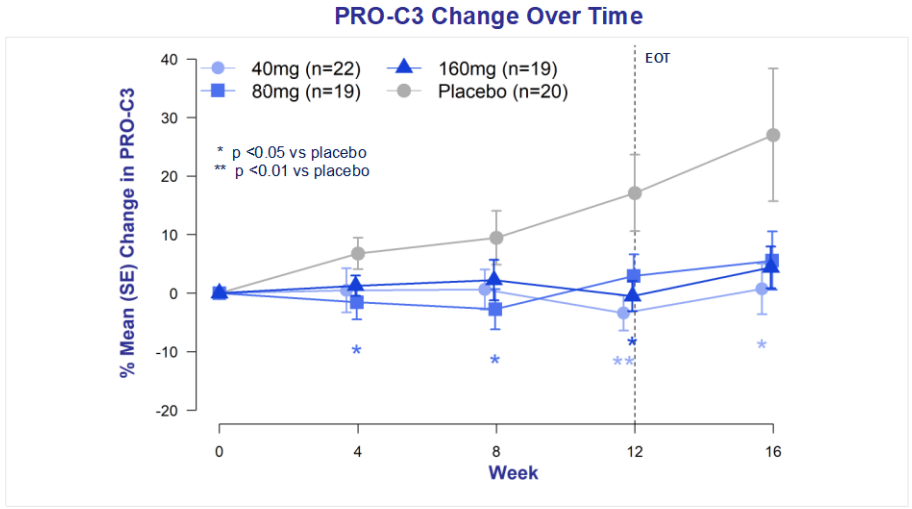
Lower Mean Change in ELF with Bexotegrast vs Placebo



All participants had baseline ELF ≥ 7.7 (moderate to severe liver fibrosis)[1]
1. Vesterhus M et al. *Hepatology* 2015 62(1):188-197
ELF, enhanced liver fibrosis; SE, standard error

PRO-C3: Dynamic marker of collagen formation

Lower Mean Change in PRO-C3 with Bexotegrast vs Placebo



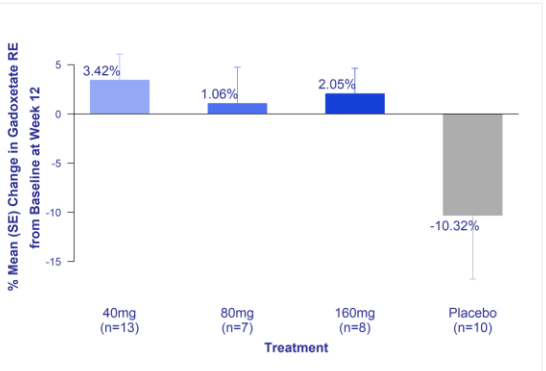
At 12 weeks, PRO-C3 change from baseline was significant for 40 mg and 160 mg

Only participants with both a baseline and post baseline are summarized
EOT, end of treatment; PRO-C3, neo-epitope pro-peptide of type III collagen formation; SE, standard error

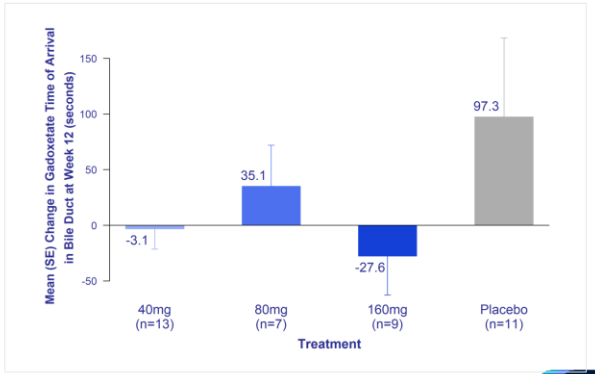
Gadoxetate-Enhanced MR of the Liver (Sub-Study)

- Using the MR contrast agent gadoxetate, relative enhancement is a measure of hepatocyte function[1,2]
- Time of arrival of gadoxetate to the common bile duct is an exploratory measure of excretory flow
- Findings are suggestive of improved hepatocyte function and excretory flow relative to placebo

Whole Liver Relative Enhancement (%): Change from Baseline at Week 12



Time of Arrival in Common Bile Duct (sec): Change from Baseline at Week 12



[1]Elkilany A, et al. *Abdominal Radiology*. 2021 46:979-991. [2]Schulze J, et al. *Clin. Gastroenterol. Hepatol*. 2019 17:192-199.
MR, magnetic resonance; RE, relative enhancement; SE, standard error

In this Interim Analysis of INTEGRIS-PSC which Evaluated Oral $\alpha_v\beta_6/\alpha_v\beta_1$ Integrin Inhibition with Bexotegrast in PSC:

Bexotegrast was well tolerated over 12 weeks of treatment

- Adverse events rates were comparable to placebo with all drug-related events mild or moderate in severity
- Low rate of discontinuation due to adverse events and no treatment-related severe or serious AEs

Bexotegrast reduced changes in serum biomarkers of liver fibrosis in a PSC population with suspected moderate to severe liver fibrosis

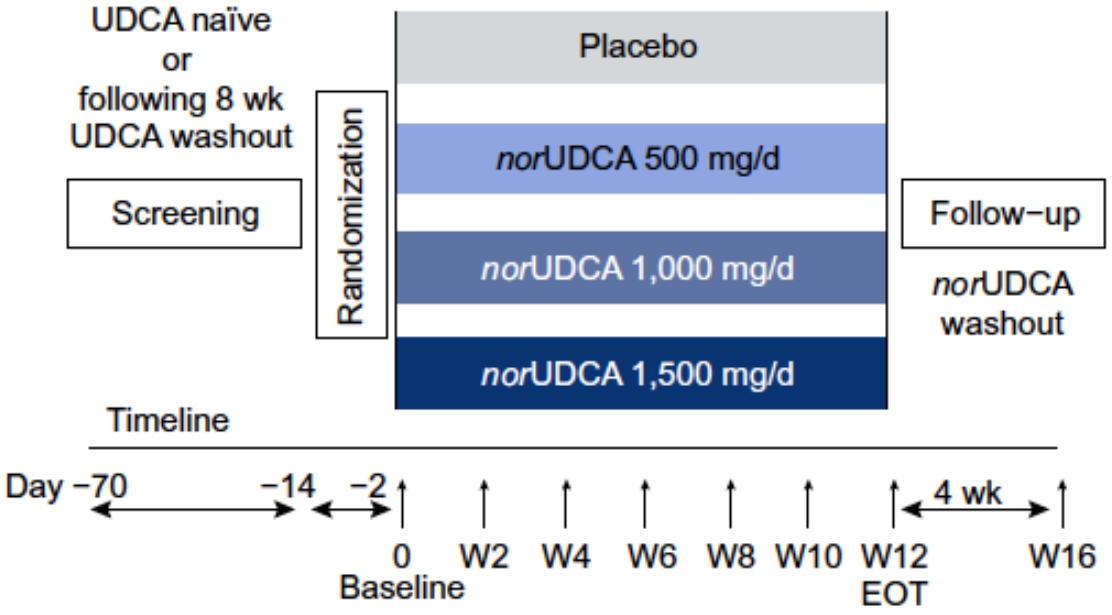
- Exploratory endpoints demonstrated all doses reduced changes in ELF scores and collagen synthesis (PRO-C3) relative to placebo with a statistically significant differences for both observed with 160mg
- Exploratory MR imaging analysis suggested improved hepatocyte function and bile flow relative to placebo at Week 12

