Stratified Medicine in Primary Biliary Cirrhosis:
Understanding Disease Mechanisms and Targeting Therapies

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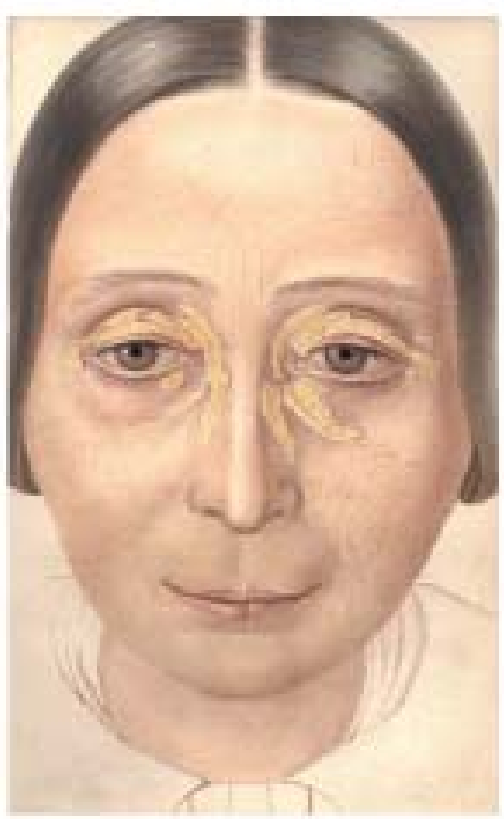
Newcastle University
PI UK-PBC Research Consortium

The Human Face of Primary Biliary Cirrhosis

Chronic Cholestasis



Addison & Gull *Guys Hospital Review 1857*

Features of End Stage Disease

Death

Jaundice
Coagulopathy
Encephalopathy
Ascites
Varices

Features Seen at all Stages

Reduced Quality of Life

Fatigue
Cognitive impairment (“dementia”)
Pruritus

Asymptomatic Disease

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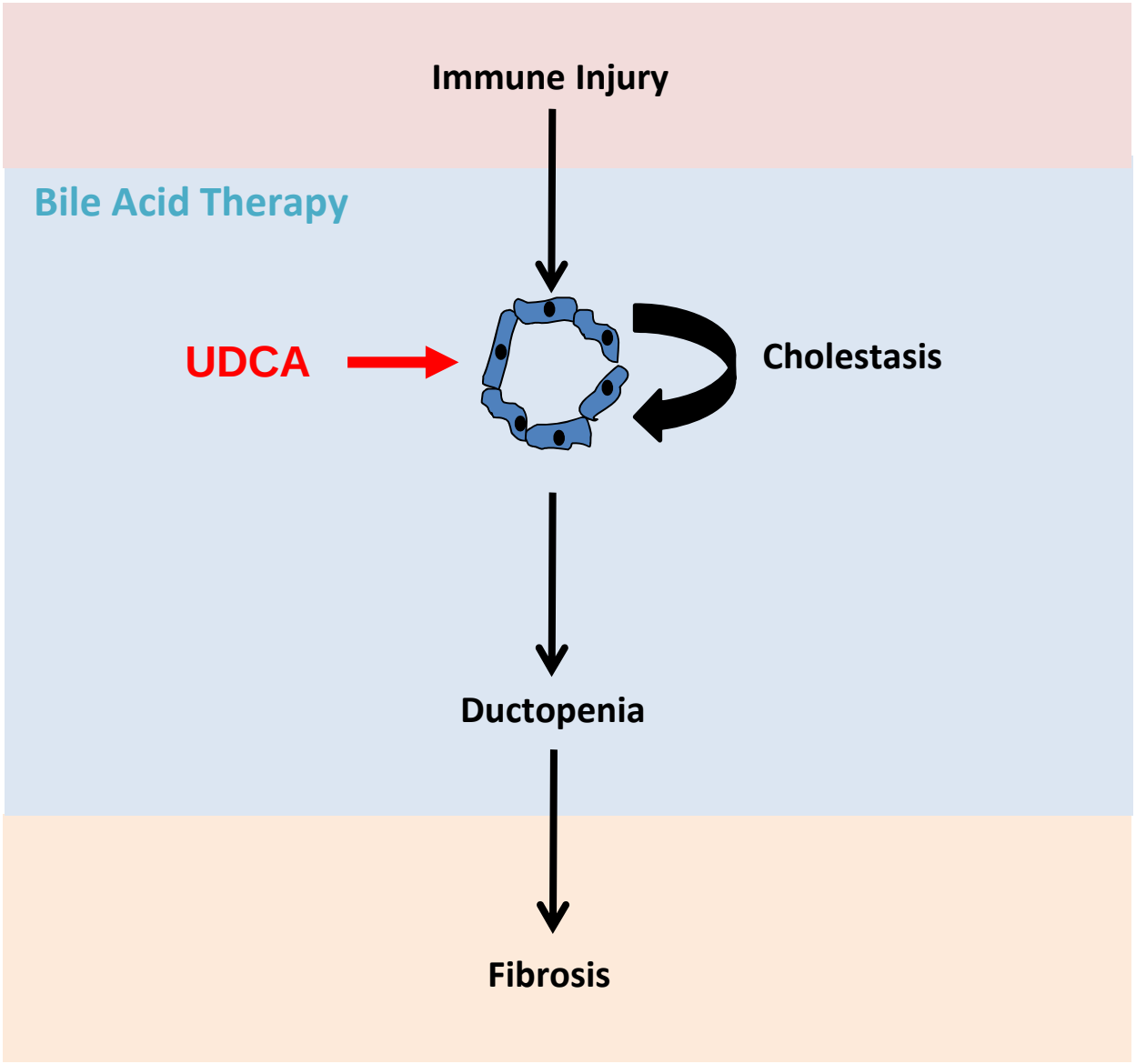
Pathogenetic & Therapeutic Model for PBC



A Case

37 Year old Woman

Profound fatigue, Alk Phos 630, ALT 122

AMA +ve at 1:320, ANA 1:80, liver biopsy showed stage 2 PBC

with marked interface hepatitis

Started UDCA

12 months later Alk Phos 488, ALT 987, bil 19, fatigued

Very worried about the future

Suboptimal Therapy in PBC—What Are the Potential Causes?

- Drugs are not as effective as we think they are and/or our biomarkers of response don’t accurately predict real response
- Effectiveness may not be as universal as we think it is
- Drugs are effective but we aren’t using them optimally
- Drugs are effective but aren’t actually getting to people
- Some combination of the above

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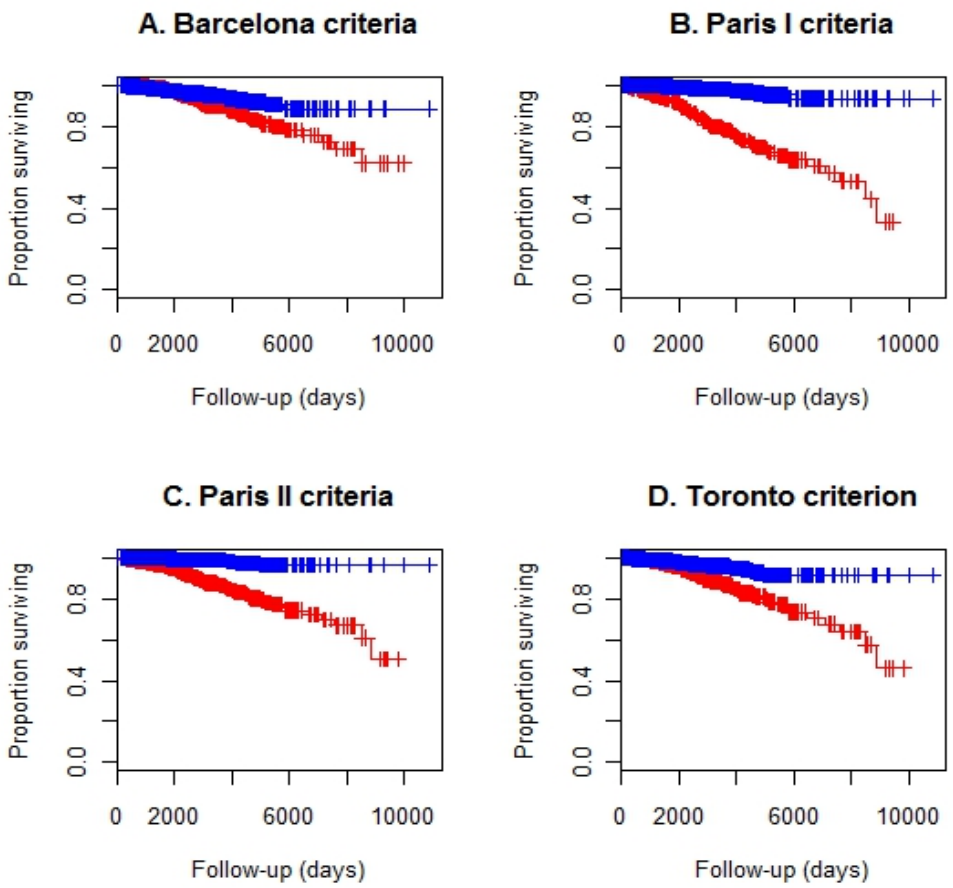
UDCA-Response Criteria in the UK-PBC Patient Cohort—Independent Validation



