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# **Cholestaticische Leverziekten**

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**Amsterdam**

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Location AMC  
Amsterdam, The Netherlands

# **Disclosures**

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## **Grant support**

German, Norwegian, American and South-African PSC patient foundations  
Netherlands Foundation for Gastroenterology & Hepatology (MLDS)  
EU Program ‘LIVERHOPE’

## **Lecture fees**

Abbvie, Falk Foundation, Gilead, Intercept, Merck, Novartis, Roche, Shire, Zambon

## **Consulting agreements**

Intercept, NGM, Novartis

## **Support for investigator-initiated studies**

Falk, Intercept

# Case report

♀ 34 yrs

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2012 (11): Fever for 3 days, increasing pruritus and progressive jaundice

(Serum liver tests elevated, markers for viral hepatitis, AIH, hereditary metabolic disease neg.)

- No relevant diseases in the past
- Family: no liver disease
- Alcohol: 2 U / week
- Drugs: none
- Medication: oral contraceptives since 15 years
- Work: post office

# Physical Examination 2013 (1)

♀ 34 yrs

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- Icteric, exhausted, intermittently scratching woman
- 165 cm, 66 kg
- No other relevant diagnostic findings

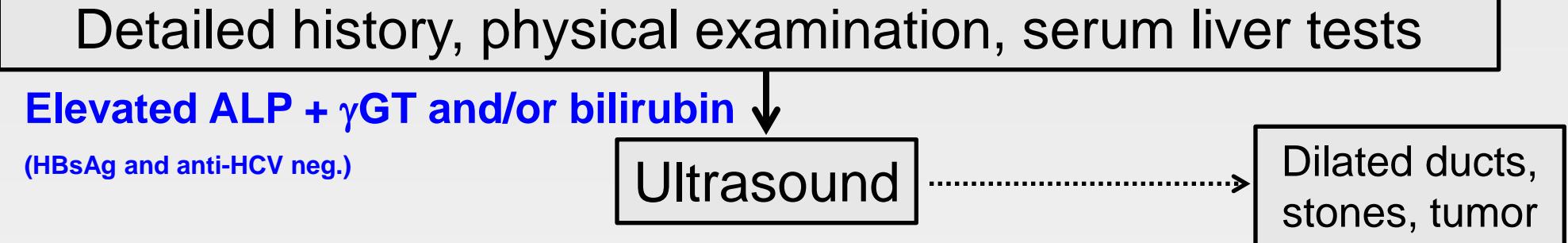
# Lab

♀ 34 yrs

2013 (1)

<b>Bilirubin</b>	(≤ 17 µmol/l)	565	>90% conjugated)
<b>ALT</b>	(≤ 45 U/l)	55	
<b>AST</b>	(≤ 40 U/l)	70	
<b>γGT</b>	(≤ 60 U/l)	23	
<b>ALP</b>	(≤ 120 U/l)	347	

# Diagnostic approach to cholestasis



# Abdominal Imaging

♀ 34 yrs

## Ultrasound:

- Normal aspect of the liver, no focal lesions
- Sludge in the gallbladder
- No bile duct obstruction (by stones or mass)

# Abdominal Imaging

♀ 34 yrs

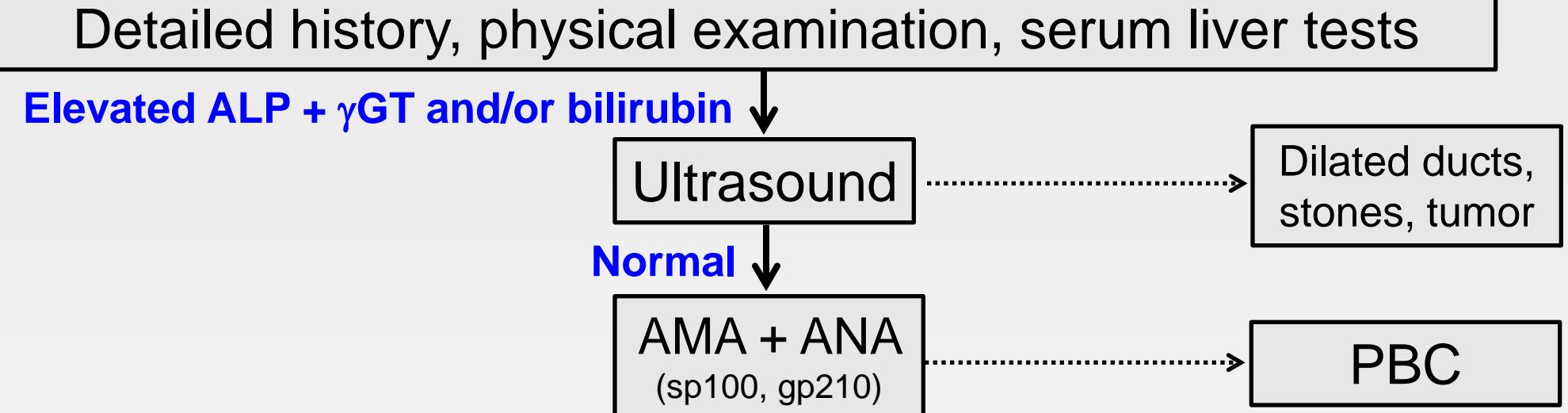
## Ultrasound:

- Normal aspect of the liver, no focal lesions
- Sludge in the gallbladder
- No bile duct obstruction (by stones or mass)

**Fibroscan:** 17.7 kPa (IQR 3.3, success rate 100%)

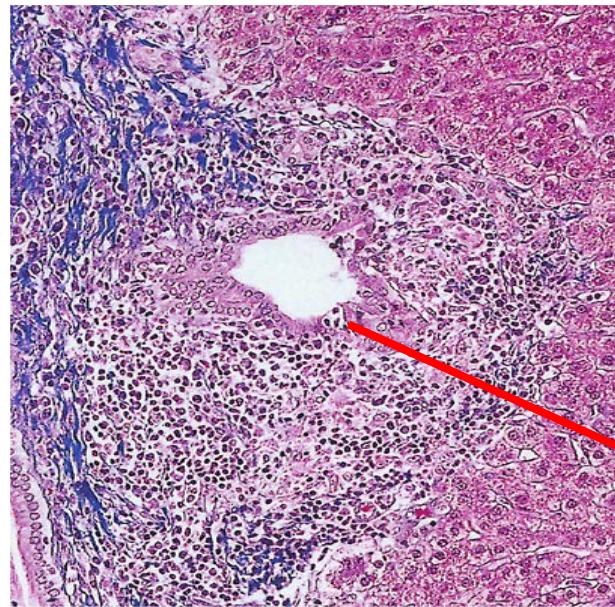
**CAP:** 154 dB/m (IQR 23)