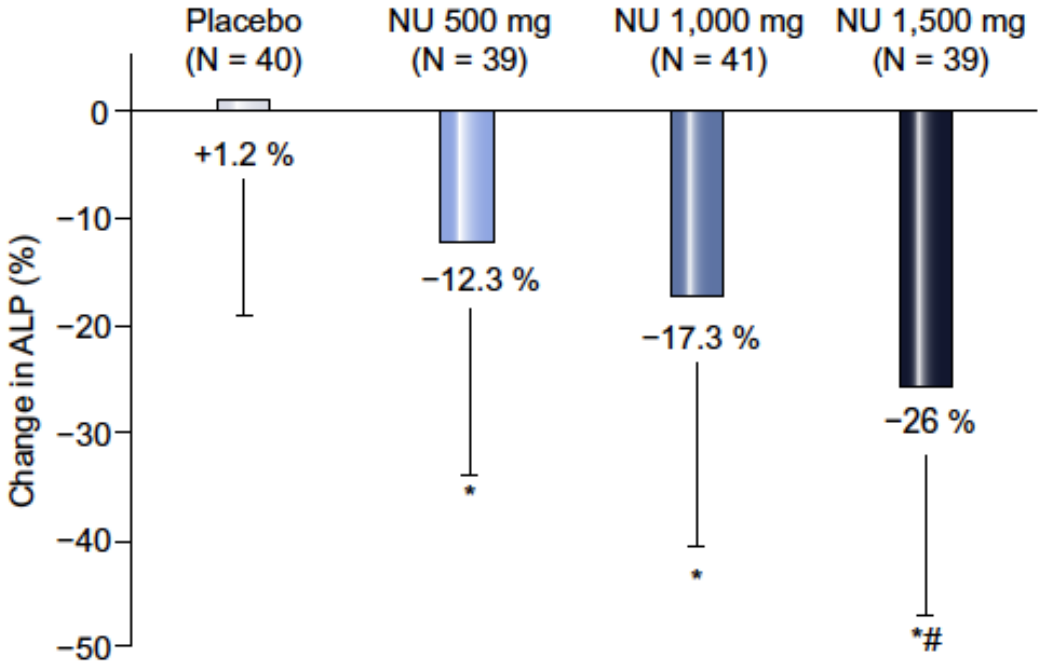
Study results support proof of concept for targeting integrin-mediated TGF-β activation as a potential antifibrotic approach in PSC

- 320mg cohort is ongoing with results expected in 2024 (NCT04480840)

AE, adverse event; ELF, enhanced liver fibrosis, MR, magnetic resonance; PRO-C3, neo-epitope pro-peptide of type III collagen formation; PSC, primary sclerosing cholangitis

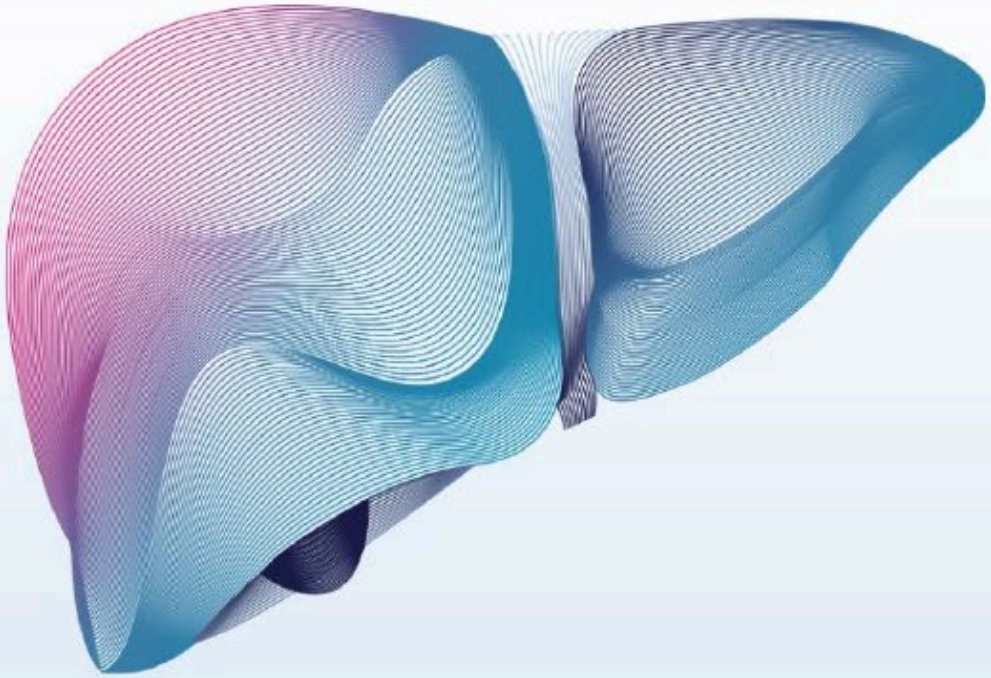
norUrsodeoxycholic acid improves cholestasis in primary sclerosing cholangitis