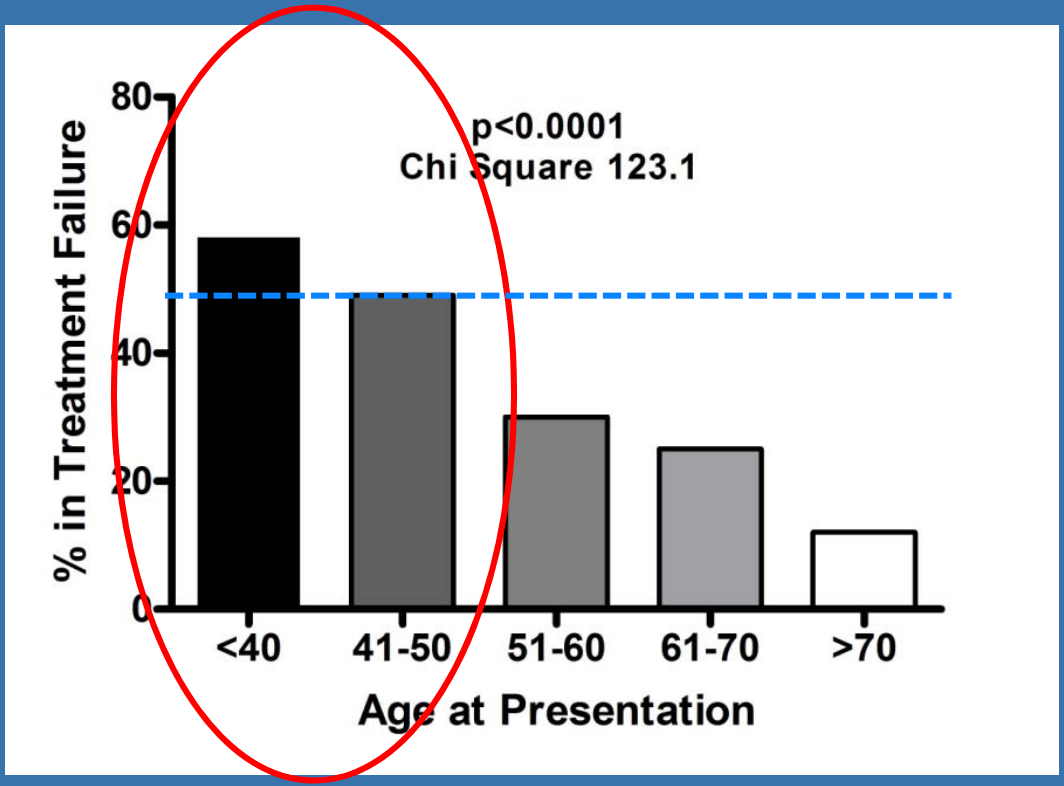
RESULTS: Log-rank test for time free from LT for PBC, PBC-related death or Bilirubin ≥ 100µmol/L

Criteria	Chi-square statistic	P-value
Barcelona	7.3	6.73E-03
Paris I	106	<1E-16
Toronto	24.2	8.78E-07
Paris II	45.7	1.40E-11

Responders
Nonresponders

Abbreviations: LT, liver transplant; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.
With permission from Carbone M, et al. *Gastroenterology*. 2013;144:560-569.e7.

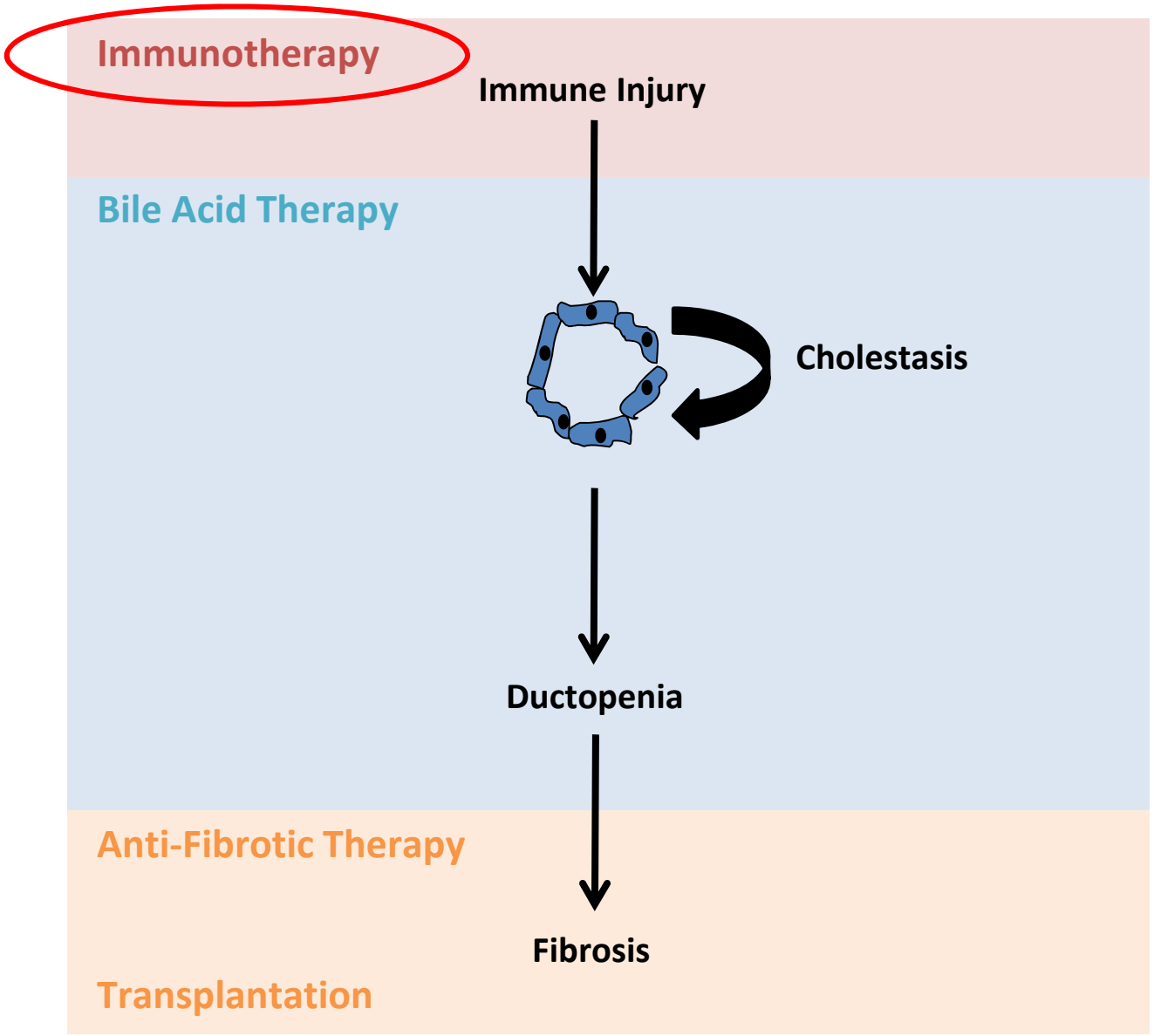
Treatment Failure in the UK-PBC Patient Cohort