# Diagnostic approach to cholestasis



# Primary biliary cholangitis\* (PBC)

## Characteristics



Florid, non-suppurative, destructive cholangitis

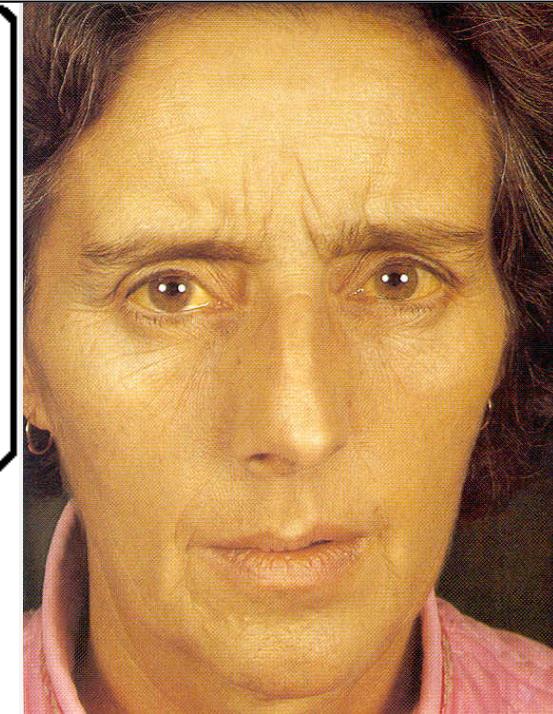
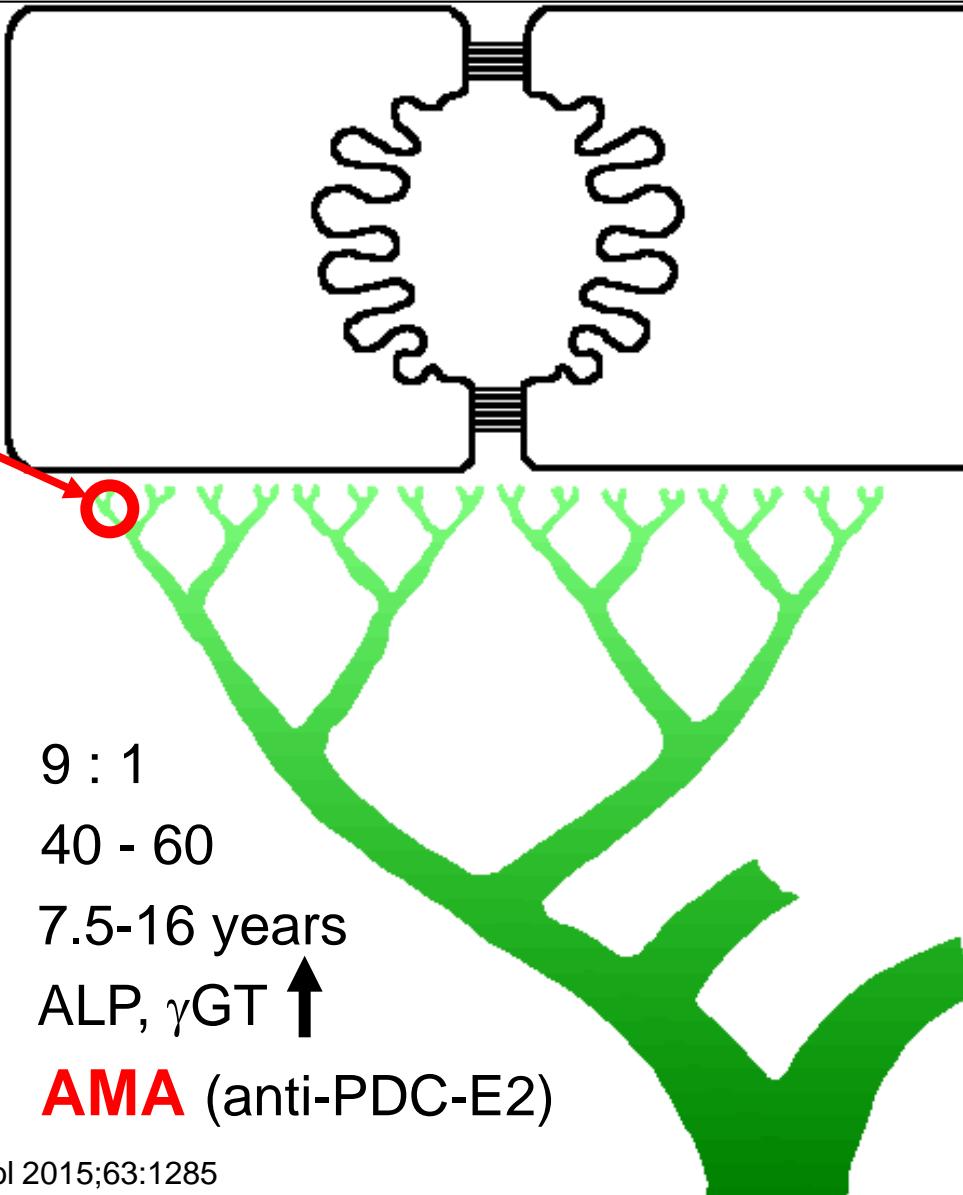
**Women : Men**

**Age at diagnosis**

**Survival** without treatment

**Cholestasis**

**Autoantibodies**



Sherlock and Summerfield, 1991

### **Symptoms**

- Fatigue
- Pruritus
- Sicca syndrome
- ...

# Primary biliary cholangitis:

## Potential pathogenetic mechanisms

Immune-mediated bile duct injury



Bile duct injury by hydrophobic bile acids



Cholestasis with retention of hydrophobic bile acids in liver



Fibrosis, cirrhosis

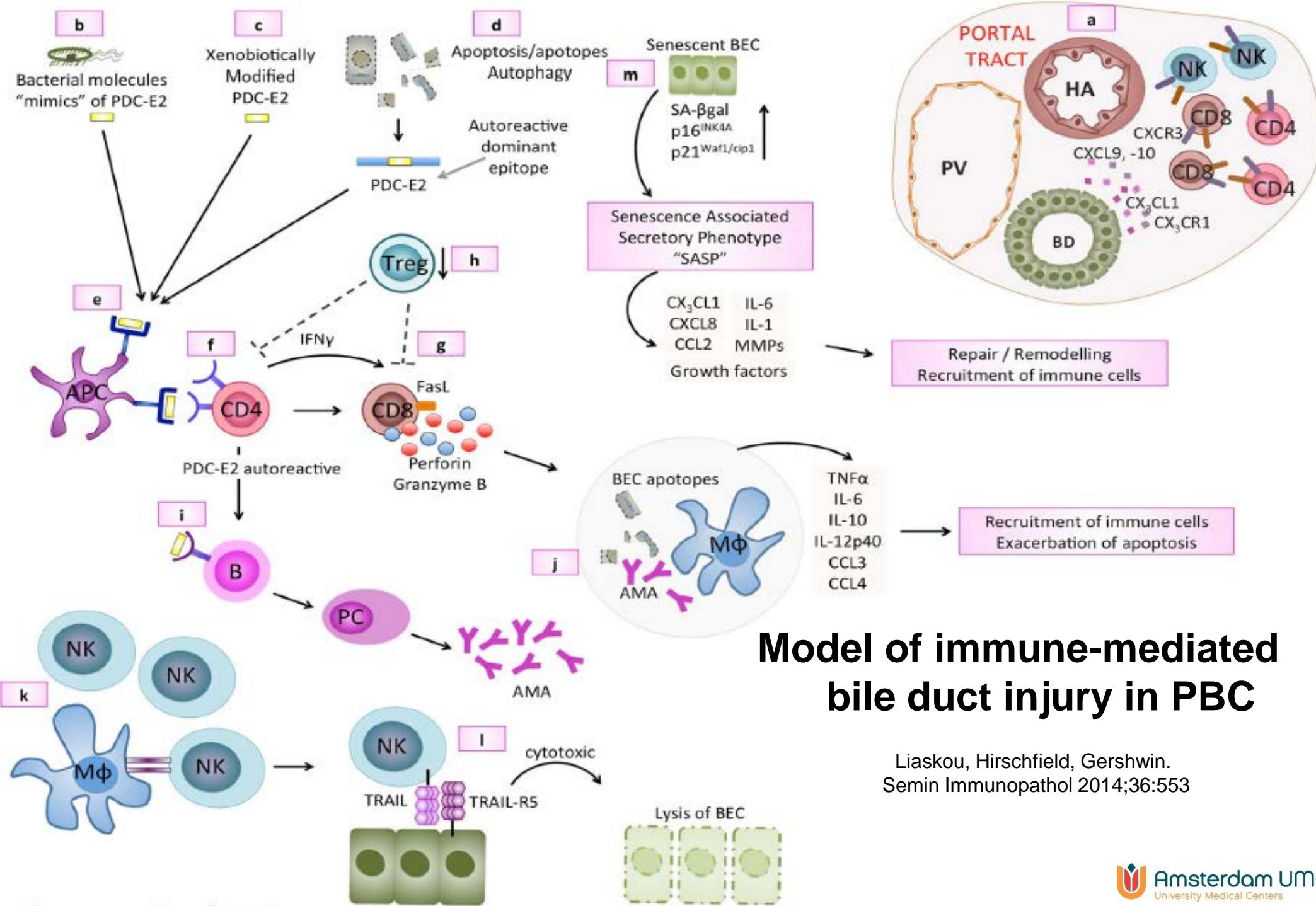


Liver failure

Genetic Predisposition

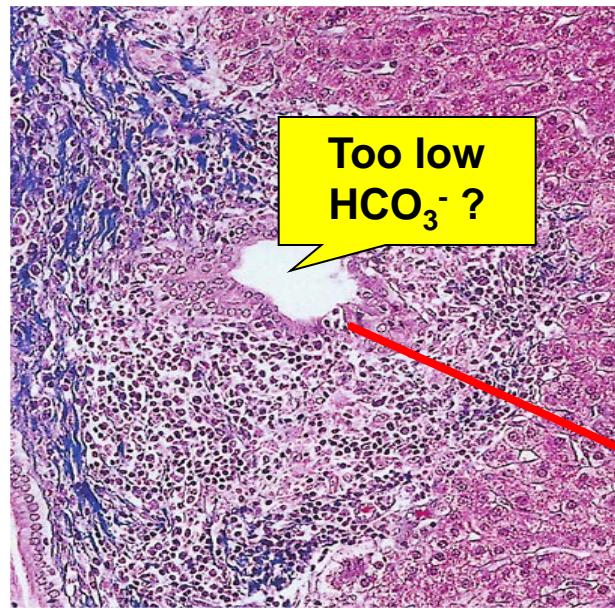
Environmental factors  
(molecular mimicry)

