INSELGRUPPE

IBAT and Other Transporters Involved in BA Transport

15.05.2024 Bible Class Gastroenterology

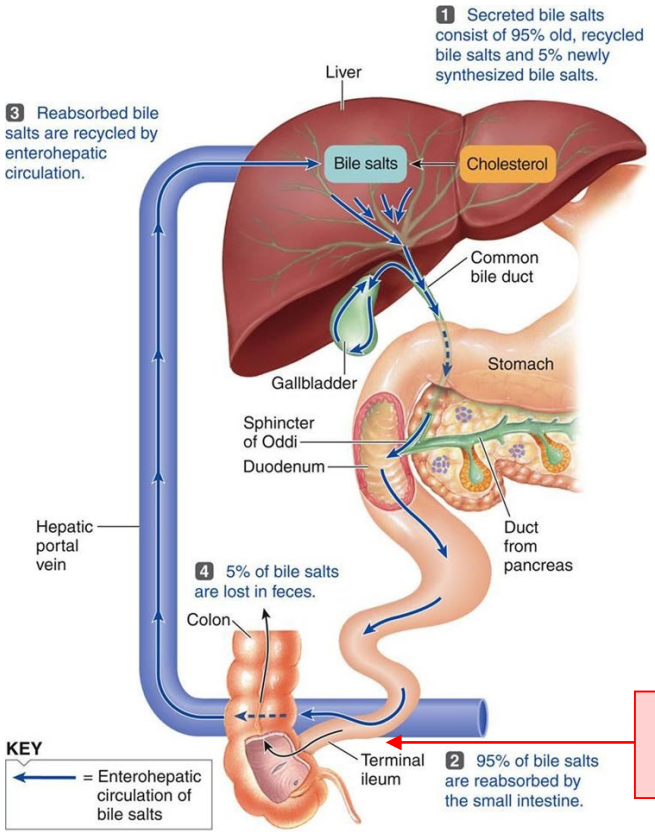
PD Dr. med. Guido Stirnimann

INSELGRUPPE

How big is the bile acids pool in humans?

What is the fraction of reabsorption of bile acids in the ileum?

Enterohepatic Circulation of Bile Acids



Bile acid pool 2-4 g

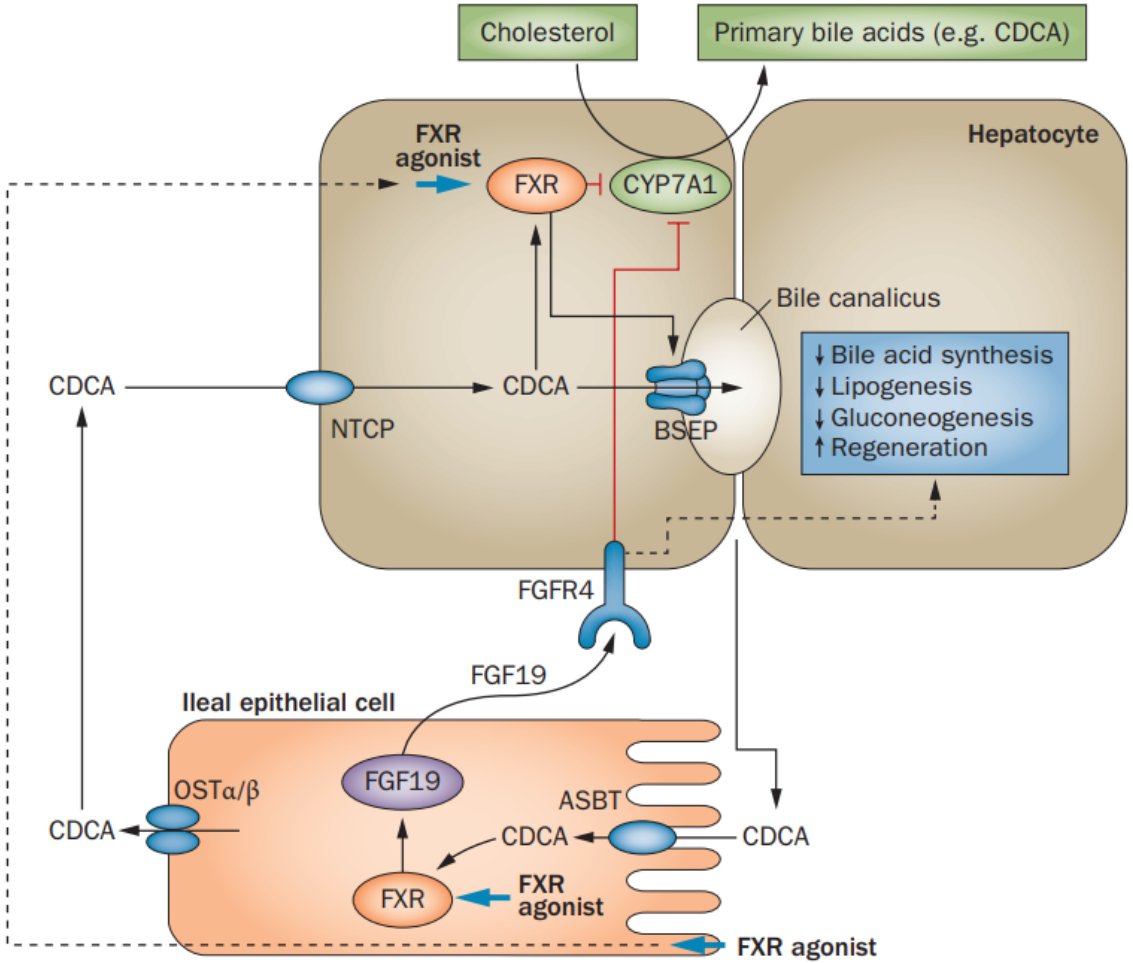
Bile storage
- Gallbladder

Active transport
- Bile salt pumps

apical sodium–bile acid transporter (*ASBT*)

INSELGRUPPE

How are bile acids regulated?



Schaap, F. G. et al. Nat. Rev. Gastroenterol. Hepatol. 11, 55–67 (2014)

INSELGRUPPE

Which transporters are important for bile acids?