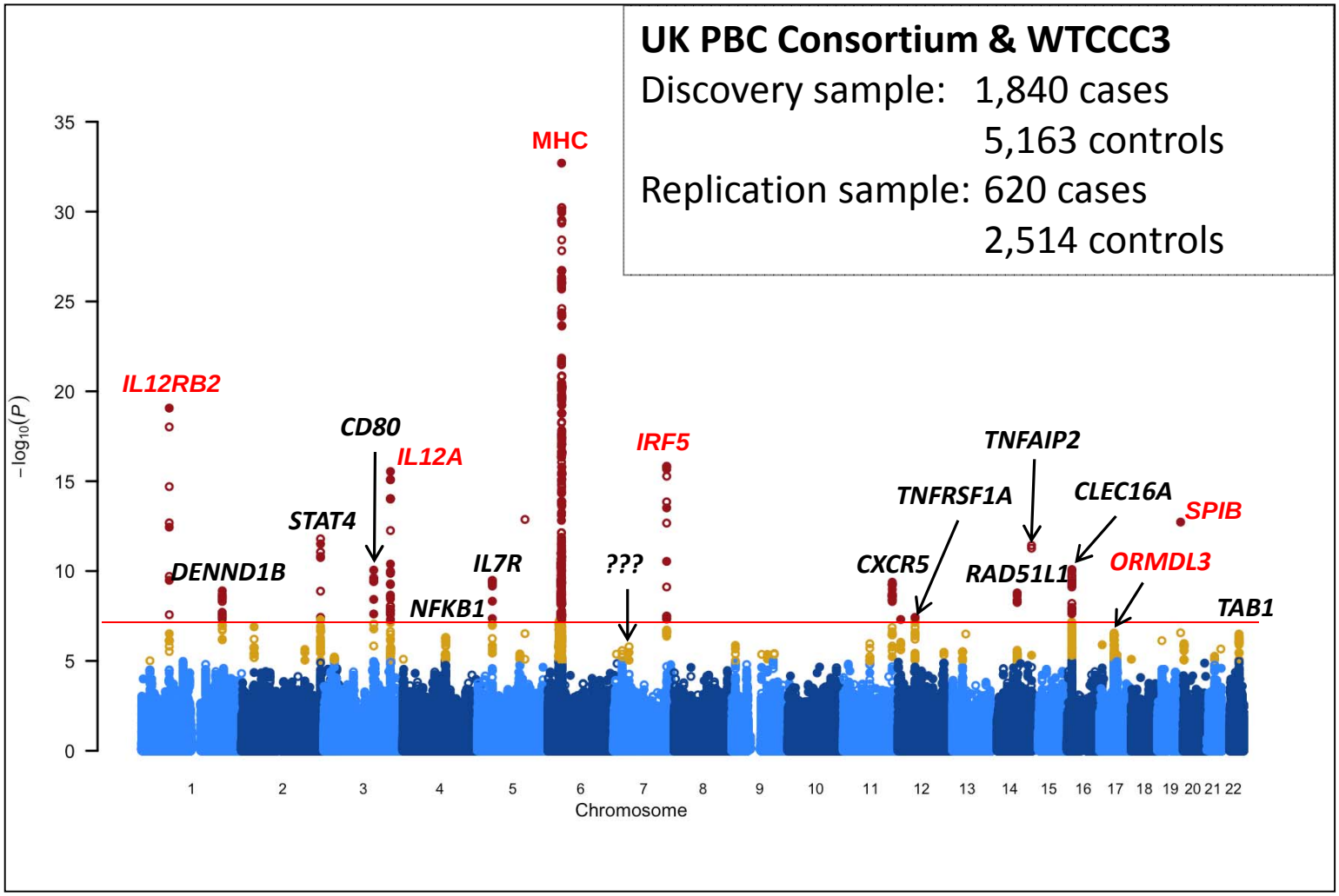
>50% of patients in the UK-PBC patient cohort who presented before the age of 50 have failed primary therapy (in a state of UDCA nonresponse or already transplanted) by the time of study

Pells G, et al. *J Hepatol.* 2013;59:67-73.

Pathogenetic & Therapeutic Model for PBC



Genome-wide association study identifies 12 new susceptibility loci for primary biliary cirrhosis



Mells et al Nature Genetics, 2011

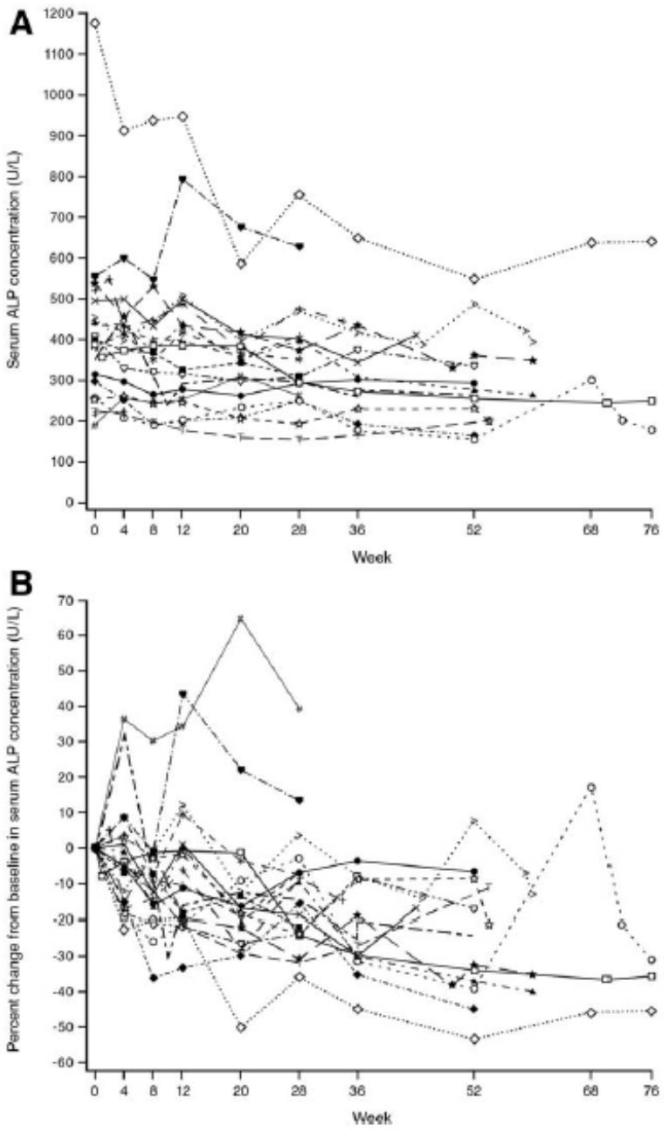


Fig. 1. Serum ALP levels (A) and percent change (B) over time through week 76 by patient among 20 treated patients. Key: U/L, units per liter.

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Ustekinumab for Patients With Primary Biliary Cholangitis Who Have an Inadequate Response to Ursodeoxycholic Acid: A Proof-of-Concept Study

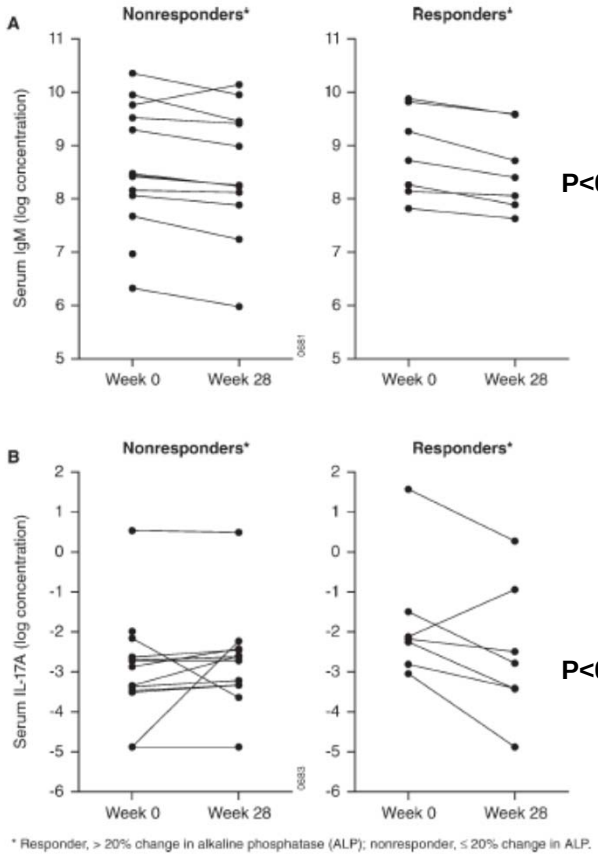
Gideon M. Hirschfield,[1] M. Eric Gershwin,[2] Richard Strauss,[3] Marlyn J. Mayo,[4] Cynthia Levy,[5] Bin Zou,[3] Jewel Johanns,[3] Ivo P. Nnane,[3] Bidisha Dasgupta,[3] Katherine Li,[3] Carlo Selmi,[6,7] Hanns-Ulrich Marschall,[8] David Jones,[9] and Keith Lindor[10]; for the PURIFI Study Group*