Cellular/humoral immune response



# Primary biliary cholangitis (PBC)

## Characteristics



Florid, non-suppurative, destructive  
cholangitis

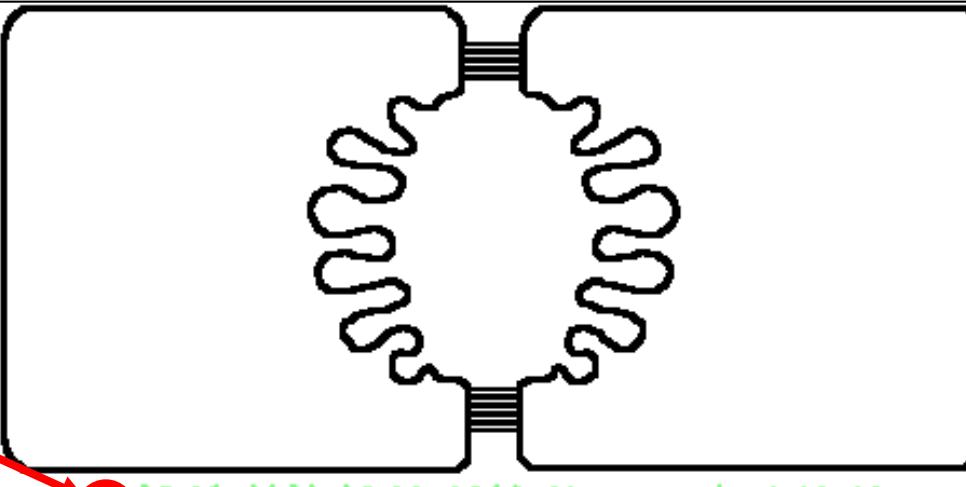
**Women : Men**

**Age at diagnosis**

**Survival** without treatment

**Cholestasis**

**Autoantibodies**



9 : 1

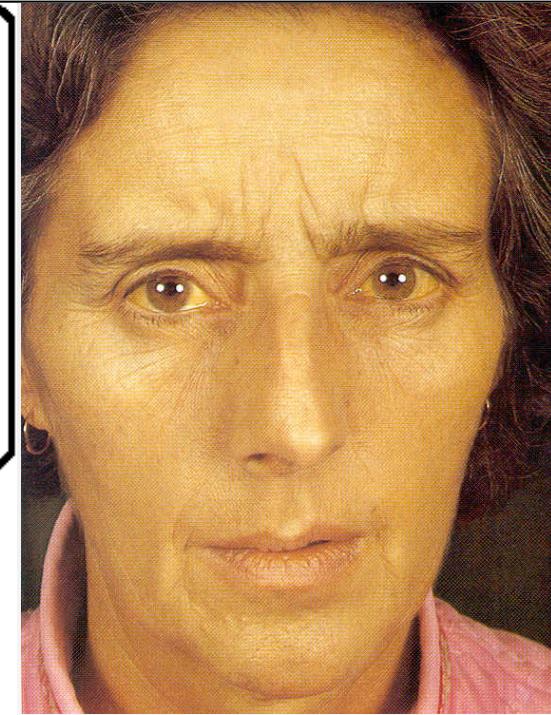
40 - 60

7.5-16 years

↑ ALP, γGT

**AMA** (anti-PDC-E2)

Prieto et al. Gastroenterology 1993;105:572  
Medina et al., Hepatology 1997;25:12  
Prieto et al., Gastroenterology 1999;117:167  
Banales et al. Hepatology 2012;56:687  
Erice et al. Hepatology 2018;67:1420



Sherlock and Summerfield, 1991

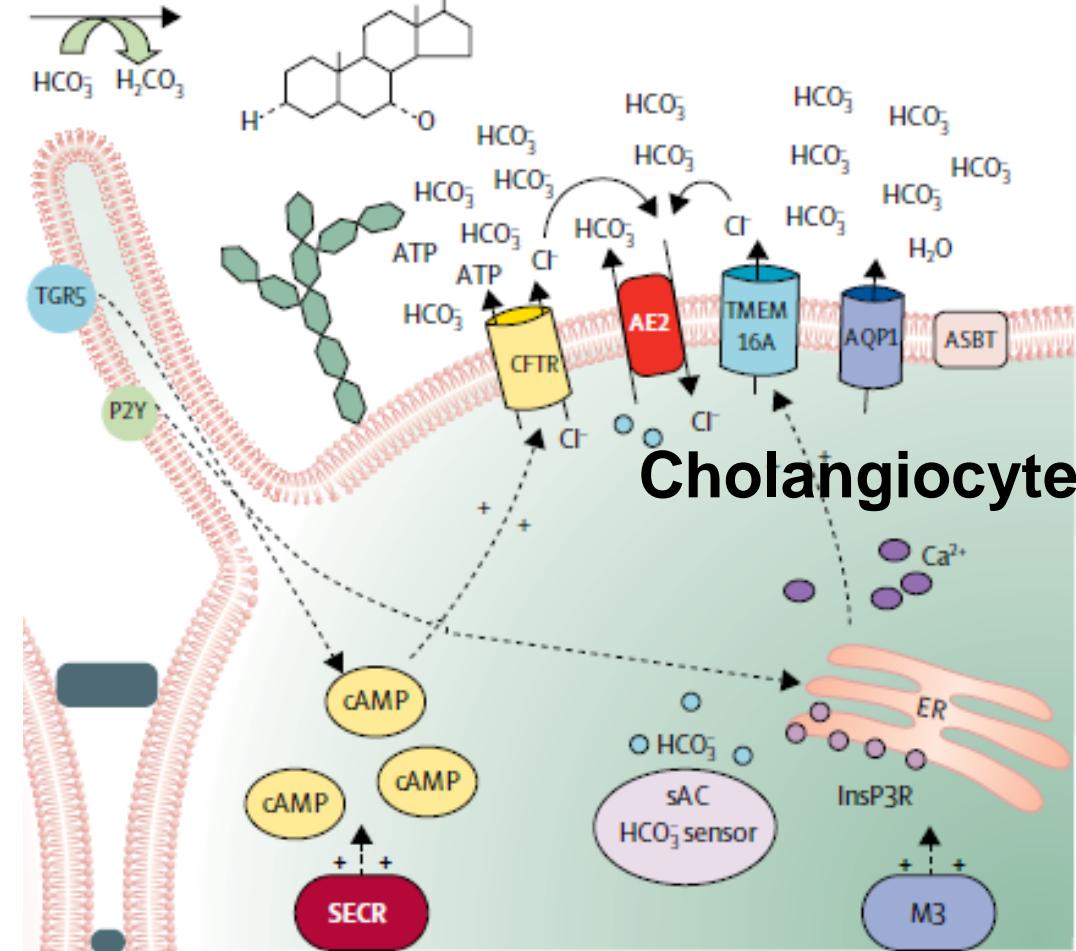
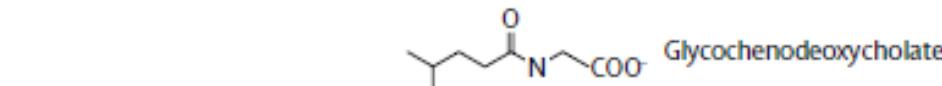
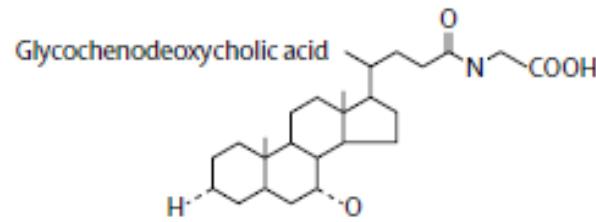
## Symptoms

- Fatigue
- Pruritus
- Sicca syndrome
- ...

# The ‘Biliary $\text{HCO}_3^-$ Umbrella’ Hypothesis

+ Activation

Bile



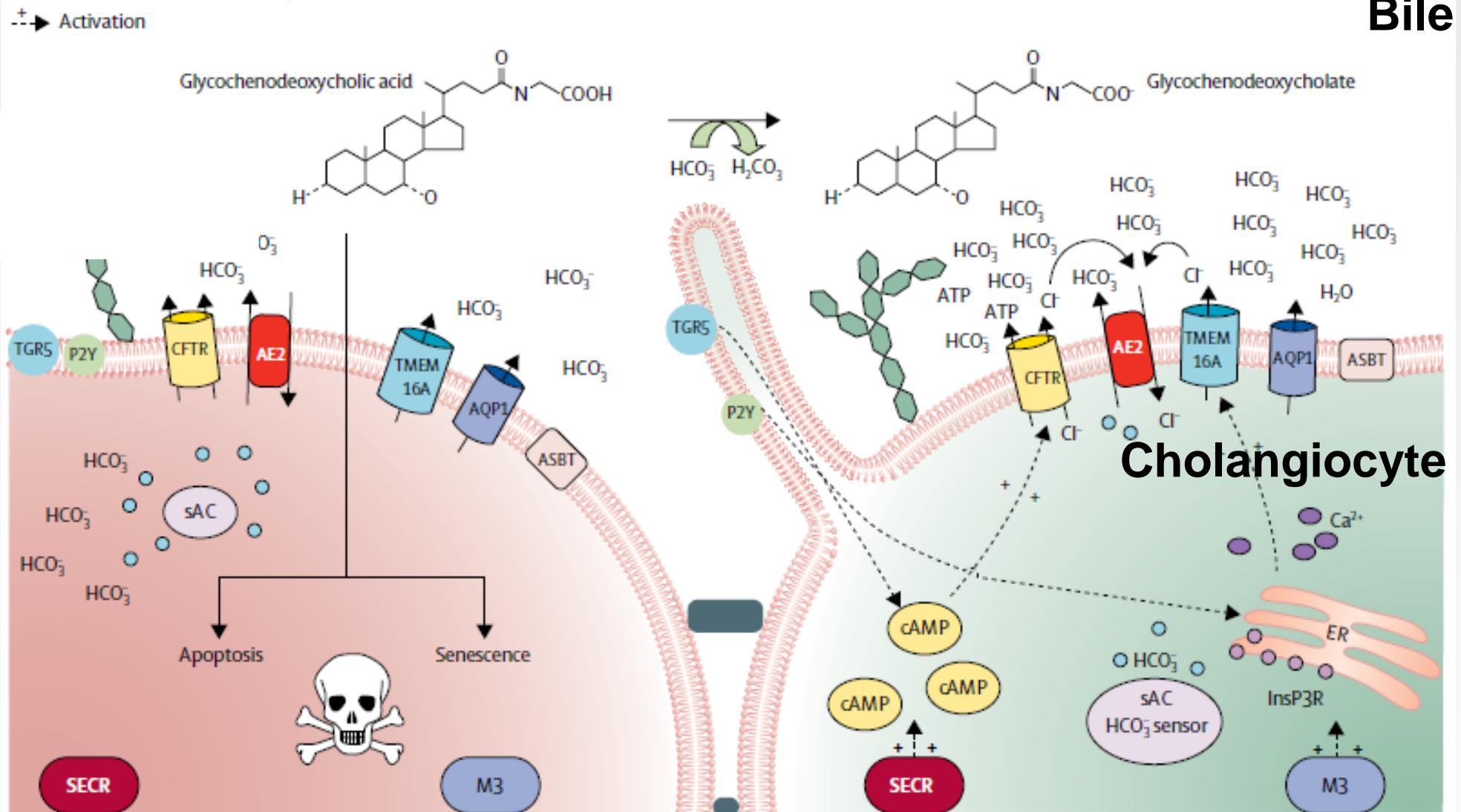
[Lancet 2018;391:2547]