Fickert et al. Journal of Hepatology 2017 vol. 67: 549–558

EASL CONGRESS 2023
Vienna, Austria
21–24 June
The International Liver Congress™



A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of cilofexor in patients with non-cirrhotic primary sclerosing cholangitis (PRIMIS)

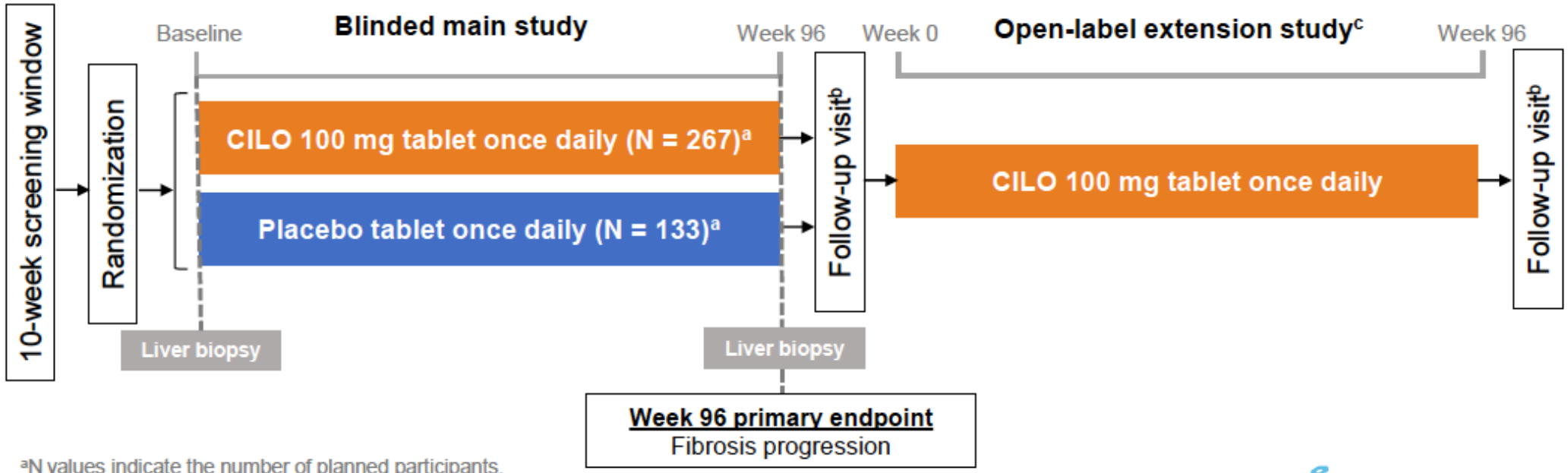
Presenting author: *Michael Trauner*[1]

Co-authors: Cynthia Levy[2,3], Atsushi Tanaka[4], Zachary Goodman[5], Douglas Thorburn[6], Deepak Joshi[7], Kimmo Salminen[8], Kidist Yimam[9], Hiroyuki Isayama[10], Aldo J. Montano-Loza[11], Mark Danta[12,13], Holger Hinrichsen[14], Pietro Invernizzi[15,16], Xiangyu Liu[17], Xiaomin Lu[17], Muhsen Alani[17], William T. Barchuk[17], Timothy R. Watkins[17], Mark C. Genovese[17], Christopher Bowlus[18]

[1]Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria; [2]Division of Digestive Health and Liver Diseases, University of Miami Miller School of Medicine, Miami, USA; [3]Schiff Center for Liver Diseases, University of Miami Miller School of Medicine, Miami, USA; [4]Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan; [5]Center for Liver Diseases, Inova Fairfax Hospital, Falls Church, USA; [6]The Sheila Sherlock Liver Centre and UCL Institute of Liver and Digestive Health, Royal Free Hospital, London, UK; [7]Institute of Liver Studies, King's College Hospital, London, UK; [8]Division of Gastroenterology, Department of Medicine, Turku University Hospital, Turku, Finland; [9]Department of Hepatology and Liver Transplantation, California Pacific Medical Center, San Francisco, USA; [10]Department of Gastroenterology, Graduate School of Medicine, Juntendo University, Tokyo, Japan; [11]Division of Gastroenterology and Liver Unit, University of Alberta, Edmonton, Canada; [12]School of Clinical Medicine, Faculty of Medicine, UNSW, Sydney, Australia; [13]Department of Gastroenterology, St Vincent's Hospital, Sydney, Australia; [14]Gastroenterologisch-Hepatologisches MVZ Kiel GmbH, Kiel, Germany; [15]Gastroenterology Unit, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy; [16]Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy; [17]Gilead Sciences, Inc, Foster City, USA; [18]Division of Gastroenterology and Hepatology, University of California Davis School of Medicine, Sacramento, USA.

PRIMIS study design

- Adults (18–75 years) with large duct PSC and liver fibrosis F0–F3 (Batts–Ludwig stage) were randomized 2:1 to receive CILO 100 mg or placebo orally once daily for 96 weeks
- Patients were stratified by the presence or absence of ursodeoxycholic acid use and presence or absence of bridging fibrosis (Batts–Ludwig fibrosis stage F3 vs F0, F1 and F2)



[a]N values indicate the number of planned participants.
[b]Follow-up visit was 4 weeks after completion of the corresponding study phase.
[c]Patients who completed week 96 with an evaluable liver biopsy (stage F0–F3) were eligible to enter a 96-week open-label extension study.
CILO, cilofexor; PSC, primary sclerosing cholangitis.