P<0.005

P<0.005

P=ns

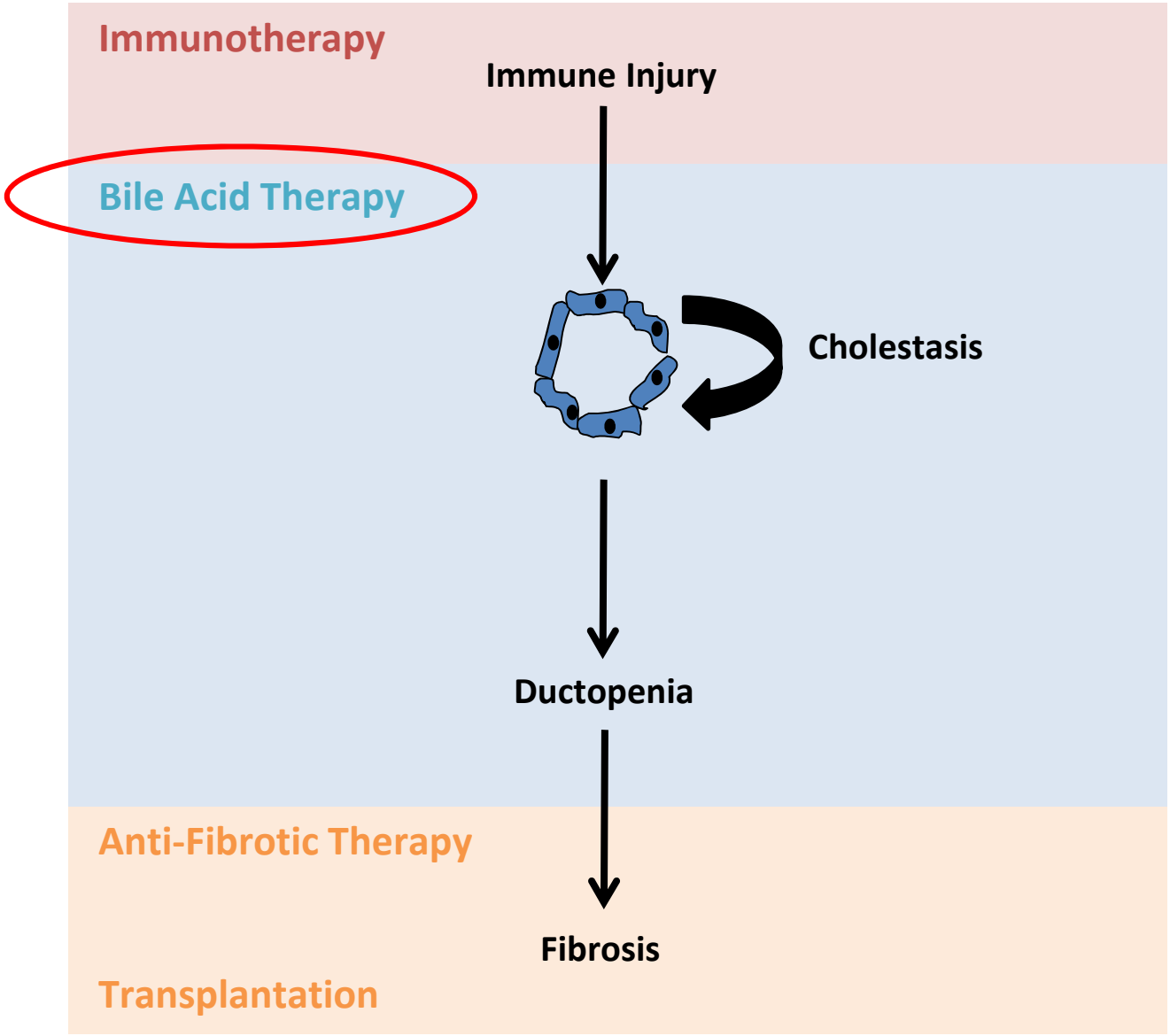
P<0.05



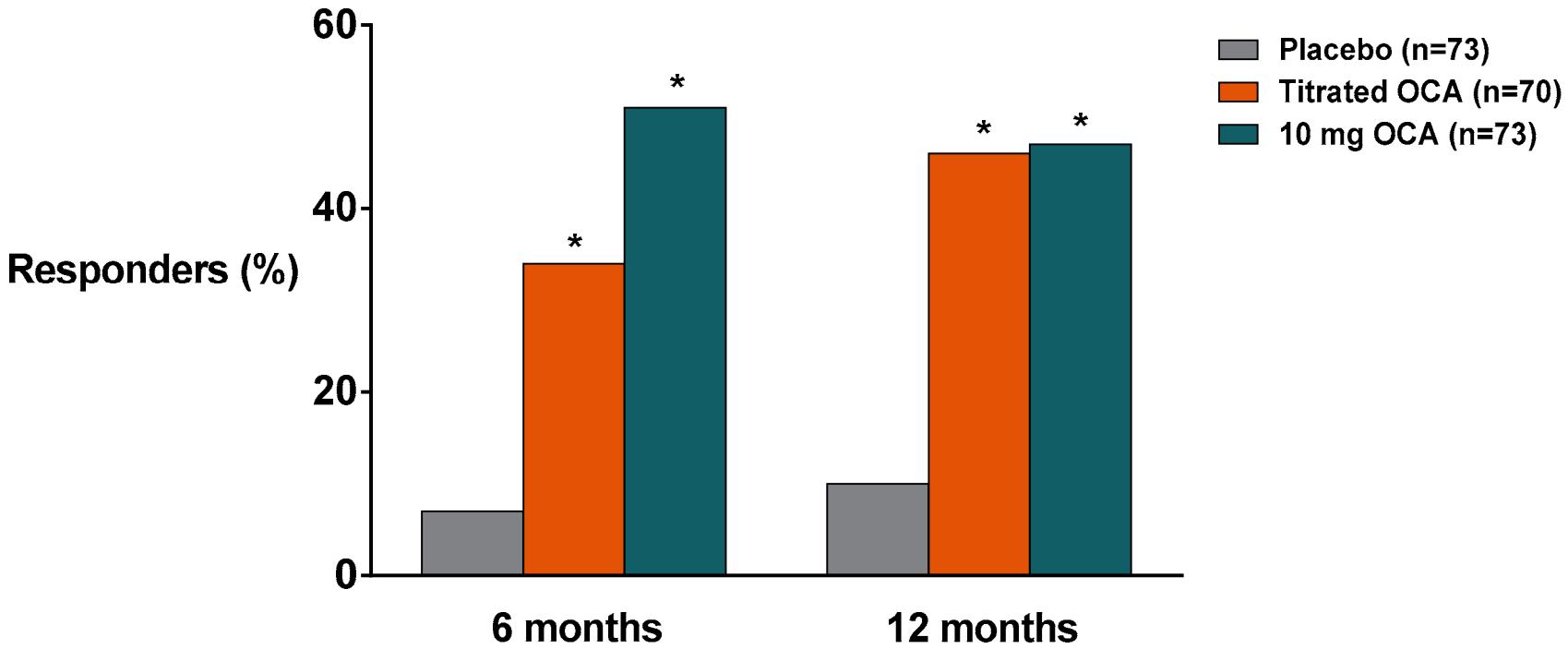
* Responder, > 20% change in alkaline phosphatase (ALP); nonresponder, ≤ 20% change in ALP.

Fig. 2. Serum IgM (A) and IL-17A (B) concentrations before and after ustekinumab treatment.

Pathogenetic & Therapeutic Model for PBC



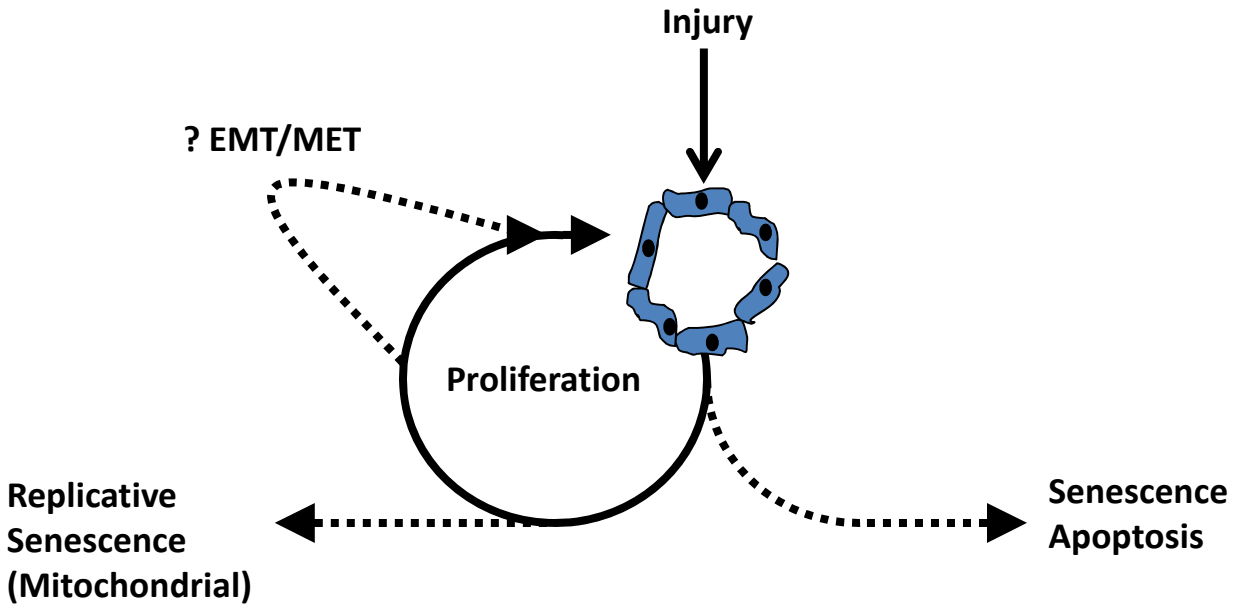
FXR-Agonism as a Therapeutic Option in PBC—Obeticholic Acid (INT-747)
Phase III Data (POISE)