Beuers et al., Hepatology 2010;52:1489

Hohenester, Wenniger et al., Hepatology 2012; 55: 173

Chang et al., Hepatology 2016;64:522

# The ‘Biliary $\text{HCO}_3^-$ Umbrella’ Hypothesis



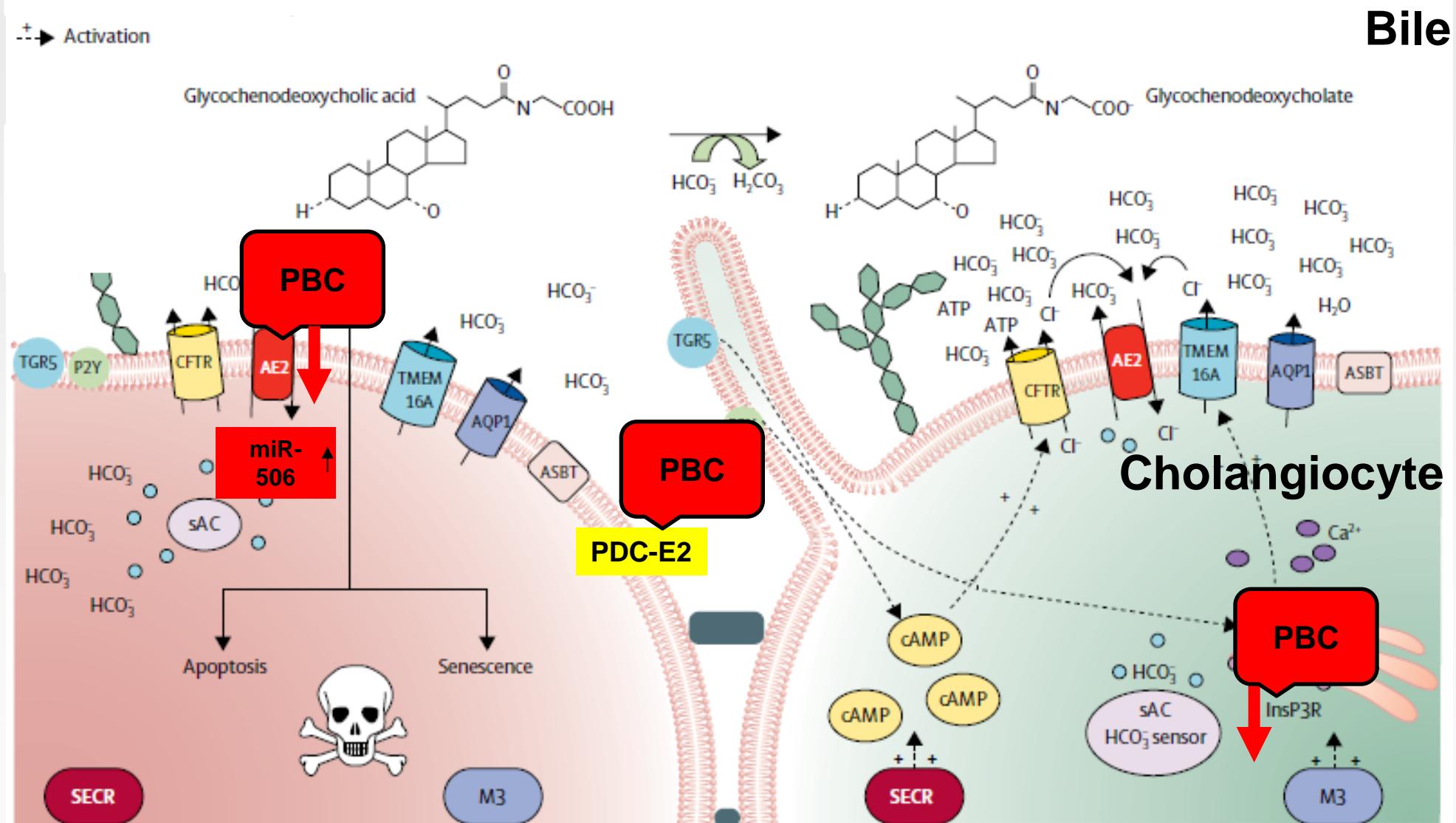
Beuers et al., Hepatology 2010;52:1489

Hohenester, Wenniger et al., Hepatology 2012; 55: 173

Chang et al., Hepatology 2016;64:522

[Lancet 2018;391:2547]

# Defects of the ‘Biliary HCO<sub>3</sub><sup>-</sup> Umbrella’ in PBC



Beuers et al., Hepatology 2010;52:1489

Hohenester, Wenniger et al., Hepatology 2012; 55: 173

Chang et al., Hepatology 2016;64:522

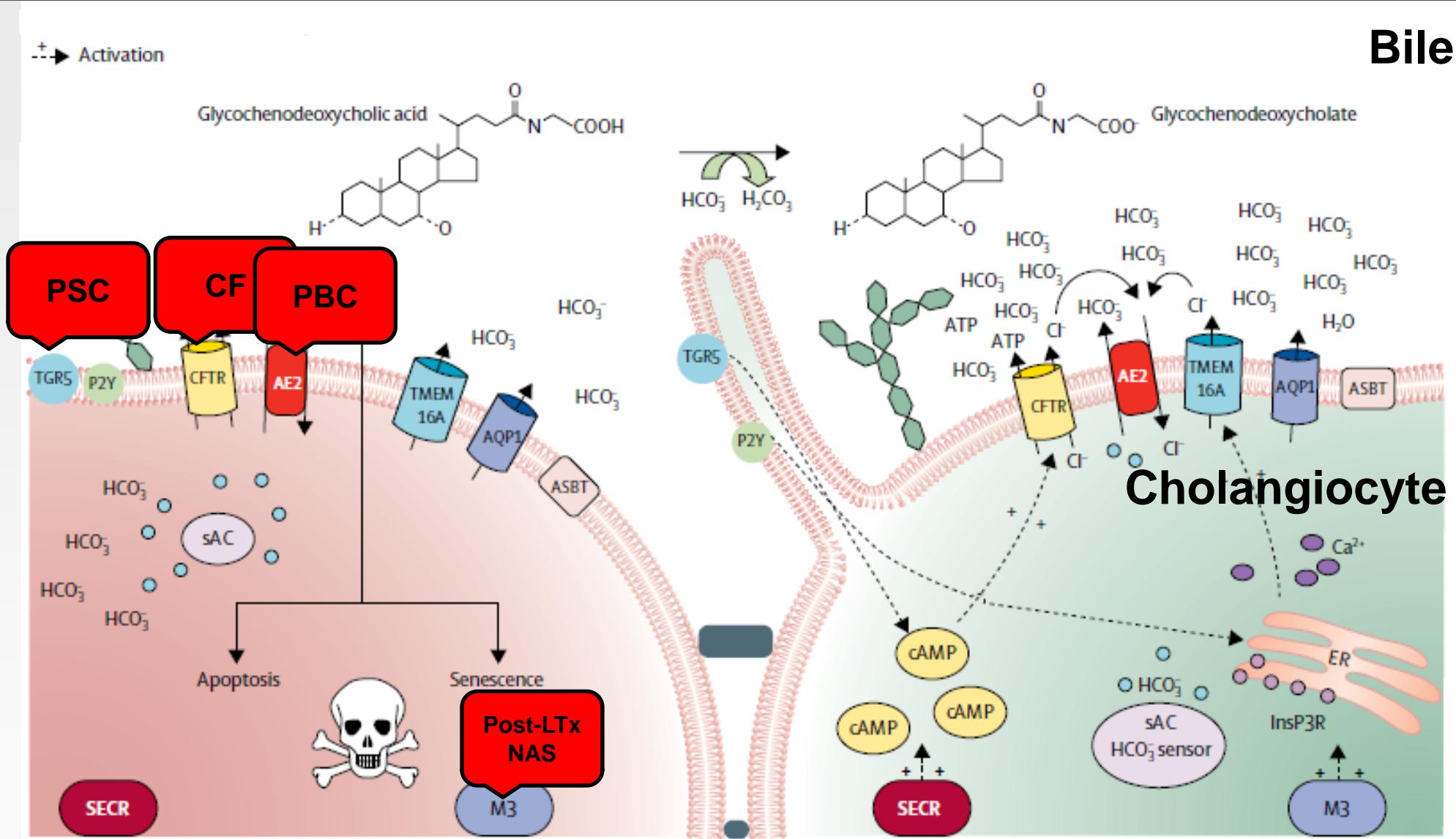
Banales et al. Hepatology 2012;56:687

Ananthanarayanan et al. JBC 2015;290:184

Erice et al. Hepatology 2018;67:1420

[Lancet 2018;391:2547]