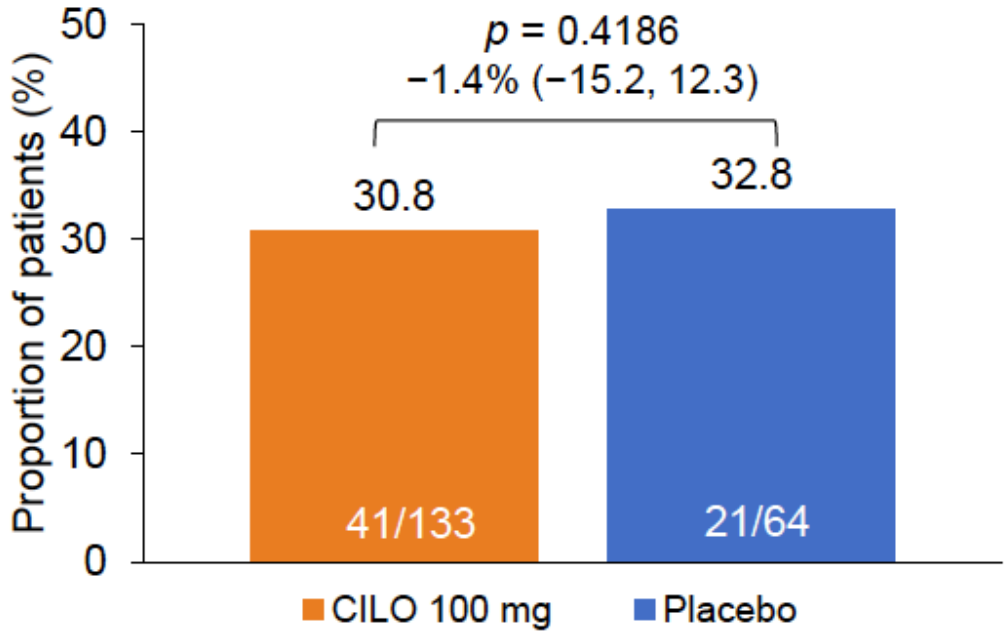
Results: Baseline characteristics

Baseline characteristic	CILO 100 mg (N = 277)	Placebo (N = 139)	Total (N = 416)
Age, years	42 (33–52)	45 (34–55)	43 (34–54)
Women	107 (38.6)	52 (37.4)	159 (38.2)
Body mass index, kg/m²	24.6 (22.2–27.9)	25.3 (23.1–29.2)	24.9 (22.7–28.1)
Concomitant UCDA	166 (59.9)	80 (57.6)	246 (59.1)
IBD	195 (70.4)	97 (69.8)	292 (70.2)
ALP, U/L	173 (107–274)	183 (108–328)	173 (107–293)
ALP category > 1.5 x ULN	126 (45.5)	71 (51.1)	197 (47.4)
Fasting total bile acids, µmol/L	10.4 (4.9–25.2)	9.5 (4.9–24.4)	10.0 (4.9–24.9)
ALT, U/L	50 (27–93)	50 (26–94)	50 (26–94)
Total bilirubin, mg/dL	0.6 (0.5–0.9)	0.6 (0.5–0.8)	0.6 (0.5–0.9)
Ludwig fibrosis stage			
0	49 (17.7)	27 (19.4)	76 (18.3)
1	73 (26.4)	40 (28.8)	113 (27.2)
2	84 (30.3)	38 (27.3)	122 (29.3)
3	71 (25.6)	34 (24.5)	105 (25.2)
ELF test score	9.06 (8.42–9.79)	9.04 (8.41–9.65)	9.06 (8.41–9.71)
Liver stiffness by FibroScan, kPa	7.0 (5.2–9.2)	7.0 (5.5–9.4)	7.0 (5.3–9.2)
MELD score	6 (6, 7)	6 (6, 7)	6 (6, 7)

All data are median (IQR) or n (%).
ALP, alkaline phosphatase; CILO, cilofexor; ELF, enhanced liver fibrosis; IBD, inflammatory bowel disease; IQR, interquartile range; MELD, model for end-stage liver disease; UCDA, ursodeoxycholic acid; ULN, upper limit of normal.

Results: patients with liver fibrosis progression at week 96

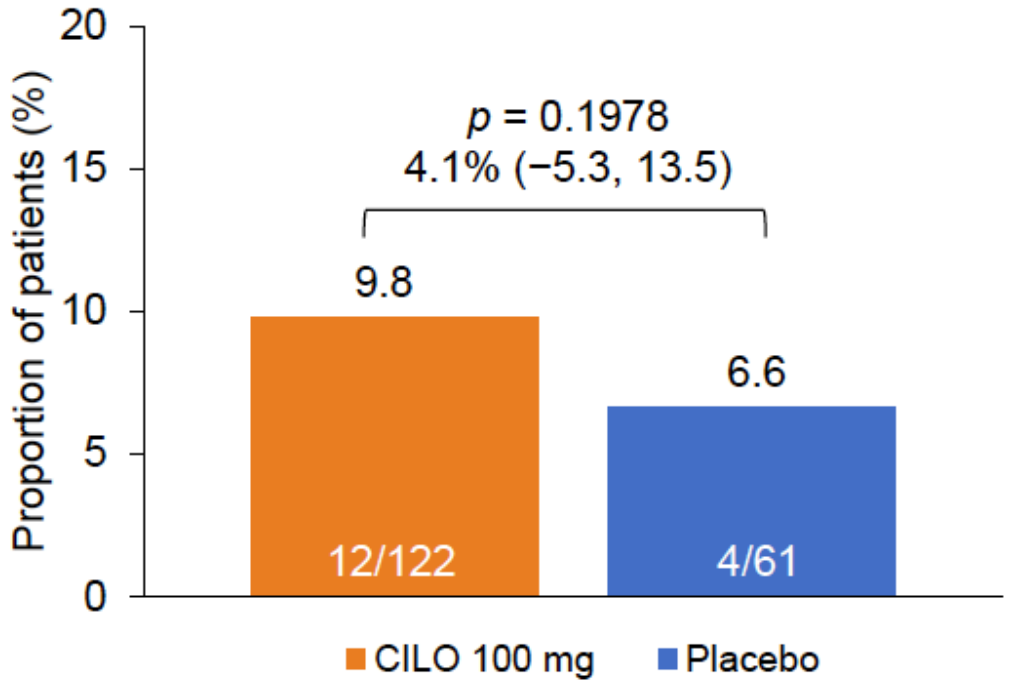
- The trial was terminated early because the interim futility analysis showed that the estimated probability of meeting the primary endpoint was 6.8%
- At week 96, the proportion of patients with a **≥ 1-stage increase in fibrosis** (Batts–Ludwig stage) was 30.8% in the CILO group compared with 32.8% in the placebo group



Treatment difference and associated 95% CI and one-sided *p* value were obtained by the stratum-adjusted Mantel–Haenszel method with baseline ursodeoxycholic acid use and Batts–Ludwig fibrosis stage (F3 vs F0, F1 and F2) as stratification factors.
CI, confidence interval; CILO, cilofexor.