Primary Endpoint:
Proportion of subjects achieving ALP <1.67 x ULN with bilirubin ≤ ULN and ≥15% reduction in ALP

**P* <.0001 vs placebo; *P*-values obtained using Cochran-Mantel-Haenszel stratified by randomization strata factor.
Abbreviations: ALP, alkaline phosphatase; FXR, farnesoid X receptor; OCA, obeticholic acid; PBC, primary biliary cirrhosis; ULN, upper limit of normal.
With permission from Nevens F, et al. *J Hepatol.* 2014:60(suppl): Abstract 0168.

Replicative Senescence as a Mechanism for Progressive BEC Loss in PBC



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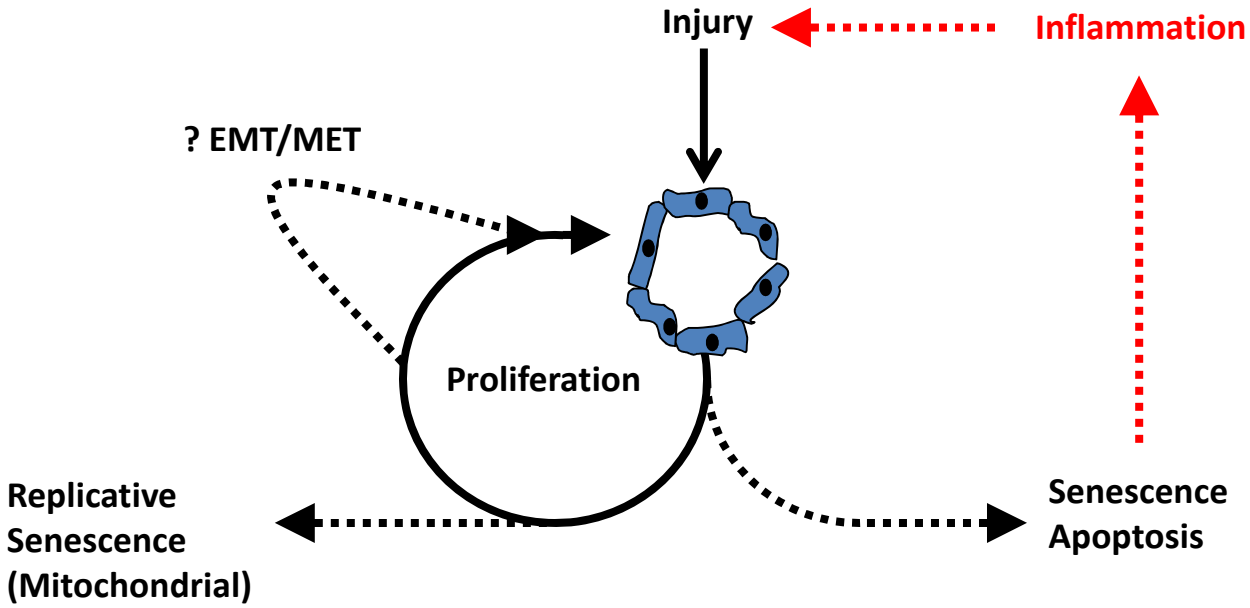
Jones Gut 2007

Replicative Senescence as a Mechanism for Progressive BEC Loss in PBC



The additional impact of the "***screaming epithelium***"

Key treatment targets

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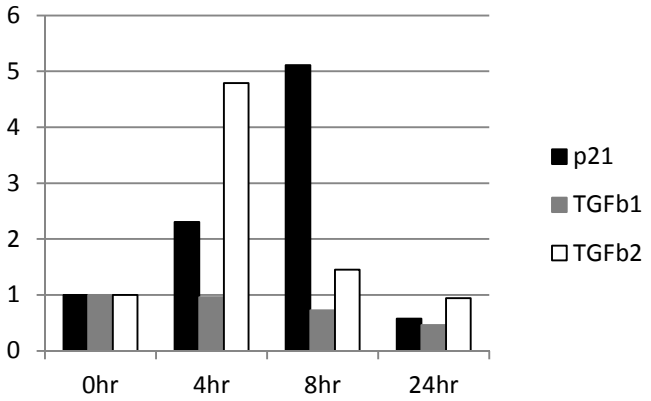
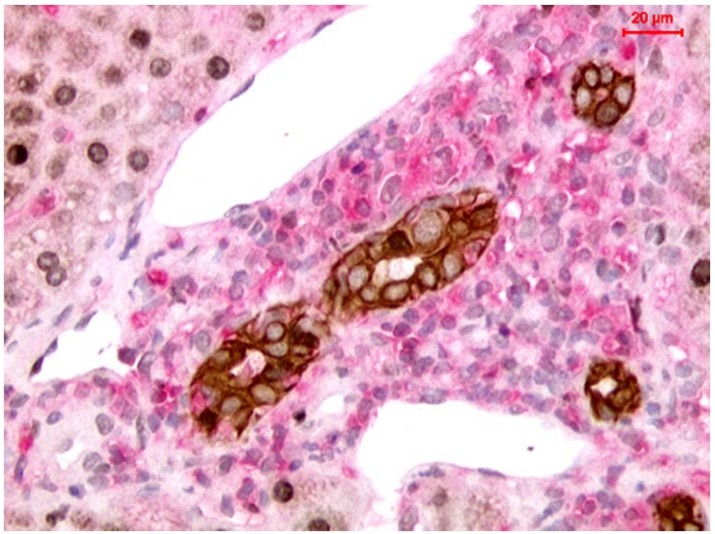
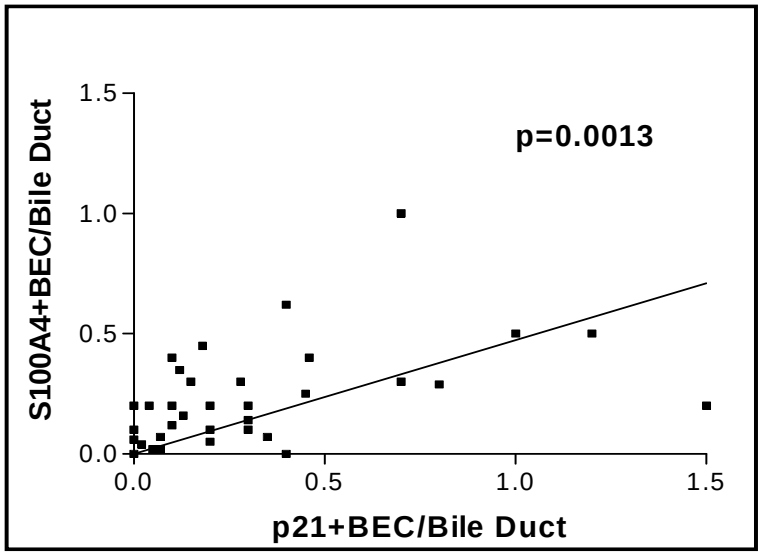
Jones Gut 2007