# Defects of the 'Biliary $\text{HCO}_3^-$ Umbrella' in fibrosing cholangiopathies?



Beuers et al., Hepatology 2010;52:1489

Hohenester, Wenniger et al., Hepatology 2012; 55: 173

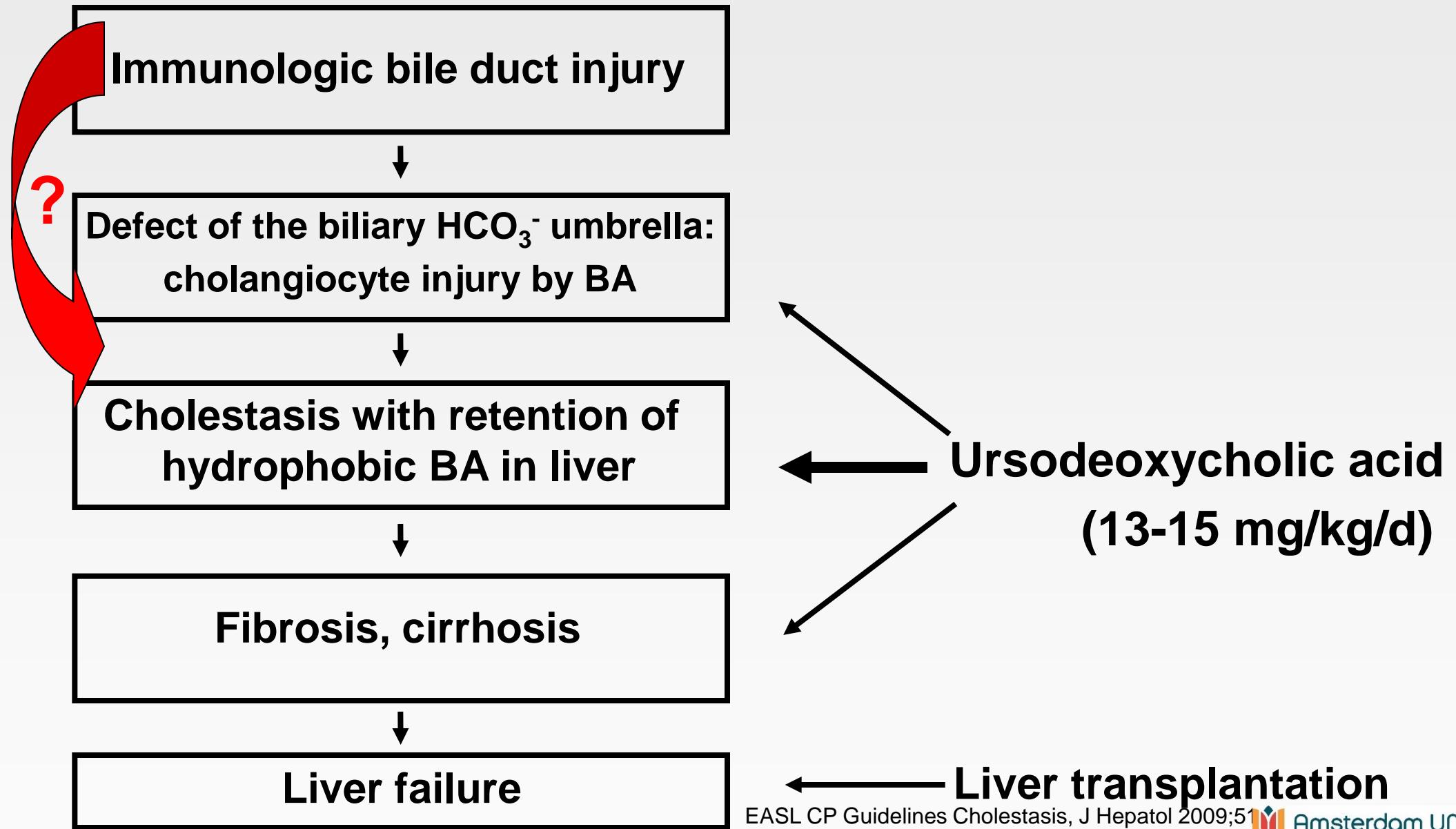
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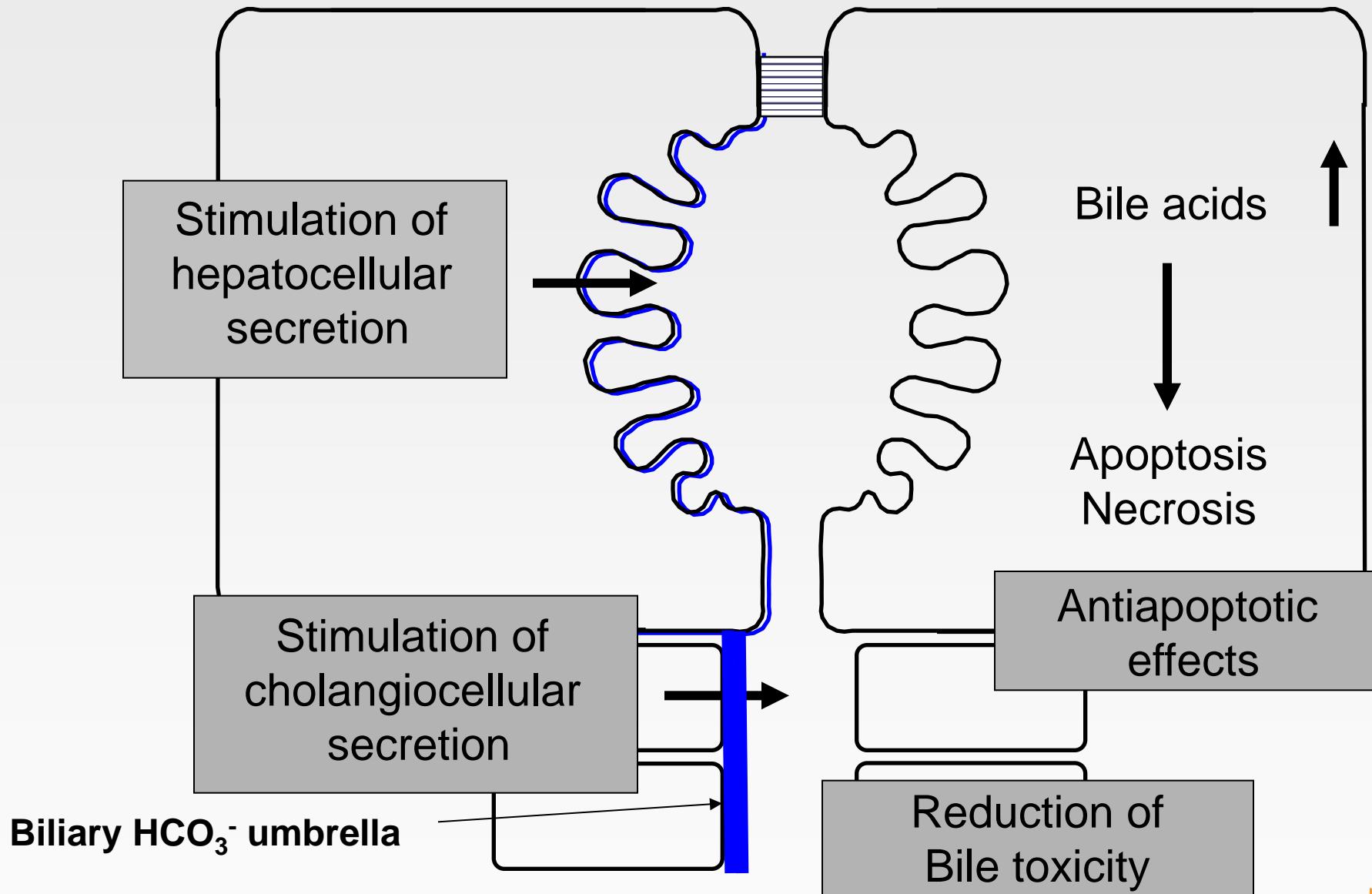
# Primary biliary cholangitis:

# Therapy

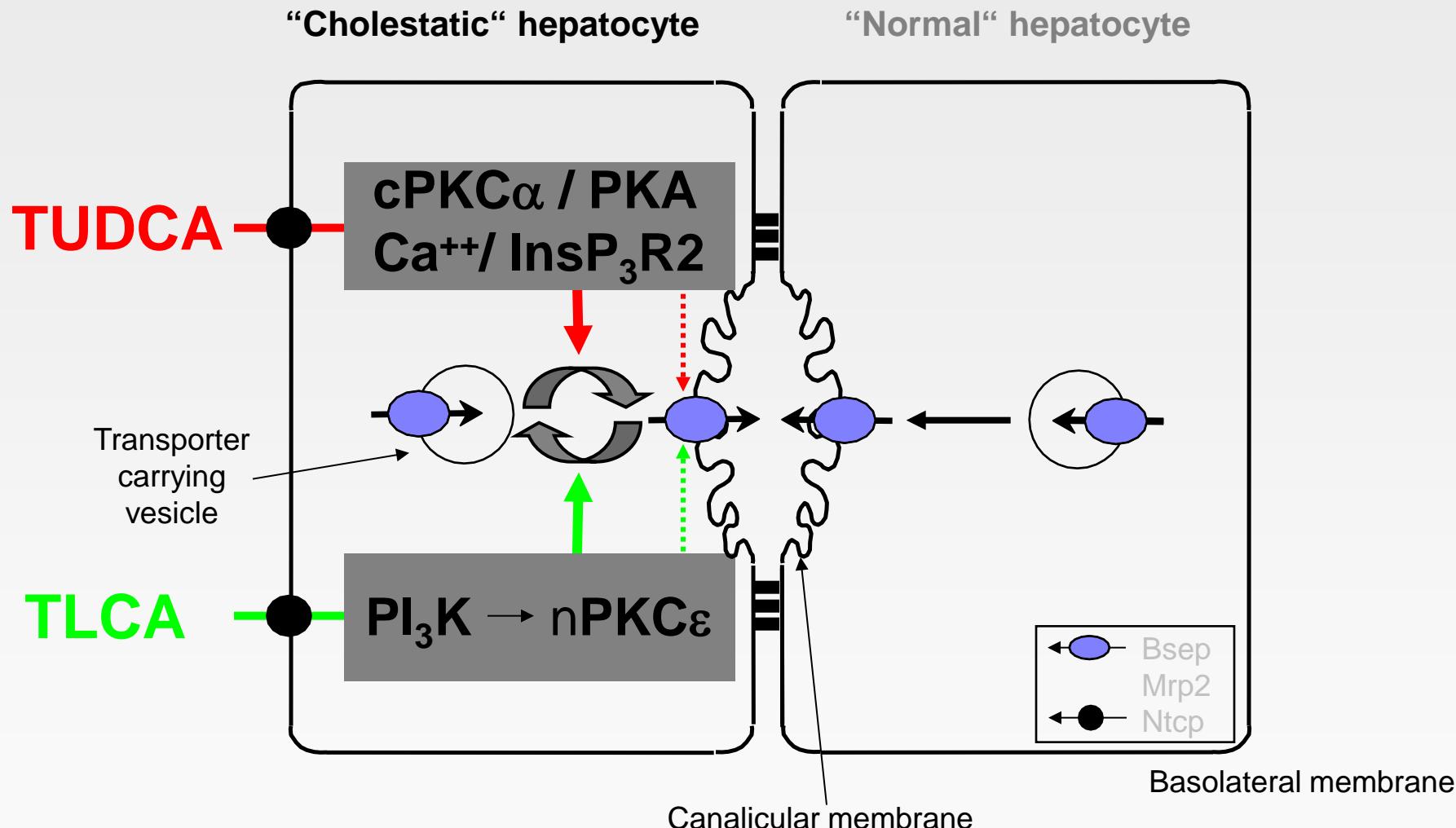
## Potential pathogenetic mechanisms



# Putative mechanisms and sites of action of UDCA in cholestatic liver diseases



# UDCA conjugates act as posttranscriptional secretagogues in experimental cholestasis



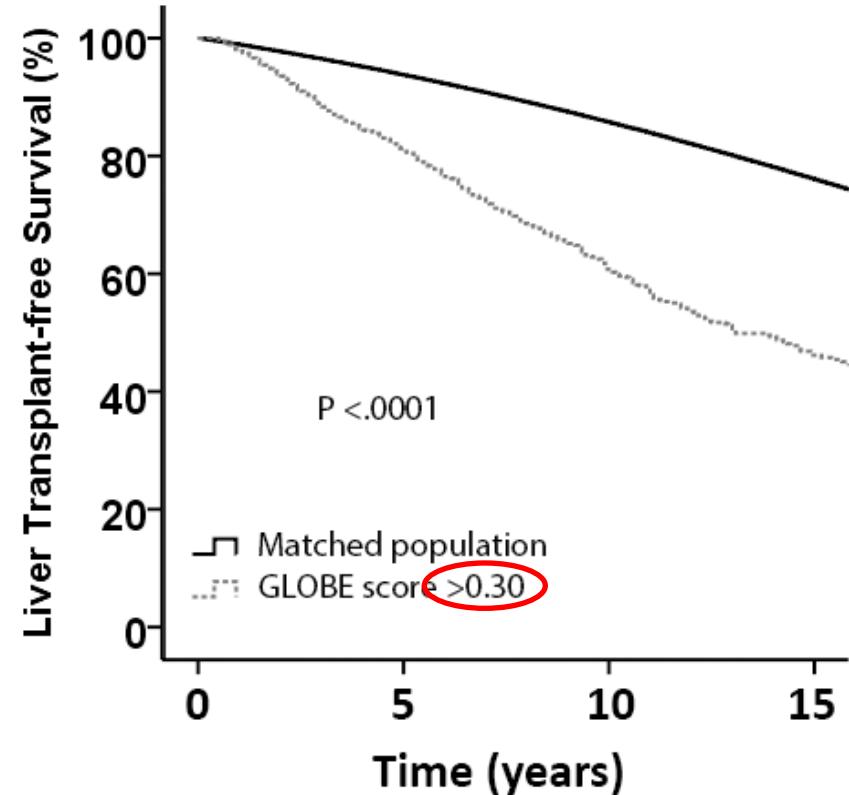
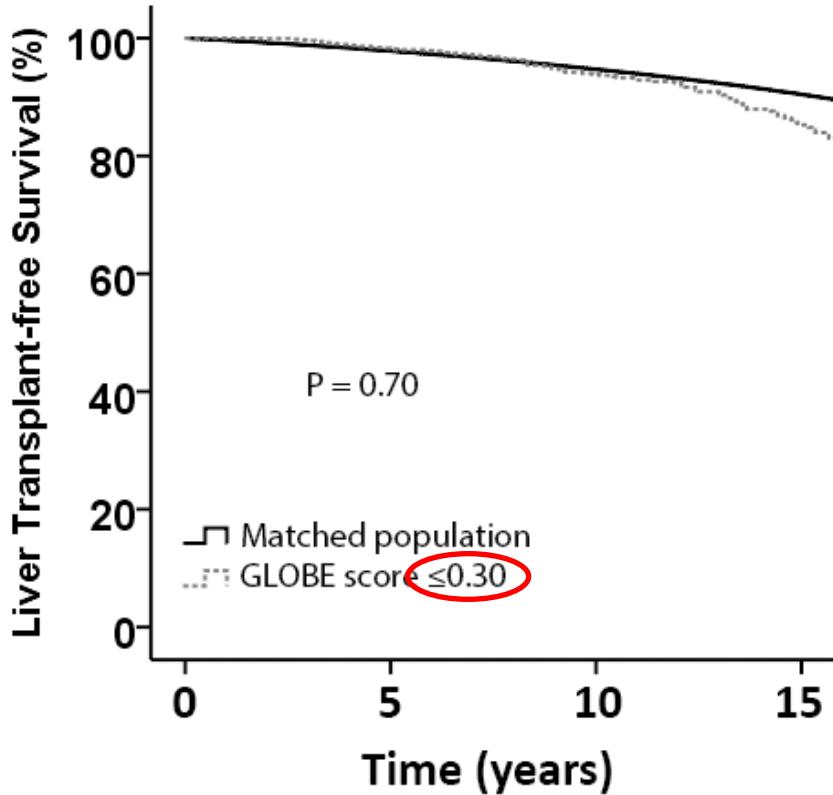
Beuers. Nature CP Gastroenterol Hepatol 2006;3:318 (references 1990-2006)