IBAT/ASBT: Ileum (BA uptake in enterocyte)

NTCP: Liver (BA uptake in hepatocyte)

BSEP: Liver (BA export pump)

ASBT: Kidney (BA uptake in proximal renal tubule cells)

INSELGRUPPE

Does IBAT inhibition affect transplant free survival in PFIC patients?

Maralixibat for the treatment of PFIC: Long-term, IBAT inhibition in an open-label, Phase 2 study

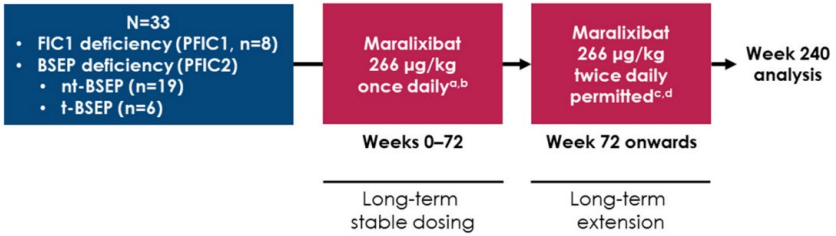
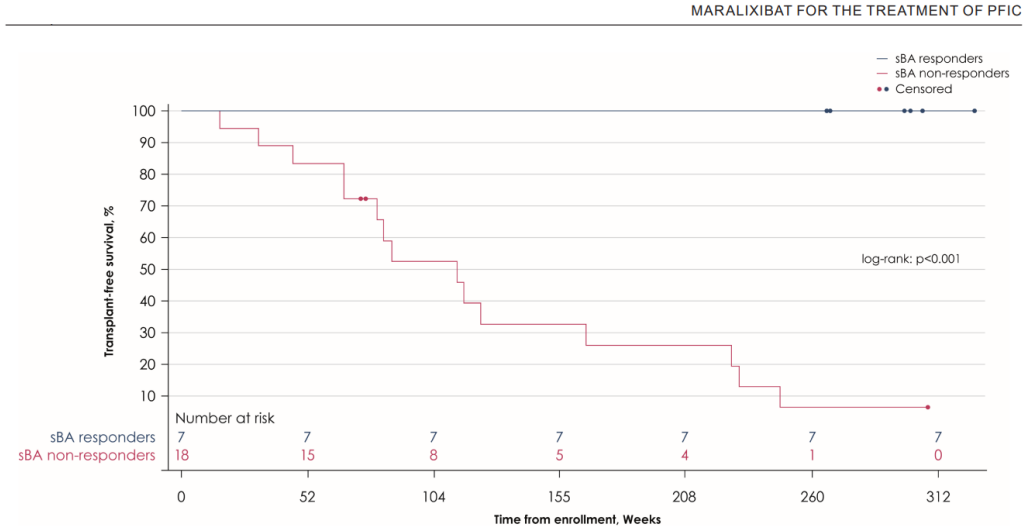


TABLE 1 Patient demographics and characteristics at baseline

	FIC1 deficiency (*n* = 8)	t-BSEP (*n* = 6)	nt-BSEP (*n* = 19)	All BSEP deficiency[a] (*n* = 25)	Overall (*n* = 33)
Median age, years (range)	2.0 (1.0, 7.0)	7.0 (1.0, 10.0)	3.0 (1.0, 13.0)	4.0 (1.0, 13.0)	3.0 (1.0, 13.0)
Male, *n* (%)	6 (75.0)	2 (33.3)	6 (31.6)	8 (32.0)	14 (42.4)
Mean sBAs, µmol/L (SD)	261.8 (99.57)	404.9 (112.40)	373.4 (161.95)	380.9 (149.97)	352.1 (147.40)
Mean ItchRO(Obs) score (SD)	2.1 (0.75)	2.9 (0.68)	2.1 (0.85)	2.3 (0.86)	2.3 (0.83)
PedsQL score (SD)	57 (18.7)	65 (17.7)	62 (12.8)	63 (13.8)	61 (15.1)
Mean ALT, U/L (SD)	56 (29.7)	152 (151.0)	116 (109.2)	125 (118.0)	108 (107.4)
Mean AST, U/L (SD)	77 (23.8)	206 (167.3)	148 (165.1)	162 (164.0)	141 (147.2)
Mean total bilirubin, mg/dl (SD)	5.5 (5.13)	2.9 (1.50)	1.8 (1.78)	2.1 (1.75)	2.9 (3.20)
Mean direct bilirubin, mg/dl (SD)	4.0 (3.67)	2.3 (1.30)	1.4 (1.33)	1.6 (1.36)	2.2 (2.33)



Hepatology Communications. 2022;6:2379–2390

INSELGRUPPE

Blocking of IBAT is associated with what type of adverse reactions?

INSELGRUPPE

	Placebo (n=20)	Odevixibat 40 µg/kg per day (n=23)	Odevixibat 120 µg/kg per day (n=19)	Odevixibat, all doses (n=42)
Any TEAE	17 (85%)	19 (83%)	16 (84%)	35 (83%)
Mild	6 (30%)	11 (48%)	8 (42%)	19 (45%)
Moderate	9 (45%)	7 (30%)	6 (32%)	13 (31%)
Severe	2 (10%)	1 (4%)	2 (11%)	3 (7%)
Serious TEAEs	5 (25%)	0	3 (16%)	3 (7%)
TEAEs leading to discontinuation	0	0	1 (5%)	1 (2%)
Liver-related TEAEs*	4 (20%)	5 (22%)	6 (32%)	11 (26%)
TEAEs occurring in ≥5% of patients overall, by preferred term				
Diarrhoea or frequent bowel movements	2 (10%)	9 (39%)	4 (21%)	13 (31%)
Pyrexia	5 (25%)	7 (30%)	5 (26%)	12 (29%)
Upper respiratory tract infection	3 (15%)	3 (13%)	5 (26%)	8 (19%)
Vomiting	0	4 (17%)	3 (16%)	7 (17%)
ALT increased	1 (5%)	3 (13%)	3 (16%)	6 (14%)
Total bilirubin increased	2 (10%)	3 (13%)	2 (11%)	5 (12%)
Abdominal pain	0	2 (9%)	1 (5%)	3 (7%)
AST increased	1 (5%)	2 (9%)	1 (5%)	3 (7%)
Blood ALP increased	1 (5%)	1 (4%)	2 (11%)	3 (7%)
Nasopharyngitis	1 (5%)	1 (4%)	2 (11%)	3 (7%)
Pruritus	1 (5%)	2 (9%)	1 (5%)	3 (7%)
Cough	3 (15%)	0	2 (11%)	2 (5%)
Urinary tract infection	3 (15%)	1 (4%)	1 (5%)	2 (5%)
Epistaxis	1 (5%)	1 (4%)	1 (5%)	2 (5%)
Viral upper respiratory tract infection	1 (5%)	2 (9%)	0	2 (5%)
Vitamin D deficiency	1 (5%)	0	2 (11%)	2 (5%)
Blood creatine phosphokinase increased	2 (10%)	0	1 (5%)	1 (2%)
Influenza	2 (10%)	0	1 (5%)	1 (2%)
Scratch	2 (10%)	1 (4%)	0	1 (2%)
Constipation	4 (20%)	0	0	0
Rash	3 (15%)	0	0	0
Drug-related TEAEs	3 (15%)	7 (30%)	7 (37%)	14 (33%)
Drug-related TEAEs occurring in ≥5% of patients overall, by preferred term				
ALT increased	1 (5%)	2 (9%)	2 (11%)	4 (10%)
AST increased	1 (5%)	2 (9%)	1 (5%)	3 (7%)
Total bilirubin increased	1 (5%)	2 (9%)	2 (11%)	4 (10%)
Diarrhoea or frequent bowel movements	1 (5%)	2 (9%)	2 (11%)	4 (10%)