Stressed Cholangiocytes Express Senescence Markers and Lose Function







Pink= S100A4
Brown= CK19
Black= p21

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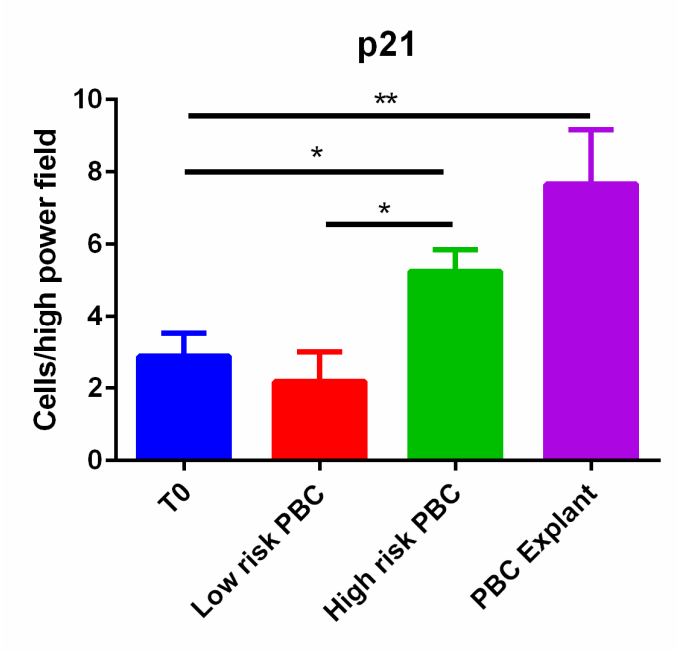
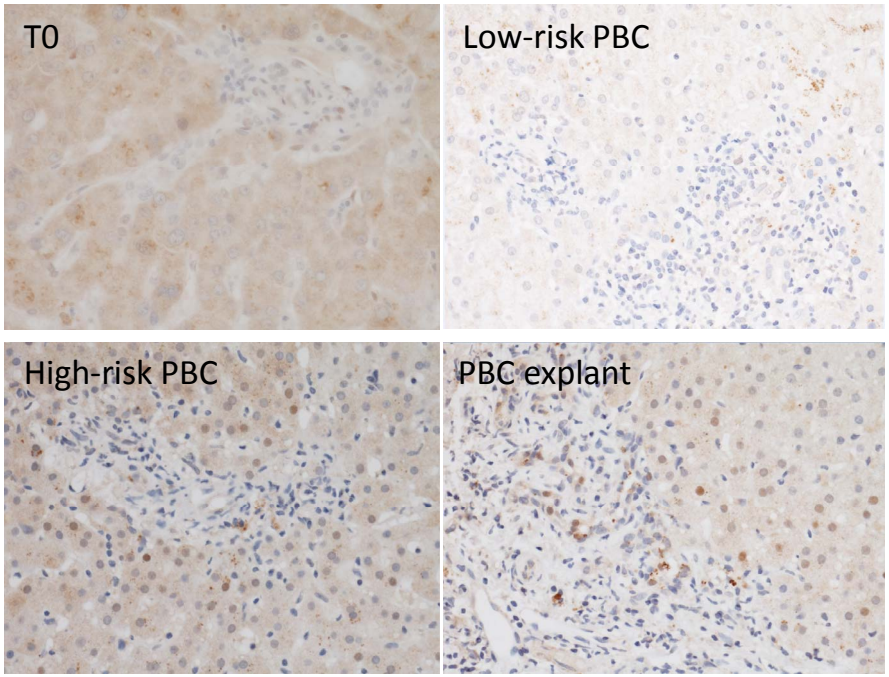
UK-PBC Pilot Data

Senescence and UDCA Non-Response in PBC





(X40 magnification)

ARTICLE

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International genome-wide meta-analysis identifies new primary biliary cirrhosis risk loci and targetable pathogenic pathways

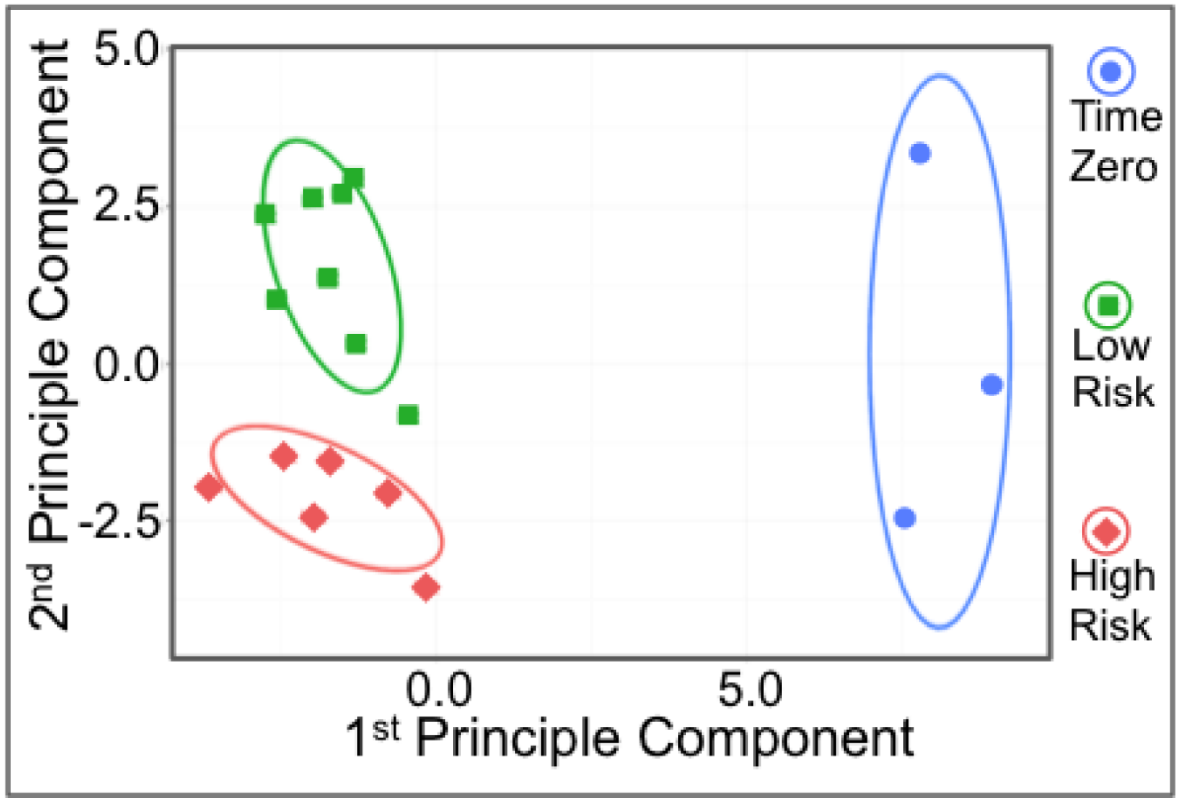
Heather J. Cordell[1], Younghun Han[2], George F. Mells[3], Yafang Li[2], Gideon M. Hirschfield[4], Casey S. Greene[5], Gang Xie[6], Brian D. Juran[7], Dakai Zhu[2], David C. Qian[2], James A.B. Floyd[8,9], Katherine I. Morley[8,10], Daniele Prati[11], Ana Lleo[12], Daniele Cusi[13,14], Canadian-US PBC Consortium[#], Italian PBC Genetics Study Group[#], UK-PBC Consortium[#], M. Eric Gershwin[15], Carl A. Anderson[8], Konstantinos N. Lazaridis[7], Pietro Invernizzi[12,15], Michael F. Seldin[15], Richard N. Sandford[3,*], Christopher I. Amos[2,*] & Katherine A. Siminovitch[6,16,17,18,*]