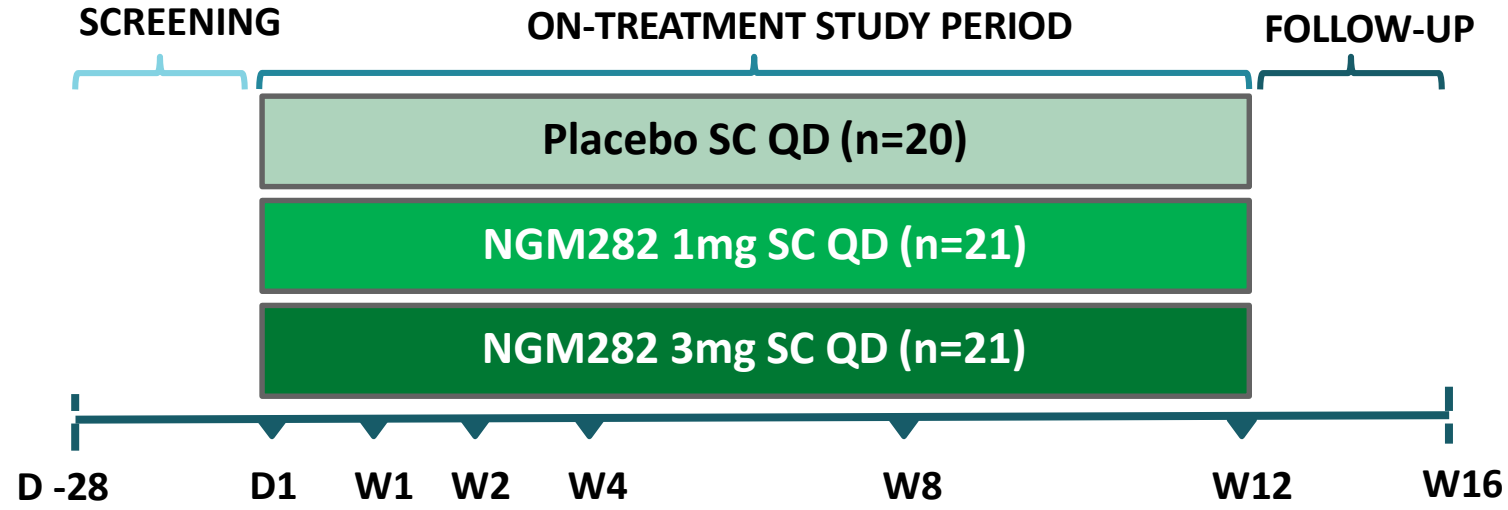
Results: patients with ≥ 25% reduction in ALP levels and an absence of fibrosis worsening at week 96

- At week 96, the proportion of patients with **≥ 25% reduction in ALP** levels from baseline **and** an **absence of fibrosis worsening** (Batts–Ludwig stage) was 9.8% in the CILO group compared with 6.6% in the placebo group



Treatment difference and associated 95% CI and one-sided nominal *p* value were obtained by the stratum-adjusted Mantel–Haenszel method with baseline ursodeoxycholic acid use and Batts–Ludwig fibrosis stage (F3 vs F0, F1 and F2) as stratification factors.
ALP, alkaline phosphatase; CI, confidence interval; CILO, cilofexor.

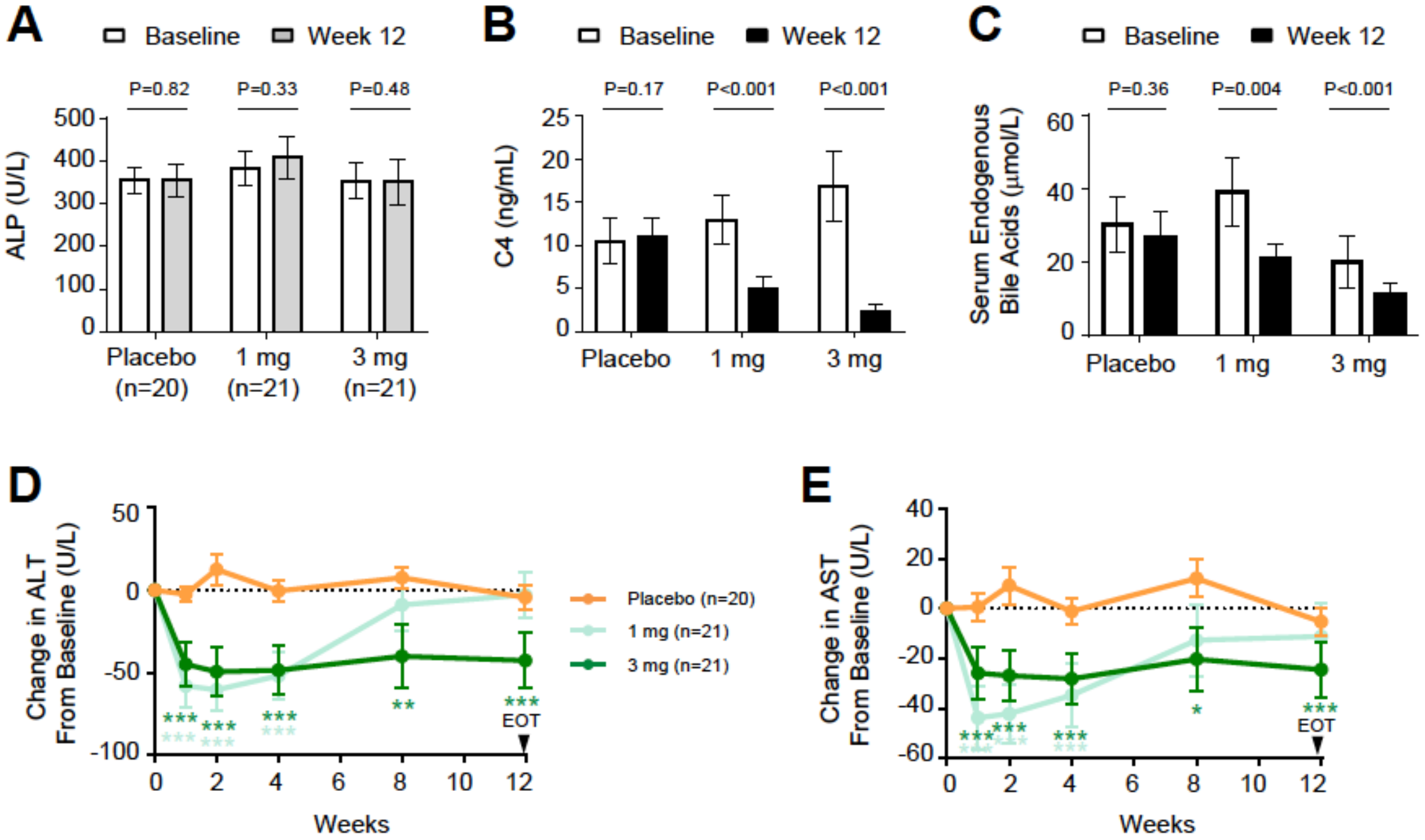
NGM282: a FGF19 analogue and primary sclerosing cholangitis