Data are patients, n (%). TEAE=treatment-emergent adverse event. ALT=alanine aminotransferase. AST=aspartate aminotransferase. ALP=alkaline phosphatase. *Study investigators were asked to indicate which reported events were considered liver related; the most commonly reported liver-related TEAEs were increased ALT (7% [n=3/42] with odevixibat vs 0% [n=0/20] with placebo) and increased blood bilirubin (5% [n=2/42] with odevixibat vs 5% [n=1/20] with placebo).

Table 2: **Summary of adverse events during the double-blind treatment period**

Lancet Gastroenterol Hepatol 2022; 7: 830–42

INSELGRUPPE

What is the name of the other approved IBAT inhibitor?

What is the indication for this IBAT inhibitor?

INSELGRUPPE

Marilixibat

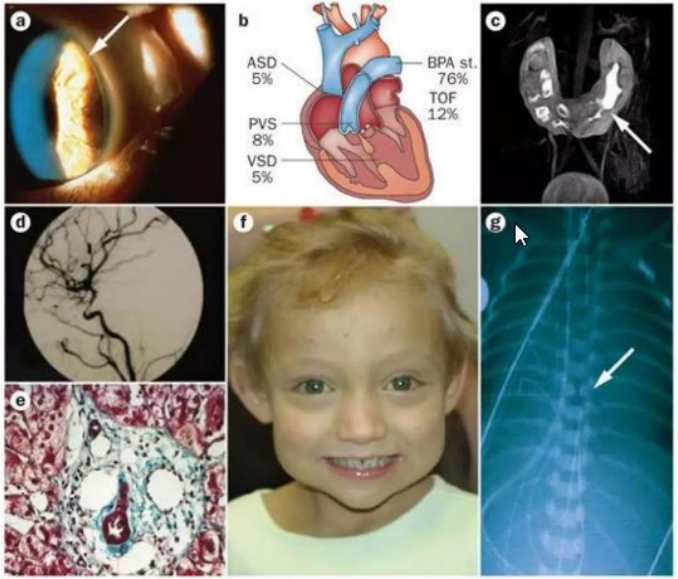
Alagille Syndrome

INSELGRUPPE

What are the characteristics of Alagille Syndrome?

INSELGRUPPE

Alagille Syndrome

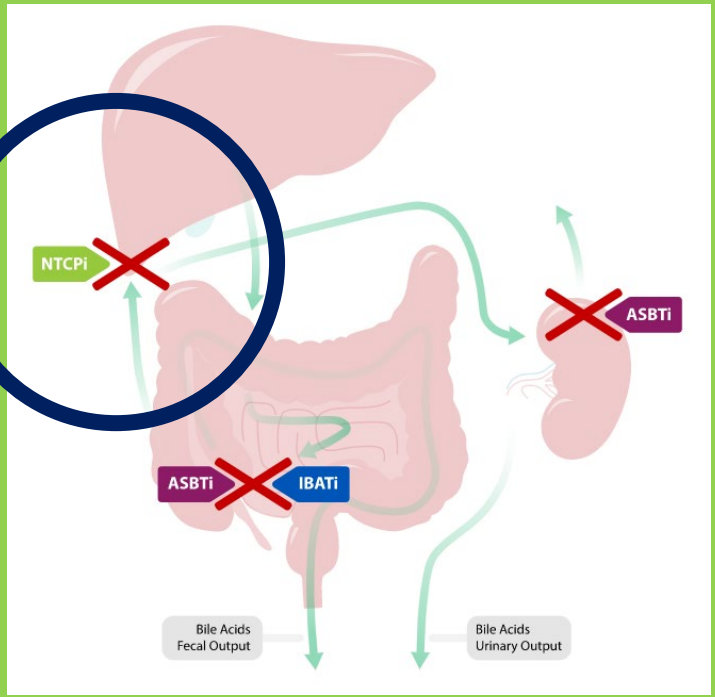


Nat Rev Nephrol 9, 409–418 (2013).

Inheritance	Autosomal dominant
Incidence estimate	1/30 000 to 1/50 000 live births[22]
Genetics	• Mutations or deletions in *JAGGED1* or *NOTCH2*, with mutations in *JAGGED1* most common[23,24]
Mechanisms of disease and pathophysiology underlying cholestasis	• Abnormal development of intrahepatic bile ducts and bile duct paucity[17,27]
Clinical presentation	• ALGS is not fully penetrant (genetic confirmation necessary)[10,11] • Cholestasis is common (typically presents within 3 mo of birth); usually diagnosed by age 1[9,10] • Other clinical characteristics may include elevated serum bile acids, pruritus, delayed growth, distinctive facial features, renal symptoms, xanthomas and vascular anomalies[9,21]
Disease progression	• Estimated 10-y survival rate among patients with ALGS born between January 1997 and May 2019:93% a. Native liver survival of this cohort: 70%[28]

Liver International. 2020;40:1812–1822.