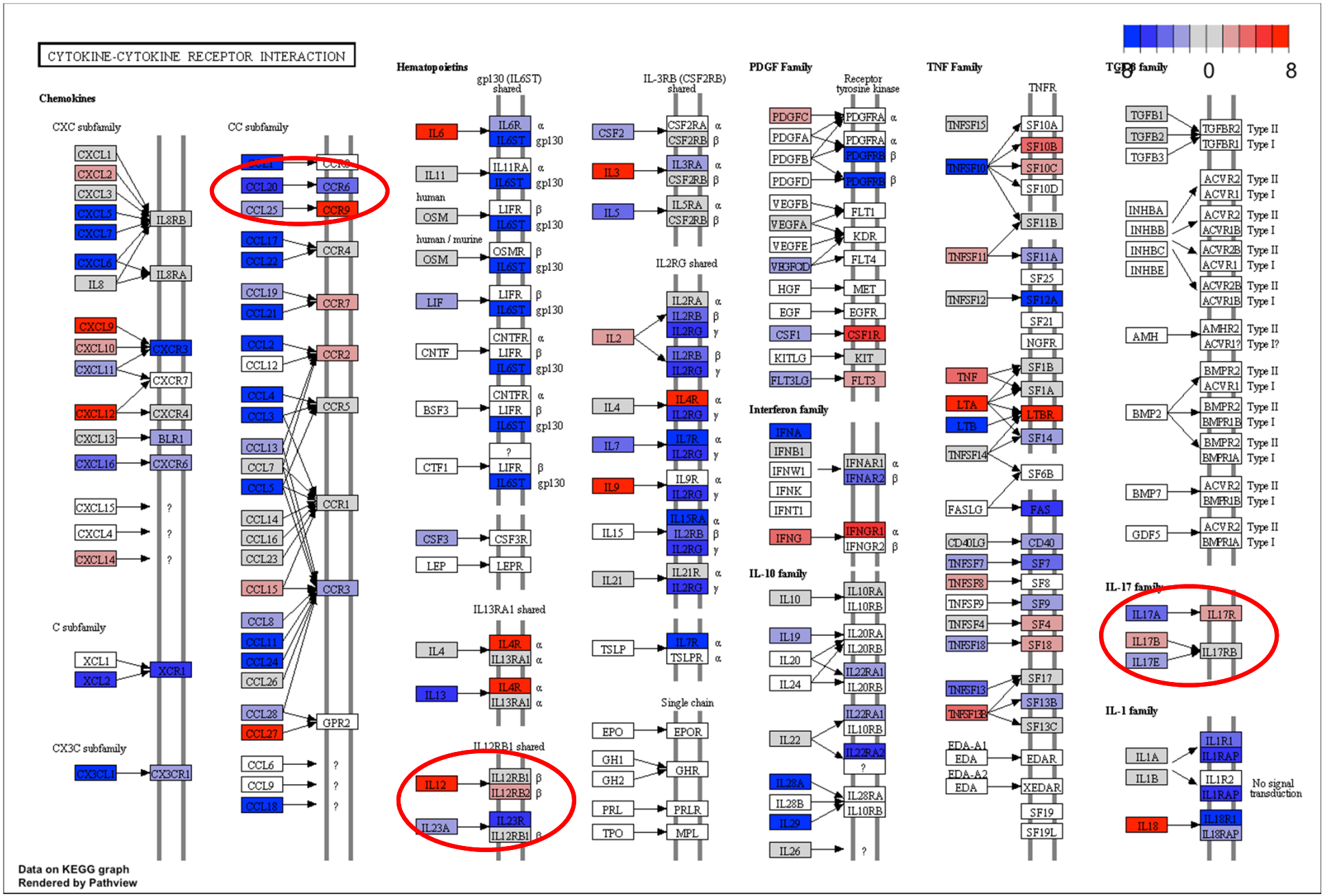
nature COMMUNICATIONS

Table 1 | PBC risk loci identified in the current study.

a. Confirmed risk loci (validation $P<4.4\times10^{-4}$ resulting in combined $P<5\times10^{-8}$)

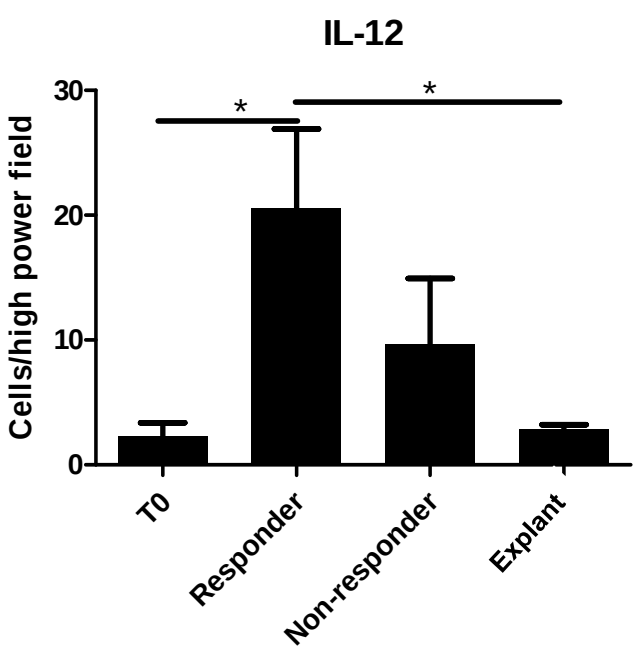
Locus	SNP	Position (build 38)	A1/A2	Discovery P	Validation P	Joint P	OR (95% CI)	Region (build 38)	Nearby genes and functional annotation*	Autoimmune overlap
2q12.1	rs12712133	102,249,813	A/G	1.62×10^{-5}	7.94×10^{-5}	5.19×10^{-9}	1.14 (1.07-1.21)	102,118,975-102,438,307	*IL1R1*, *IL1RL2*†, *FAM183DP*, *IL1RL1*‡, *IL18R1*, *LOC100422339*, *IL18RAP*, *MIR4772*	CD, CeD
2q36.3	rs4973341	227,795,646	C/T	6.48×10^{-7}	7.73×10^{-5}	2.34×10^{-10}	0.82 (0.74-0.90)	227,747,828-227,815,647	*RNA5SP121*, *SNRPGP8*, *LOC100533842*, *CCL20*†,§	
4p16.3	rs11724804	971,991	A/G	3.67×10^{-7}	4.25×10^{-6}	9.01×10^{-12}	1.22 (1.12-1.33)	853,681-1,014,424	*GAK*, *TMEM175*, *DGKQ*†, *SLC26A1a*, *IDUA*, *FGFRL1*	
5q21.1	rs526231	103,345,680	T/C	3.10×10^{-5}	9.39×10^{-5}	1.14×10^{-8}	0.87 (0.81-0.93)	102,939,698-103,416,571	*PAM*§, *EIF3KP1*, *GIN1*, *PPIP5K2*, *C5orf30*‡,§	RA
5q33.3	rs2546890	159,332,892	G/A	1.20×10^{-6}	1.89×10^{-5}	1.06×10^{-10}	0.87 (0.82-0.93)	159,117,927-159,414,310	*RNF145*, *UBLCP1*, *RNU4ATAC2P*, *IL12B*, *LOC285626*†	Pso, MS, CD
6q23.3	rs6933404	137,638,098	C/T	9.47×10^{-7}	2.84×10^{-5}	1.27×10^{-10}	1.18 (1.09-1.27)	137,571,557-137,803,754	*LOC102723649*, *LOC442263*, *OLIG3*†, *TNFAIP3*†	RA, SLE, SjS, CeD, UC, MS

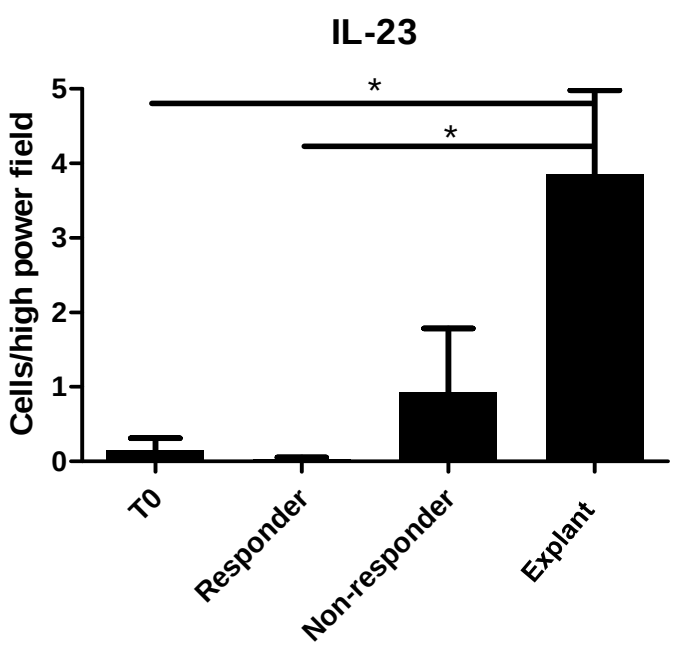

5.0
2.5
0.0
-2.5
2nd Principle Component
0.0
5.0
1st Principle Component
Time Zero
Low Risk
High Risk