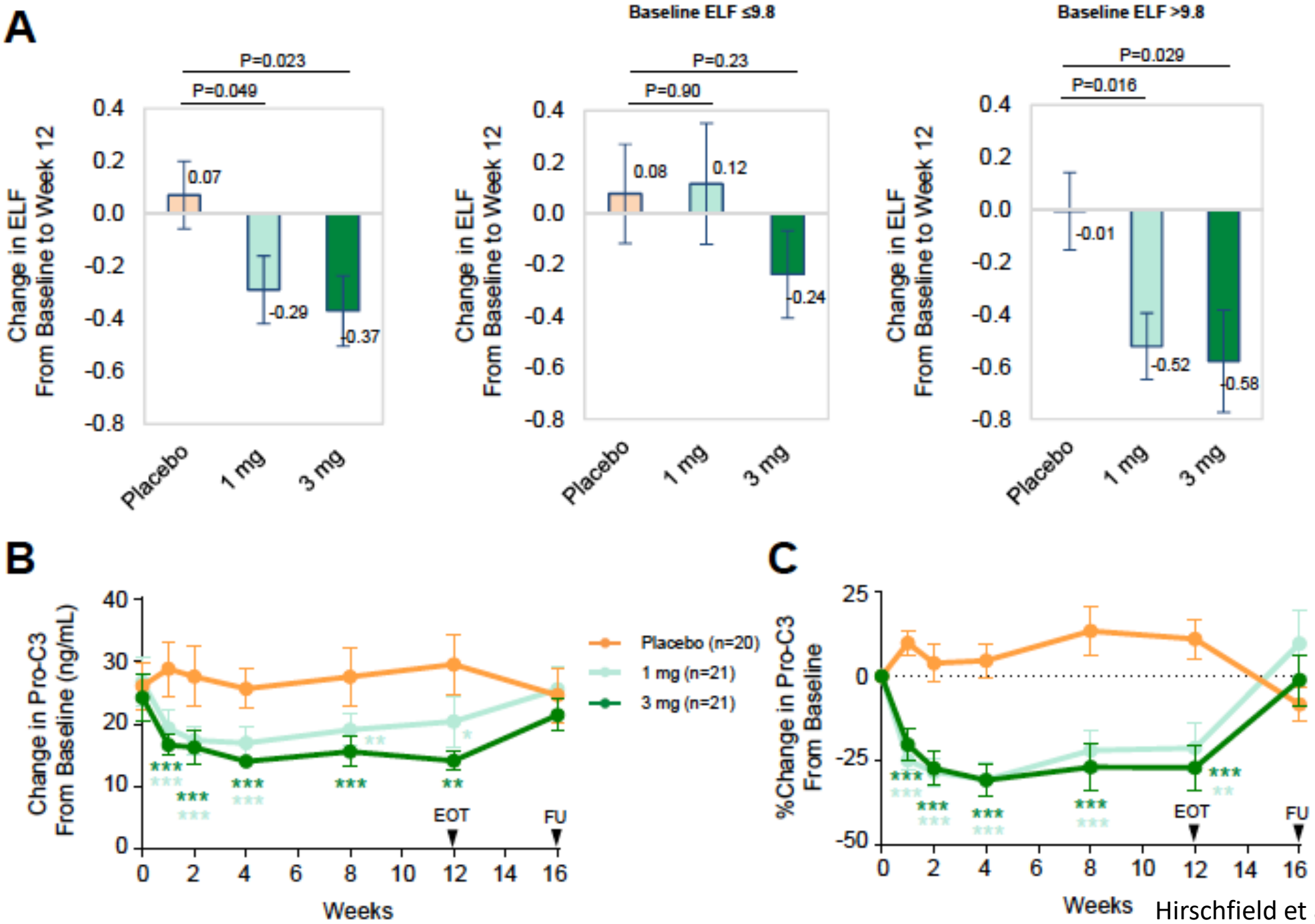
- Randomized (1:1:1), double-blinded, placebo controlled
- 62 subjects randomized at 27 sites in Europe and US
- Confirmed diagnosis of PSC by EASL Guidelines
  - *Included subjects with features of AIH, small duct disease, stable dominant strictures and compensated cirrhosis*
- ALP ≥ 1.5 x ULN, total bilirubin < 2.5 mg/dL, ALT/AST < 5 x ULN
- Subjects were stratified across dosing groups by UDCA use

- **Primary endpoint: Mean change in ALP from Baseline at W12**

Hirschfield et al. J Hep 2019



Hirschfield et al. J Hep 2019



Hirschfield et al. J Hep 2019

Safety and Tolerability of A3907 in Primary Sclerosing Cholangitis
ClinicalTrials.gov ID NCT05642468
Sponsor Albireo
Information provided by Albireo (Responsible Party)
Last Update Posted 2023-08-23

A Study to Assess Safety and Effectiveness of Elafibranor in Adult Participants With Primary Sclerosing Cholangitis. (ELMWOOD)
ClinicalTrials.gov ID NCT05627362
Sponsor Ipsen
Information provided by Ipsen (Responsible Party)
Last Update Posted 2023-08-28