Wimmer, Hohenester et al., Gut 2008; 57: 1448

Cruz et al., Hepatology 2010; 52: 327

# The PBC GLOBE score predicts outcome after 1 year of UDCA

## Derivation cohort

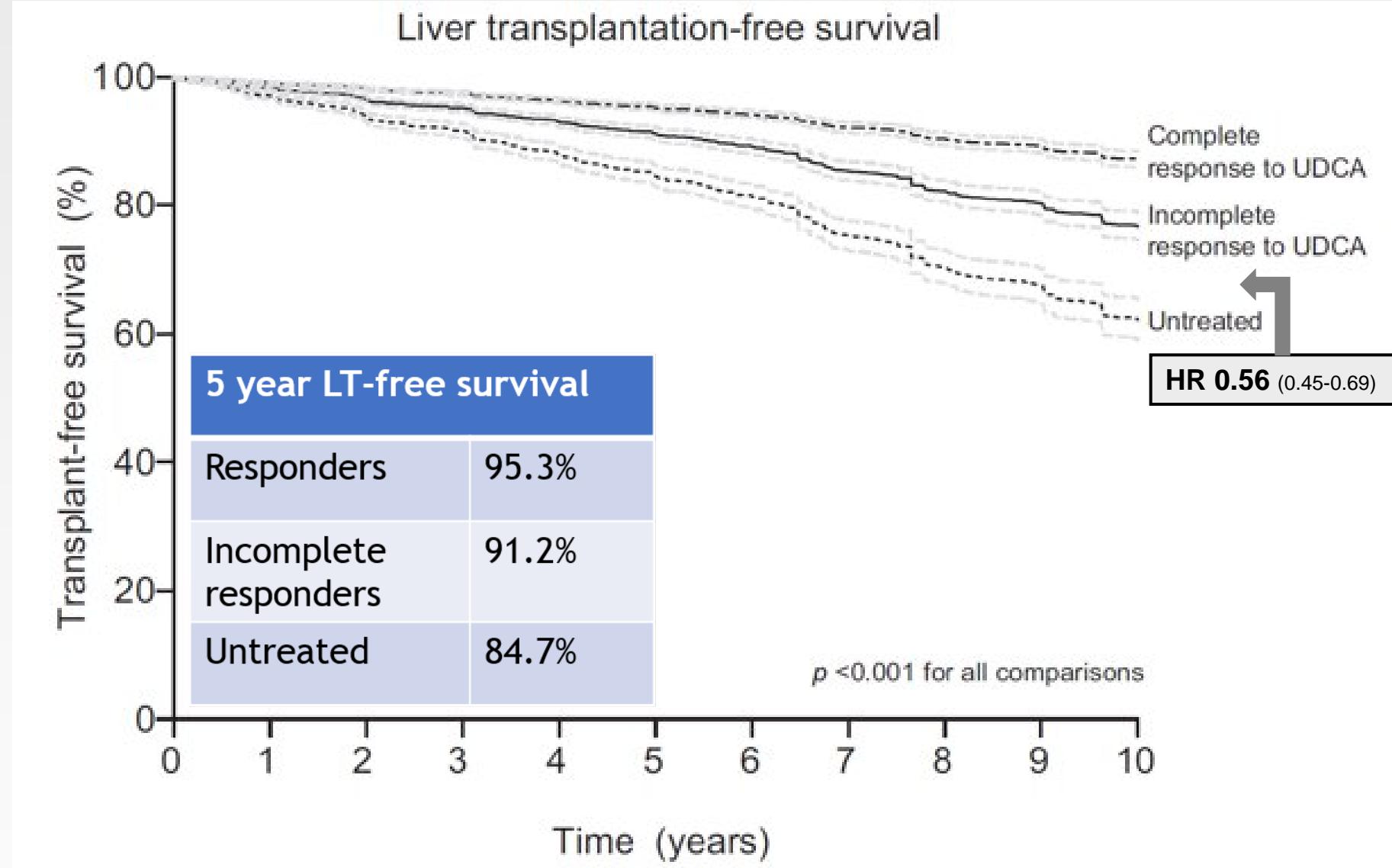


**GLOBE score:** Age, bilirubin, alkaline phosphatase, albumin, platelets

n=4111 PBC patients

Lammers et al., Gastroenterology 2015;149:1804

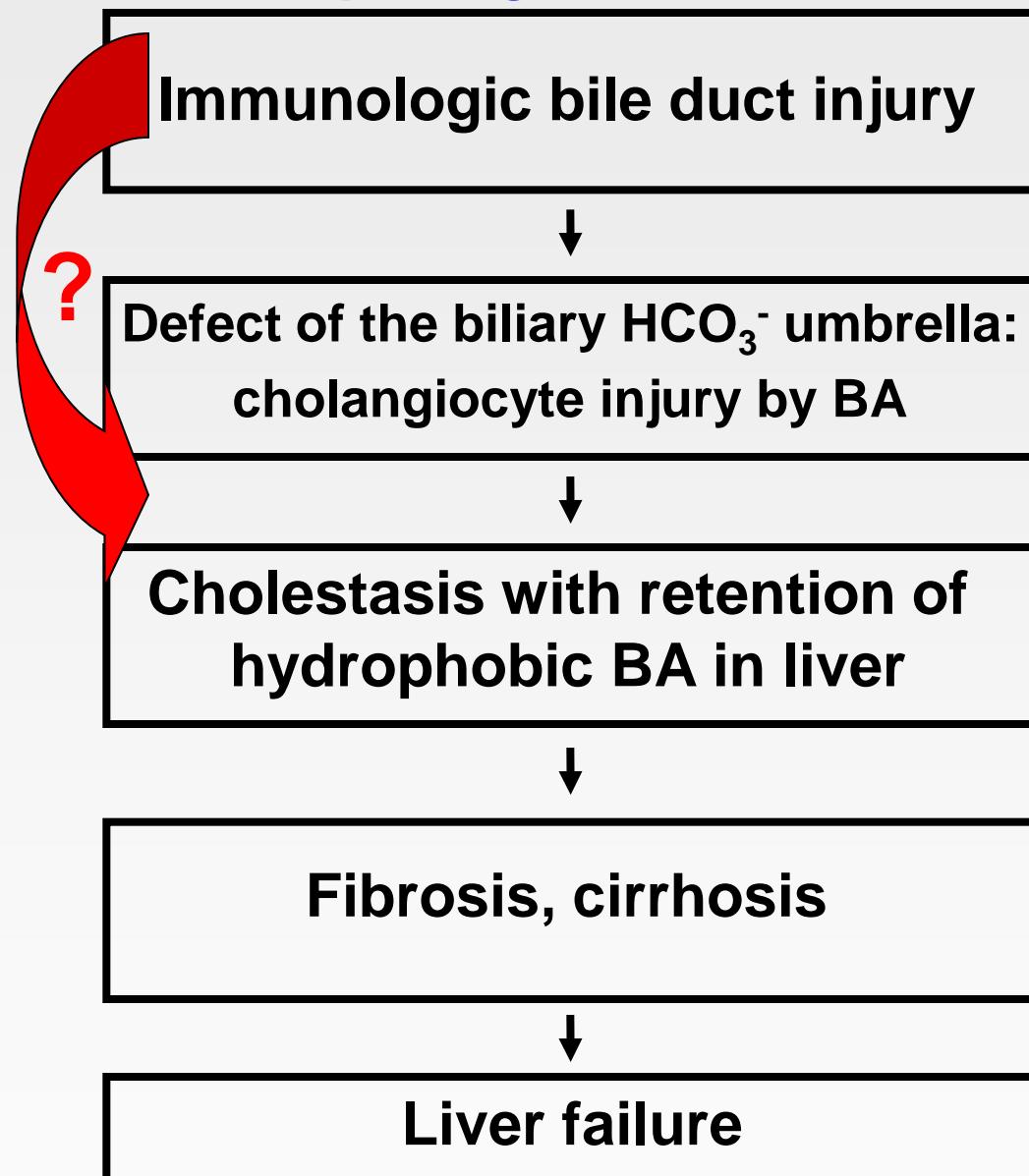
# UDCA improves transplant-free survival of patients with PBC in complete and 'incomplete' responders