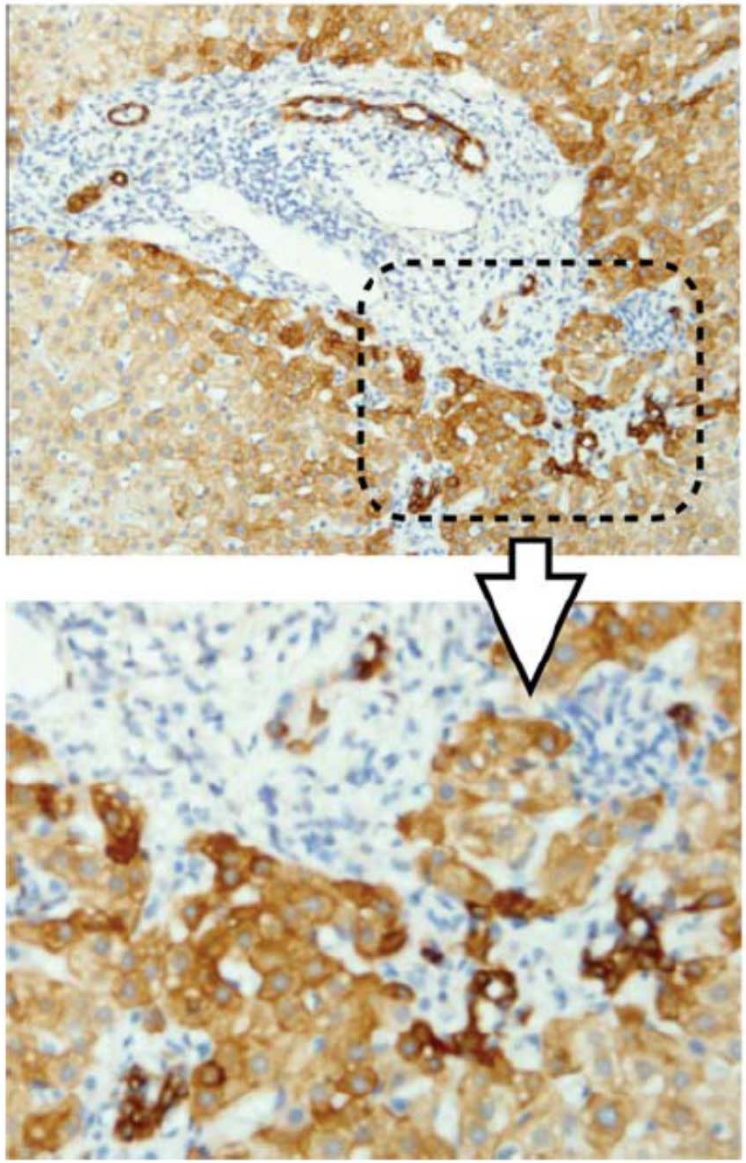
UK-PBC Work in Progress

Th1 and Th17 in UDCA Responsive and Unresponsive PBC



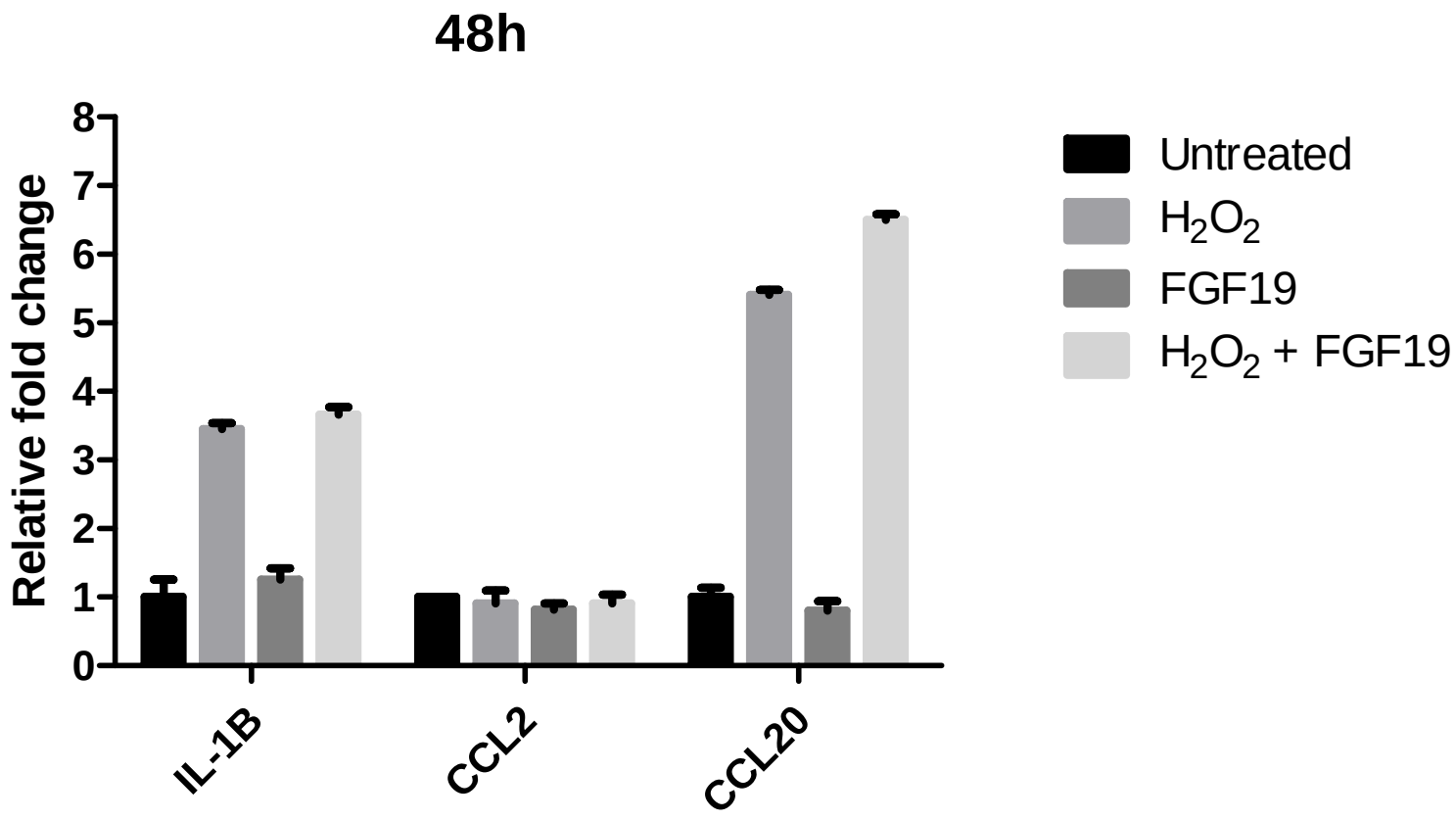


IL-23 is of Cholangiocyte Origin in PBC



Yang et al: **Hepatology** 2014

BEC Stress Causes CCL20 Upregulation not Ameliorated by FGF19



Challenges for Trial Design for Stratified Therapy in PBC

- Definition of the “at-risk” population requiring enhanced therapy
- Outcome measures (do UDCA response criteria apply to other therapies?)
- Lack of relevant biomarkers
- Impossibility of carrying out a hard endpoints trial due to prolonged disease
- Difficulty in performing a histology-based trial (acceptability and lack of scoring systems)
- “Phasing”/Combination of therapy use

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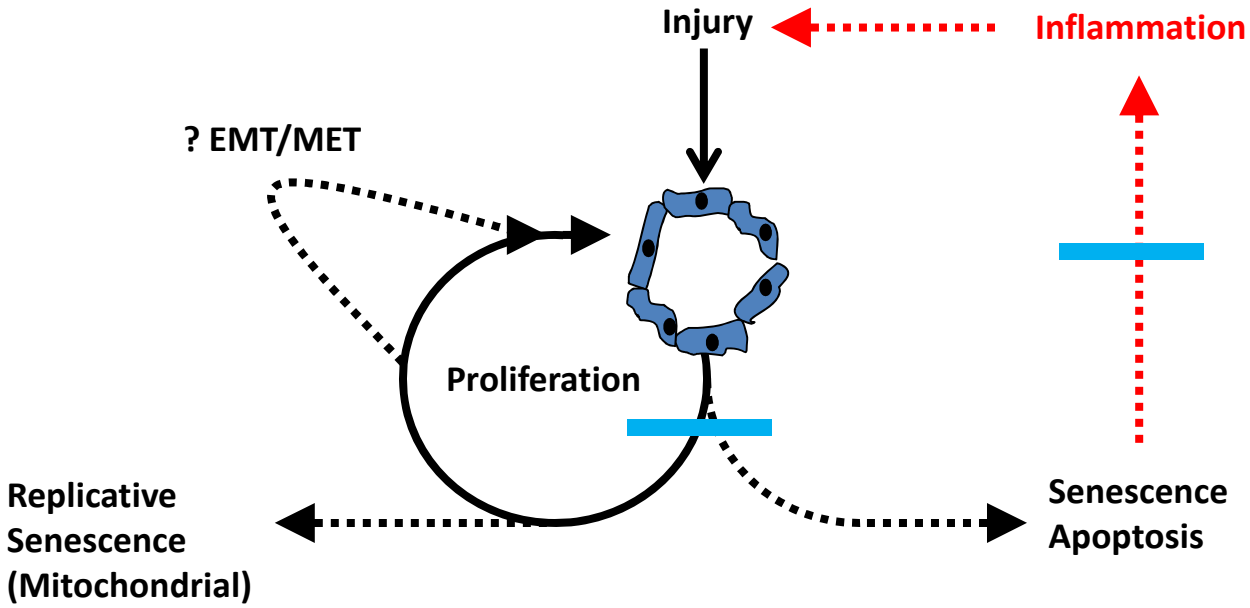
Replicative Senescence as a Mechanism for Progressive BEC Loss in PBC



The additional impact of the "***screaming epithelium***"

Key treatment targets

PBC: Time for Combination Therapy?

Newcastle University

Jones Gut 2007

MRC Medical Research Council

Newcastle University