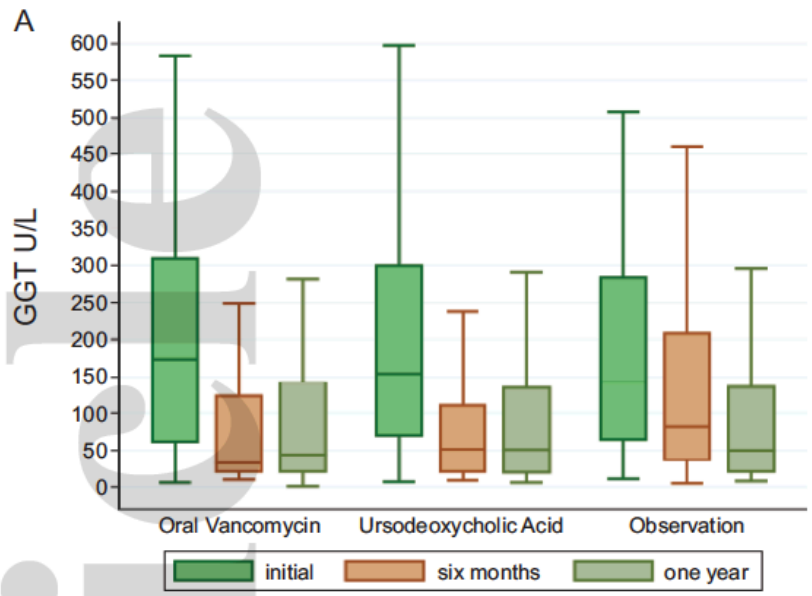
Effect of Simvastatin on the Prognosis of Primary Primary Sclerosing Cholangitis (PSC) (PiSCATIN)
ClinicalTrials.gov ID NCT04133792
Sponsor Annika Bergquist
Information provided by Annika Bergquist, Karolinska University Hospital (Responsible Party)
Last Update Posted 2022-11-01

A Study to Evaluate Efficacy and Safety of an Investigational Drug Named Volixibat in Patients With Itching Caused by Primary Sclerosing Cholangitis (PSC) (VISTAS)
ClinicalTrials.gov ID NCT04663308
Sponsor Mirum Pharmaceuticals, Inc.
Information provided by Mirum Pharmaceuticals, Inc. (Responsible Party)
Last Update Posted 2023-09-07

Vancomycin for Primary Sclerosing Cholangitis
ClinicalTrials.gov ID NCT03710122
Sponsor Elizabeth Carey
Information provided by Elizabeth Carey, Mayo Clinic (Responsible Party)
Last Update Posted 2023-09-05

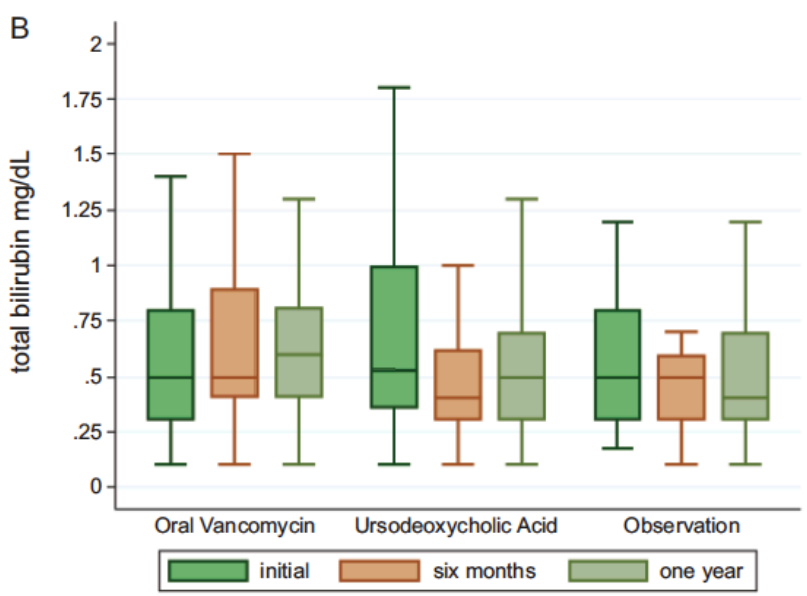
CM-101 in PSC Patients -The SPRING Study
ClinicalTrials.gov ID NCT04595825
Sponsor ChemomAb Ltd.
Information provided by ChemomAb Ltd. (Responsible Party)
Last Update Posted 2023-08-24

Vancomycin and PSC



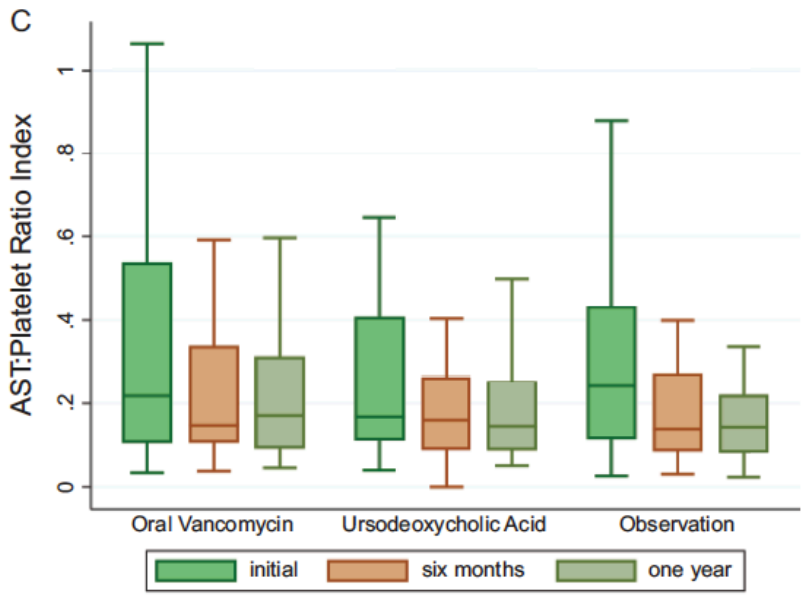
	inital v. 6mo	6mo v. 12mo	initial v. 12mo
Vanco	<0.001	0.026	<0.001
Urso	<0.001	0.709	<0.001
Obs	<0.001	0.92	<0.001

	Vanco v. Urso	Vanco v. Obs	Urso v. Obs
initial	0.763	0.81	0.997
6mo	0.76	0.012	0.075
12mo	0.611	0.486	0.732



	inital v. 6mo	6mo v. 12mo	initial v. 12mo
Vanco	0.372	0.602	0.056
Urso	0.023	0.046	0.082
Obs	0.017	0.197	0.065

	Vanco v. Urso	Vanco v. Obs	Urso v. Obs
initial	0.768	0.903	0.659
6mo	0.022	0.045	0.729
12mo	0.029	0.002	0.475



	inital v. 6mo	6mo v. 12mo	initial v. 12mo
Vanco	0.269	0.461	0.019
Urso	0.163	0.759	0.098
Obs	0.015	0.392	0.001

	Vanco v. Urso	Vanco v. Obs	Urso v. Obs
initial	0.493	0.877	0.325
6mo	0.515	0.467	0.891
12mo	0.531	0.189	0.504

Controversies beyond needing more trial data:

1) Should the endpoint be biochemical or colonic mucosal healing?
2) What if rare subgroups of patients derive substantial benefit?