INSELGRUPPE



albireopharma.com

INSELGRUPPE

Which transporters are involved in BRIC/PFIC?

INSELGRUPPE

Canalicular transporters and canalicular

Canalicular transporter (synonym)	Canalicular transport defect (synonym)	Disease characteristics	Biochemical and histological characteristics	Disease associated with heterozygous canalicular transport defect
ATP8B1 (FIC1)	**ATP8B1 deficiency** (FIC1 disease, PFIC1, Byler disease and Greenland familial cholestasis, BRIC1, Tygstrup-Summerskill and Walshe cholestasis)	Spectrum of intrahepatic cholestasis comprising PFIC1 and BRIC1 **PFIC1**: progressive intrahepatic cholestasis, pruritus and in some patients extrahepatic symptoms **BRIC1**: episodic cholestasis, pruritus and in some patients extrahepatic symptoms. In between episodes no symptoms	High serum bile salts but low GGT concentrations. Liver biopsy: bland cholestasis with coarse and granular bile	ICP
ABCB11 (BSEP)	**ABCB11 deficiency** (PFIC2, BRIC2)	Spectrum of intrahepatic cholestasis comprising PFIC2 and BRIC2 **PFIC2**: progressive intrahepatic cholestasis, pruritus and in some patients cholelithiasis **BRIC2**: episodic cholestasis, pruritus and in some patients cholelithiasis. In between episodes no symptoms	High serum bile salts but low GGT concentrations. Liver biopsy: portal-tract fibrosis, bile duct proliferation and amorphous canalicular bile	ICP, drug induced cholestasis, transient neonatal cholestasis
ABCB4 (MDR3)	**ABCB4 deficiency** (PFIC3)	Progressive intrahepatic cholestasis, high serum GGT concentrations. Pruritus less prominent	High serum bile salts and high GGT concentrations. Liver biopsy: fibrosis and marked bile duct proliferation	ICP, drug induced cholestasis, transient neonatal cholestasis LPAC
ABCC2 (MRP2)	**Dubin Johnson syndrome**	Asymptomatic but in some patients gastrointestinal symptoms	High serum conjugated bilirubin concentrations. Liver biopsy: dark blue or black due to pigmentation	
ABCG5/8	**Sitosterolemia**	Xanthomas, arthralgias and premature coronary artery disease	High serum sitosterols with relatively low cholesterol concentration. Liver biopsy: unknown	

PFIC, progressive familial intrahepatic cholestasis; BRIC, benign recurrent intrahepatic cholestasis; GGT, gamma-glutamyl transpeptidase; ICP, intrahepatic cholestasis of pregnancy; LPAC, low-phospholipid associated cholelithiasis syndrome.

Stapelbroek et al. Journal of Hepatology 2010.52:258–271

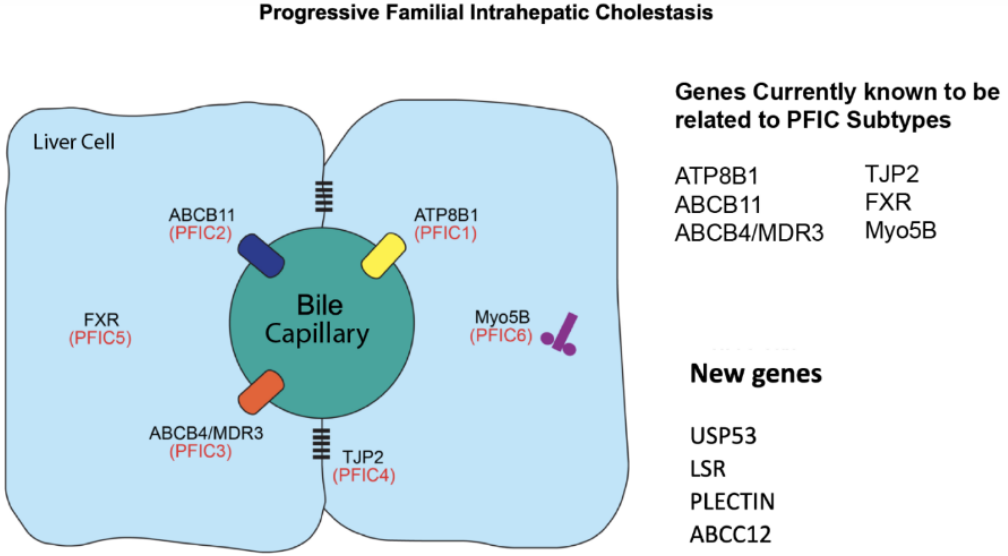
INSELGRUPPE

Are there new PFIC types around?

INSELGRUPPE

PFIC (group of disorders)

- PFIC 4 is caused by the loss of function of tight junction protein 2 (TJP2)
- PFIC 5 is due to NR1H4 mutation causing Farnesoid X receptor deficiency.
- PFIC6: MYO5B gene mutation causes microvillous inclusion disease (MVID) and is also associated with isolated cholestasis.

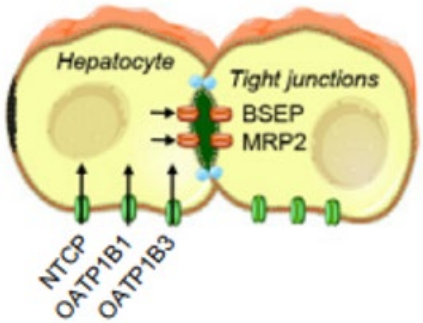


	PFIC 1	PFIC 2	PFIC 3	PFIC 4	PFIC 5	PFIC 6	PFIC (kein #)
Protein	FIC 1	BSEP	MDR3	TJP2	FXR	MYO5B	USP53
Mutiertes Gen	*ATP8B1*	*ABCB11*	*ABCB4*	*TJP2*	*NR1H4*	*MYO5B*	*USP53*

PFIC.org

INSELGRUPPE

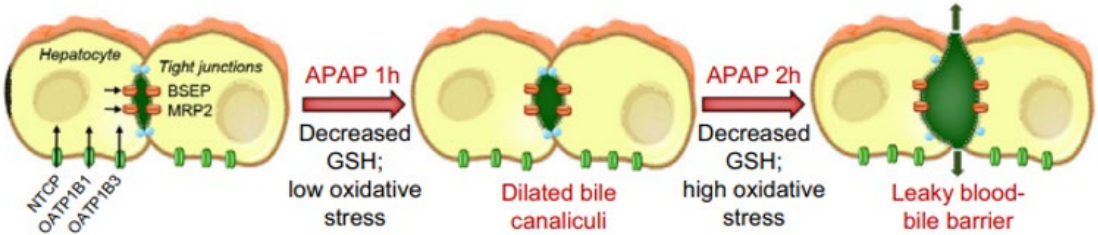
Which transporters are important for BA transport into and out of the hepatocytes?



Ghallab, Hengstler et al. Journal of Hepatology.2022: 71–83

INSELGRUPPE

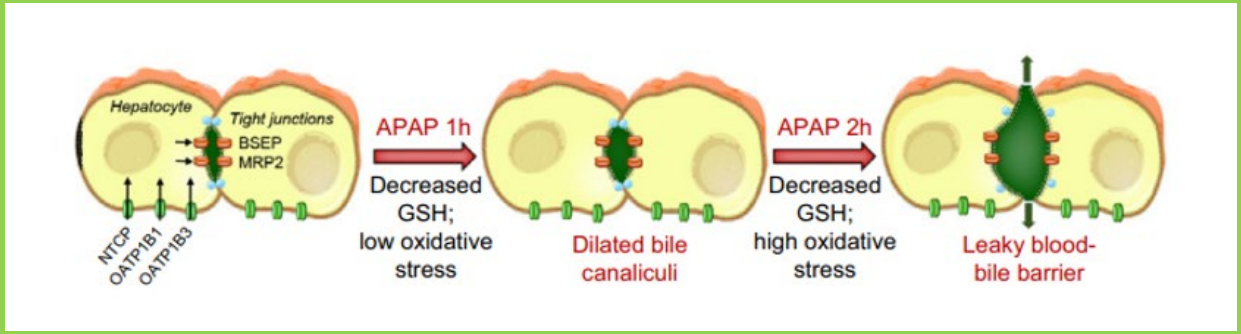
What happens in APAP (paracetamol) toxicity in the liver?



Ghallab, Hengstler et al. Journal of Hepatology.2022: 71–83

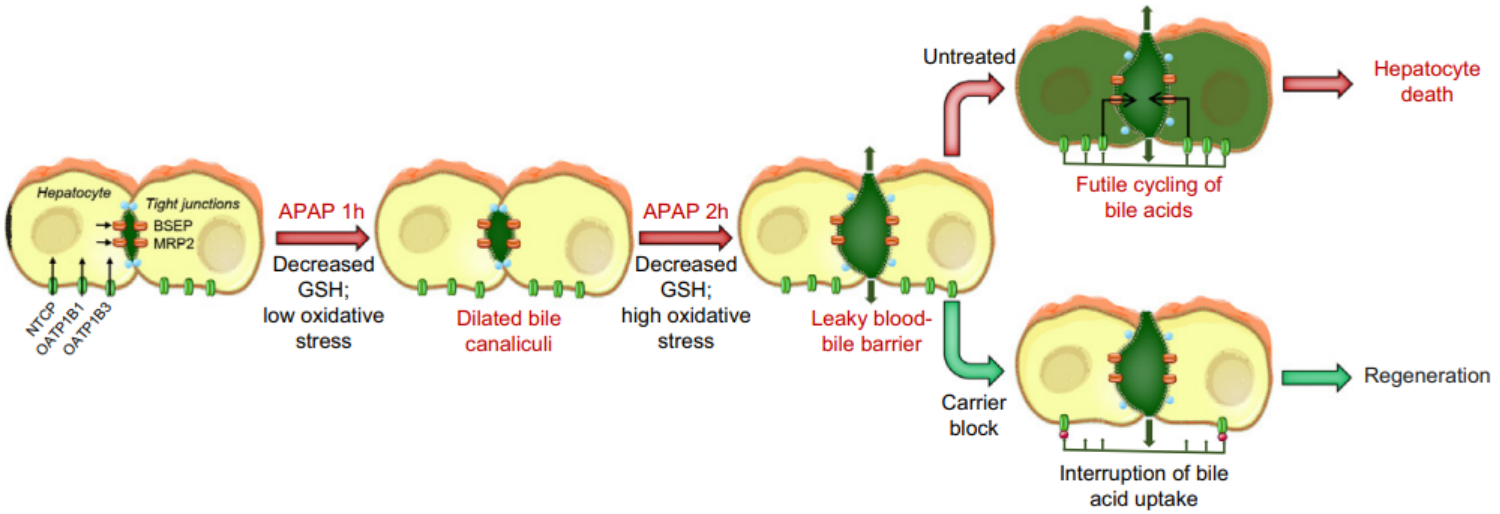
INSELGRUPPE

Which transporter would you block to minimize hepatocyte damage in case of APAP intoxication?