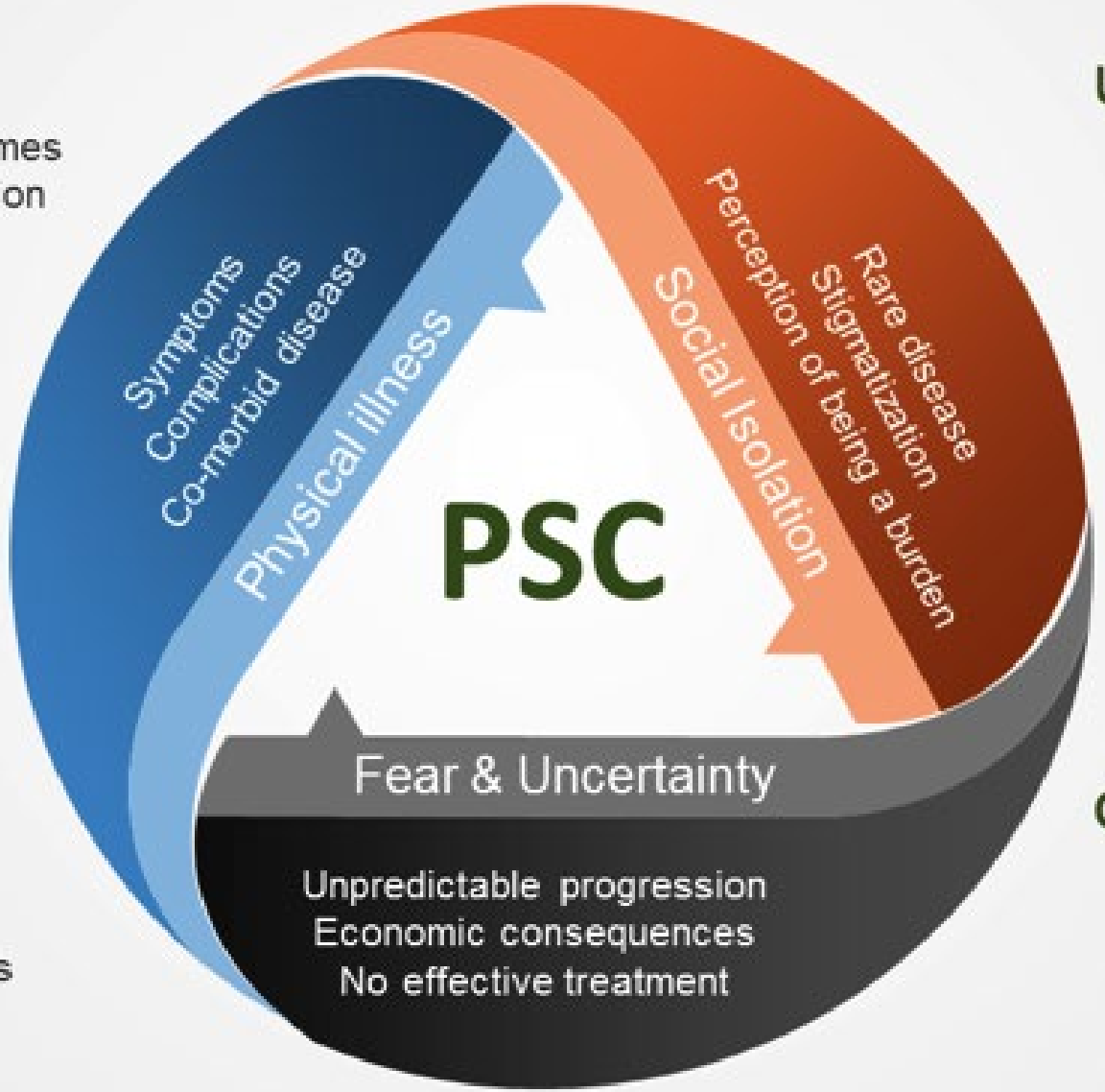
Hepatology. 2021 Mar;73(3):1061-1073.

Five POINTS for PSC care

TORONTO CENTRE FOR LIVER DISEASE

Criteria	Parameters
1. Diagnose PSC with compassion and carefully	**MRCP is usually sufficient** • ERCP is for intervention and bile duct histology • Colonoscopy with biopsies to assess colon • Liver biopsy is infrequently needed clinically
2. Explain risk and offer choices	**Appreciate the long natural history of disease** • UDCA is controversial • Follow with serum liver tests and elastography • Don’t be too early or too late with transplantation (the hardest disease to time)
3. Manage symptoms in parallel to disease modifying therapy	**Symptoms particularly pruritus and pain, are very important parts of living with PSC and should be carefully evaluated** • There are effective interventions for pruritus that patients should be offered • Patient support groups are important
4. Survey for cancer smartly but honestly	**Cancer risk is heightened** • Cholangiocarcinoma (annual MRI?) • Gall bladder cancer (annual ultrasound?) • Colon cancer (annual colonoscopy if IBD present)
5. Think trials	**If PBC treatment can advance so dramatically so can PSC!** • Refer patients early for trial consideration • Appreciate how hard it is to prove the benefit of new therapies • Recognise we will have to have failures to succeed

A PSC-IBD Programme looks like this in an ideal world



Monitoring

Patient reported outcomes
Timing of transplantation
Cancer risk

Understanding

Communication
Information
Support

Research

Clinical trials
Risk stratification
Surrogate end-points

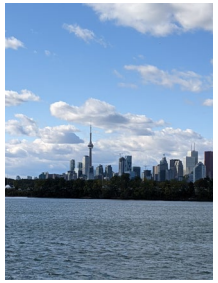
Quality of Care

Access
Expertise
Consistency

Hepatology 2018

Thank you!

TORONTO CENTRE FOR LIVER DISEASE



Gideon Hirschfield