JOURNAL
OF HEPATOLOGY

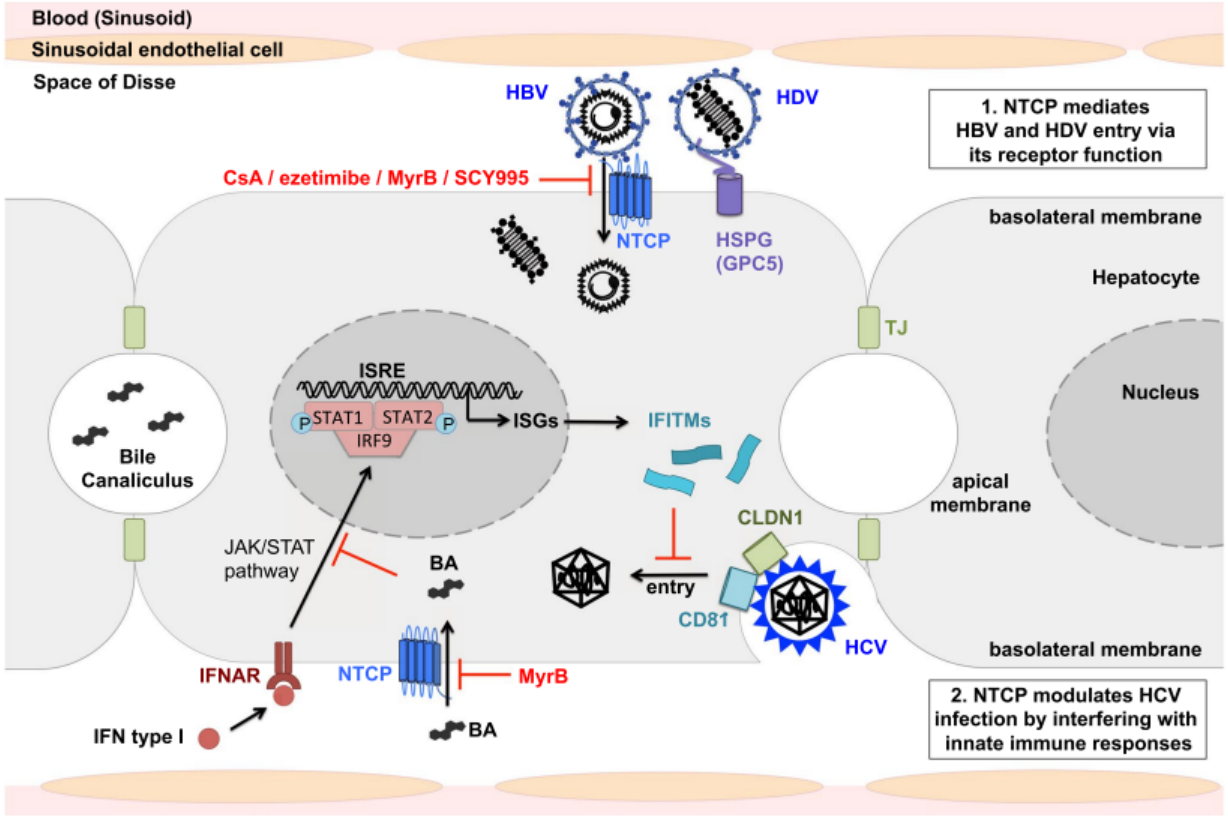
Interruption of bile acid uptake by hepatocytes after acetaminophen overdose ameliorates hepatotoxicity



Ghallab, Hengstler et al. Journal of Hepatology.2022: 71–83

INSELGRUPPE

For which other liver disease(s) is NTCP important?



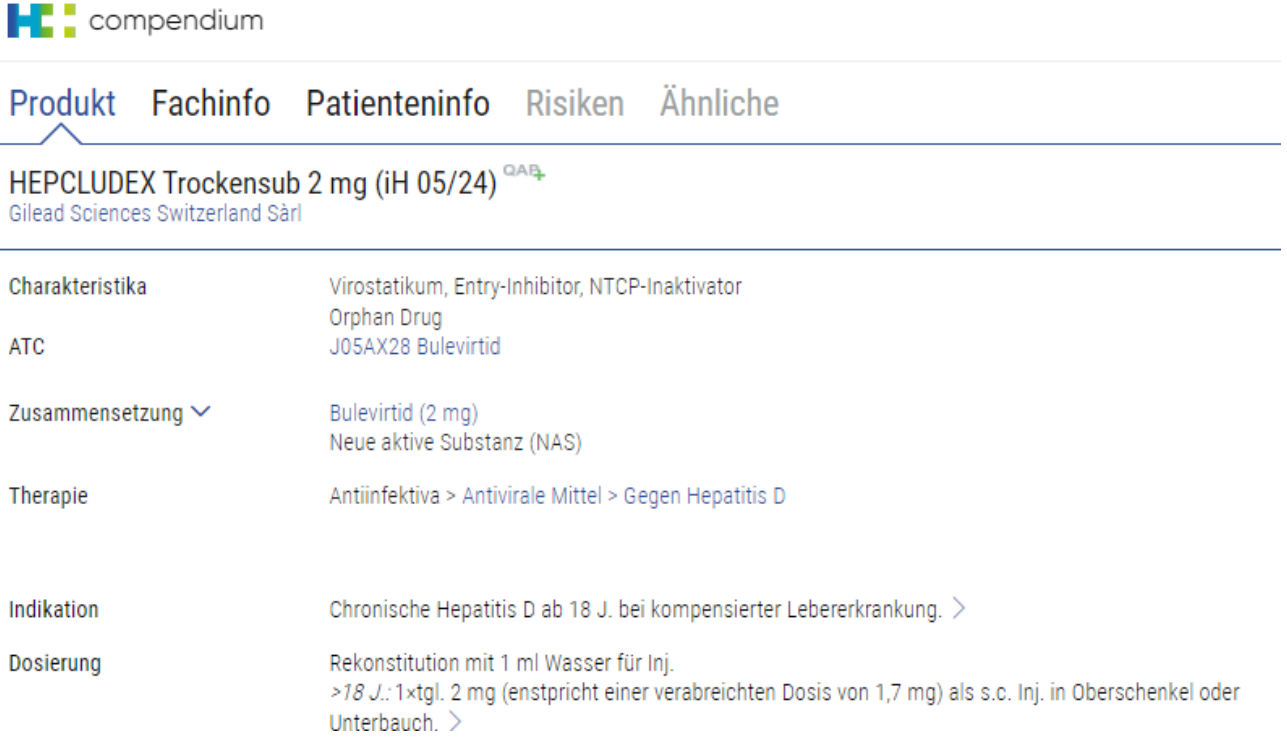
Cellular and Molecular Life Sciences (2018) 75:3895–3905

INSELGRUPPE

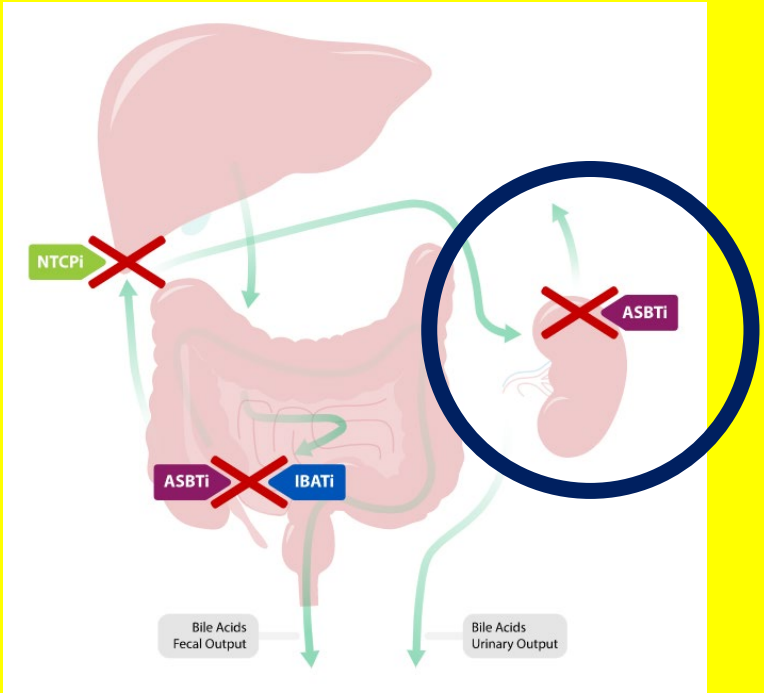
What is the name of the approved drug for NTCP inhibition?

What is the indication for this drug?

INSELGRUPPE



INSELGRUPPE



albireopharma.com

INSELGRUPPE

Which complication of liver disease could be treated with renal ASBT inhibition?

INSELGRUPPE

Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

JOURNAL
OF HEPATOLOGY

Inhibition of the renal apical sodium dependent bile acid transporter prevents cholemic nephropathy in mice with obstructive cholestasis

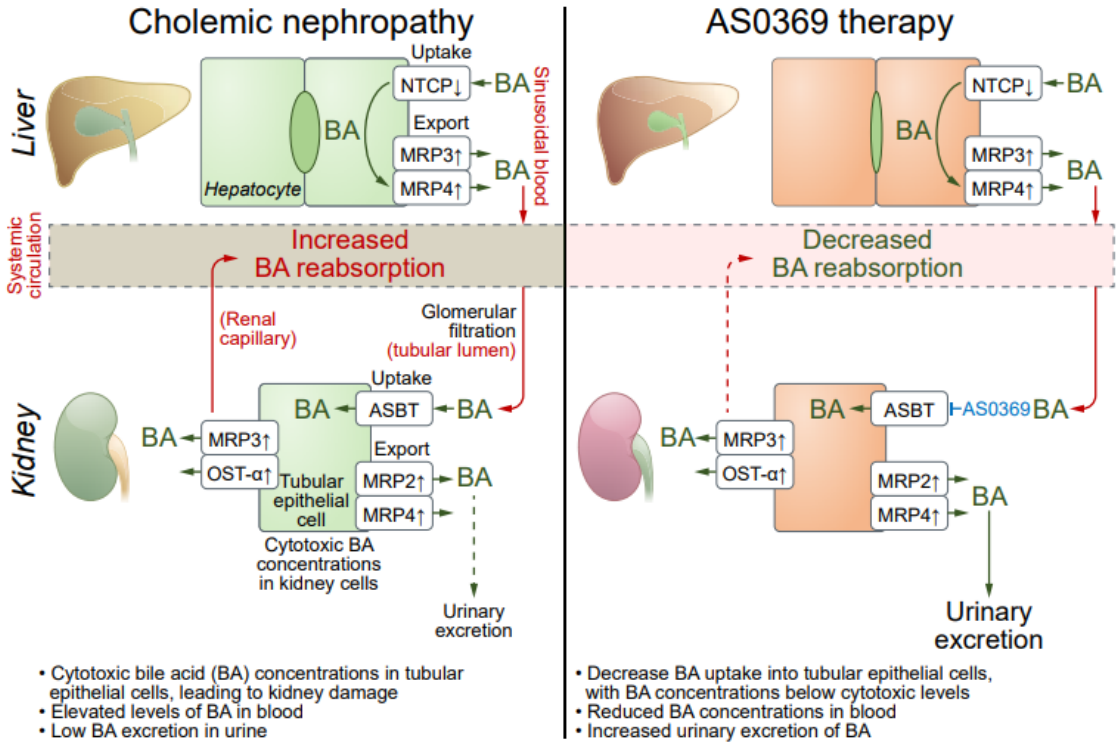
Authors

Ahmed Ghallab, Daniela González, Ellen Strängberg, …, Paul A. Dawson, Erik Lindström, Jan G. Hengstler

INSELGRUPPE

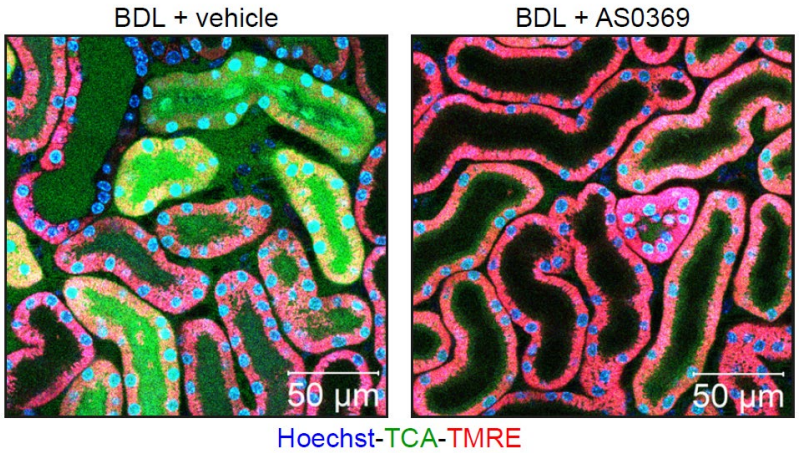
What happens if ASBT is inhibited in the kidney?

INSELGRUPPE



Journal of Hepatology 2024. vol. 80 I 268–281

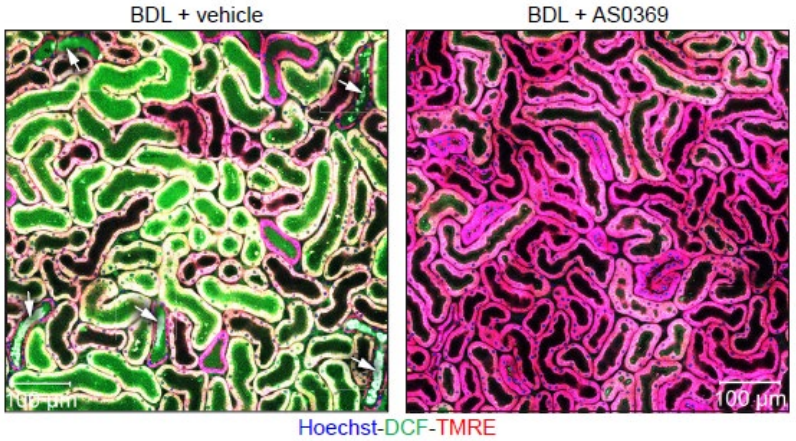
Development of a systemic ASBT-specific inhibitor



ASBT inhibition reduces TCA (taurocholic acid) uptake into TECs (tubular epithelial cells).

Intravital imaging was performed 3 days after BDL and AS0369 treatment (60 mg/kg, twice per day).

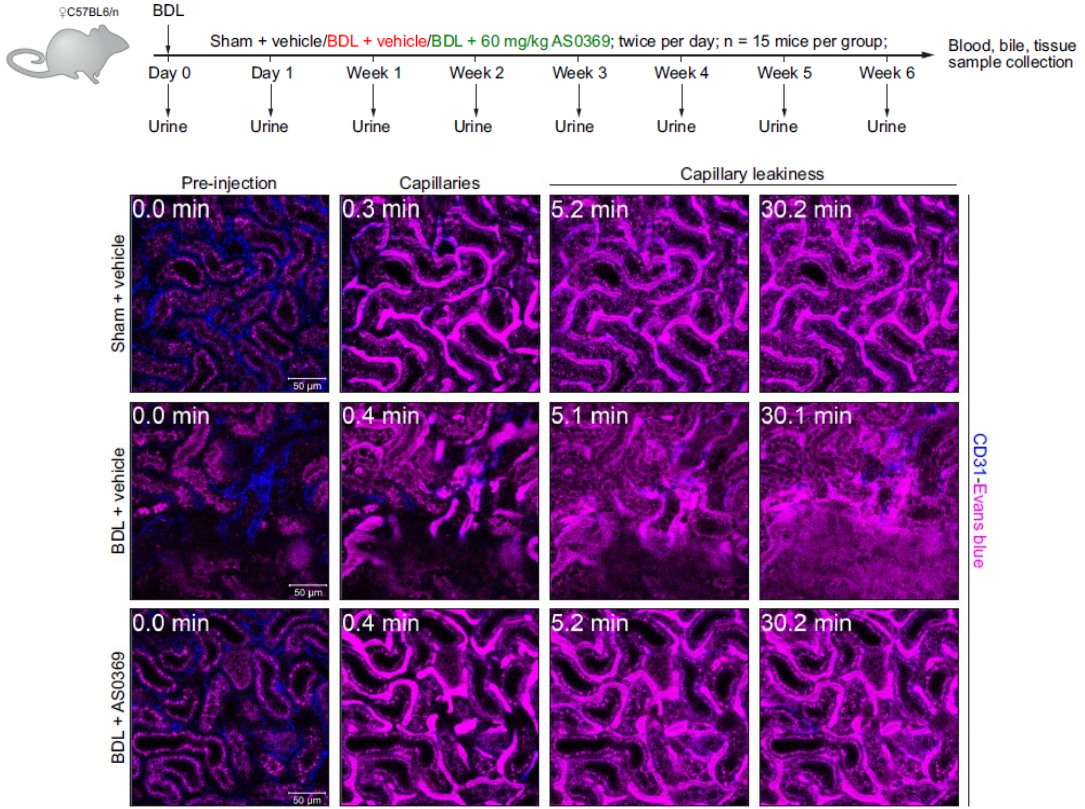
Imaging was performed approximately 2 h after administration of the last AS0369 dose.



Overview of renal tissue in mice on day 2 after BDL showing reduced oxidative stress and tubule casts after AS0369 treatment compared to vehicle treated mice.

Journal of Hepatology 2024. vol. 80 I 268–281

Prevention of peritubular capillary leakiness by ASBT inhibition



The peritubular capillaries are visualized by anti-CD31 antibody (blue)

Journal of Hepatology 2024. vol. 80 I 268–281

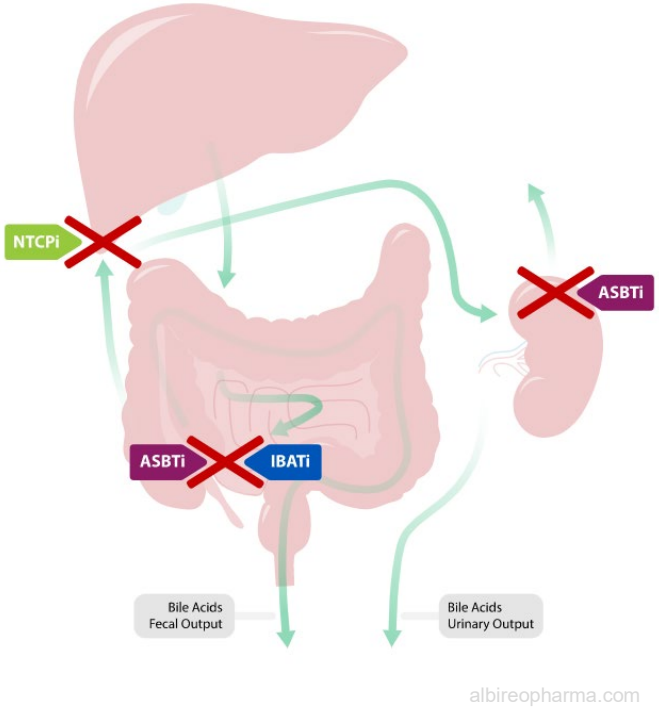
INSELGRUPPE

Transporter targets for bile acids modulation?

INSELGRUPPE

Bile Acid Modulation

- Pharmacological IBAT inhibition in the ileum results in an increased bile acid load in the colon and subsequently a lower bile acid pool.
  - Maralixibat (PFIC)
  - Odevixibat (Alagille Syndrome)



Further potential drug targets to modulate bile acids:

- NTCP -> NTCP inhibitor
  - Bulevirtide (treatment for hepatitis D)
  - no bile acid modulating indication so far
- ASBT -> ASBT inhibitor kidney

INSELGRUPPE