# Primary biliary cholangitis:

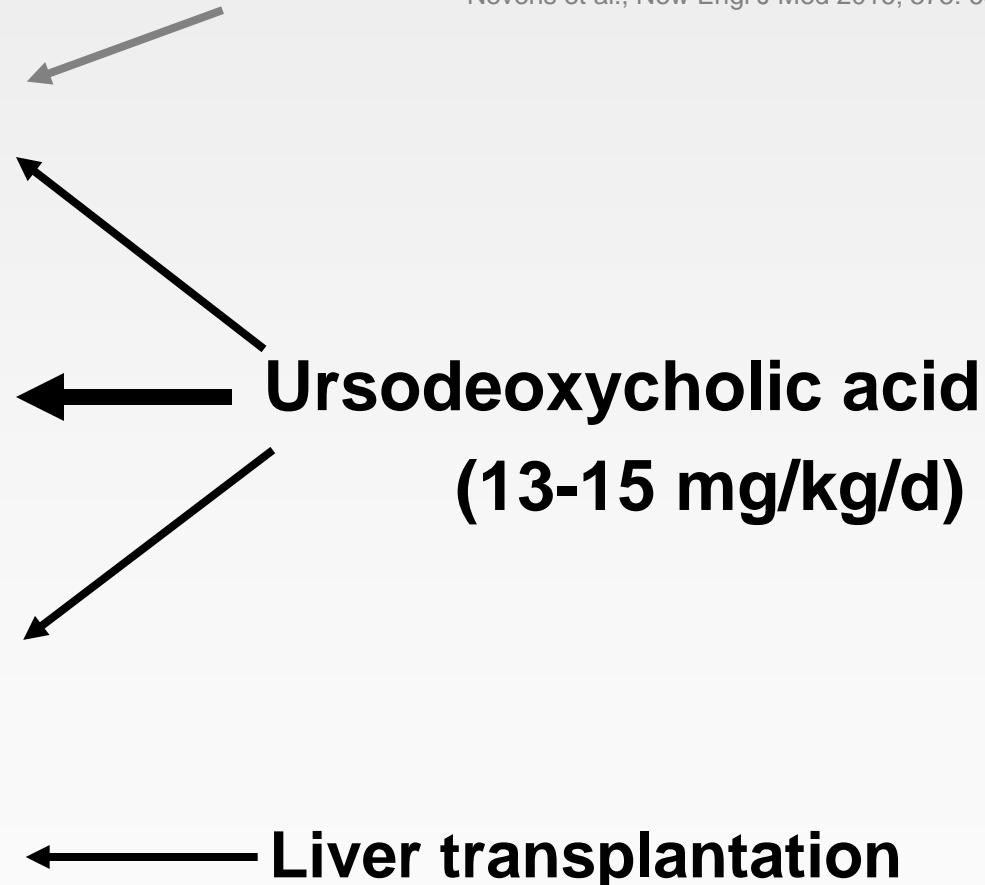
Potentially new **Therapy**

## Potential pathogenetic mechanisms



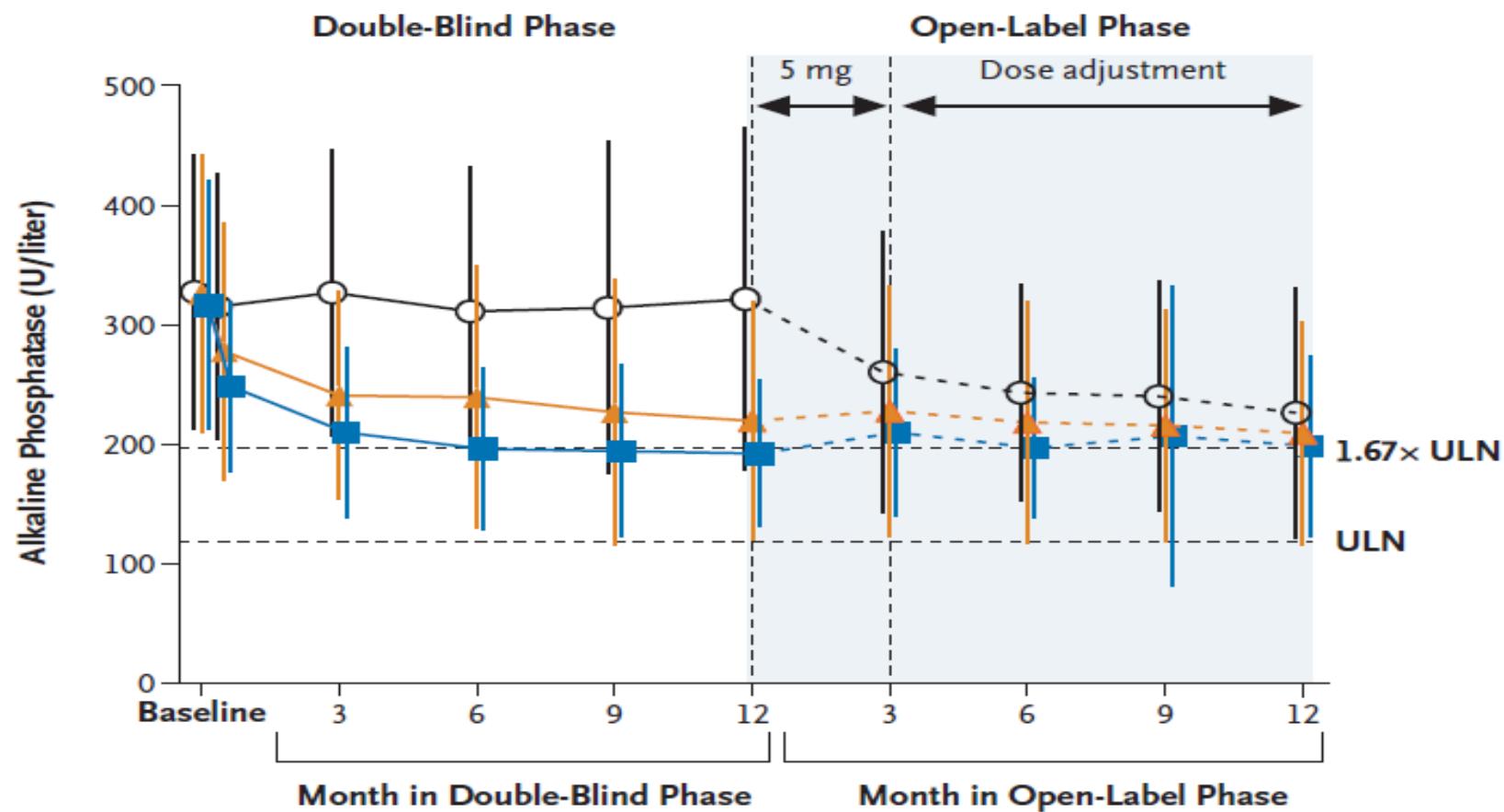
**FXR agonist: Obeticholic acid**

Nevens et al., New Engl J Med 2016; 375: 631



# Obeticholic acid improves serum alkaline phosphatase in PBC patients with incomplete response to UDCA

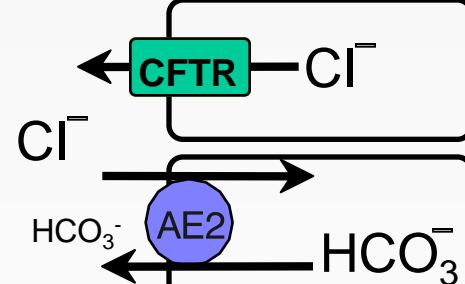
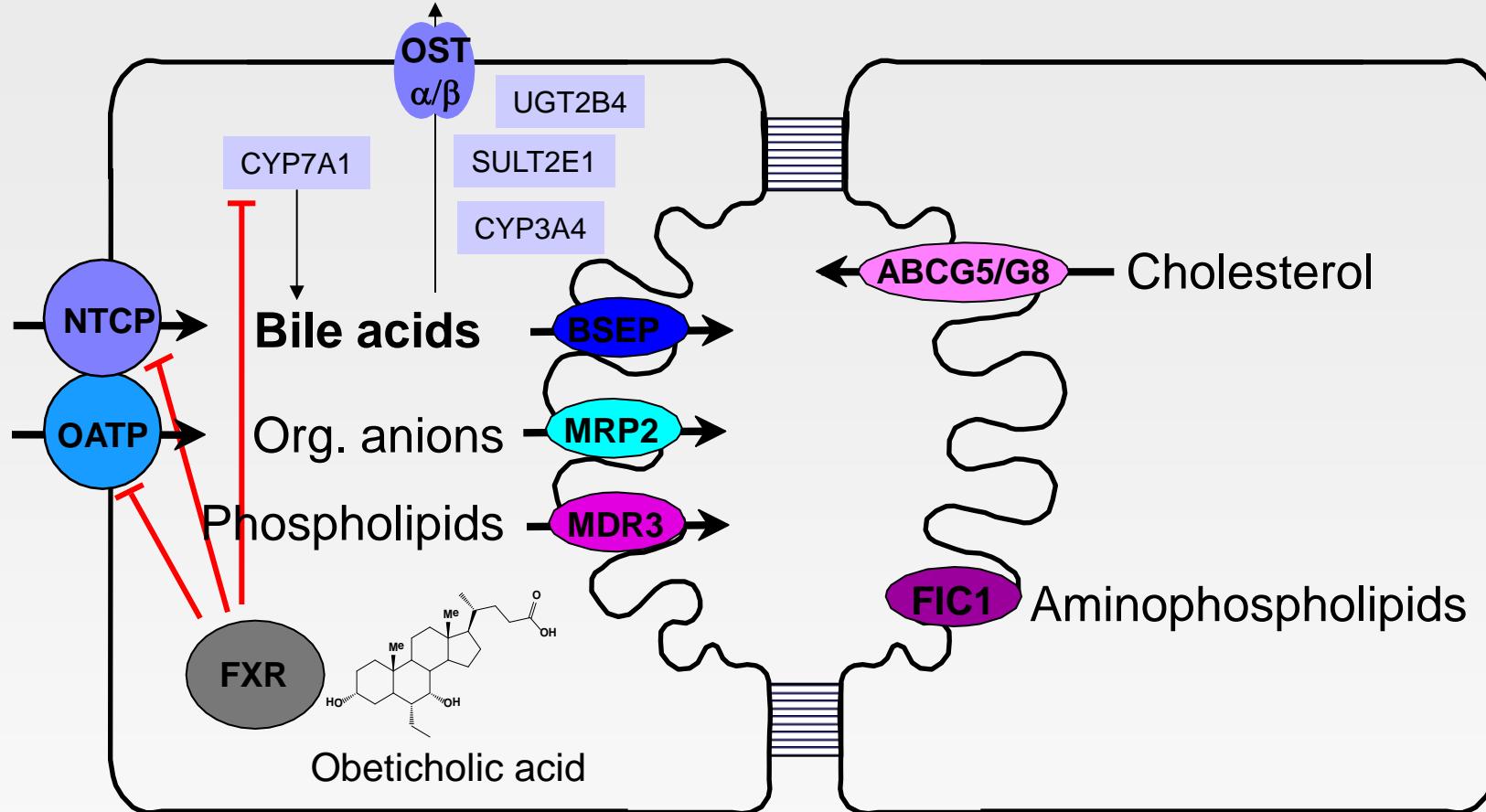
## Phase 3



### No. of Patients

	73	69	71	69	70	64	60	59	59
Placebo	73	69	71	69	70	64	60	59	59
Obeticholic acid, 5–10 mg	70	69	69	66	64	63	62	62	60
Obeticholic acid, 10 mg	73	66	64	64	62	64	59	61	59

# The Farnesoid X receptor (FXR) protects against toxic effects of hydrophobic bile acids

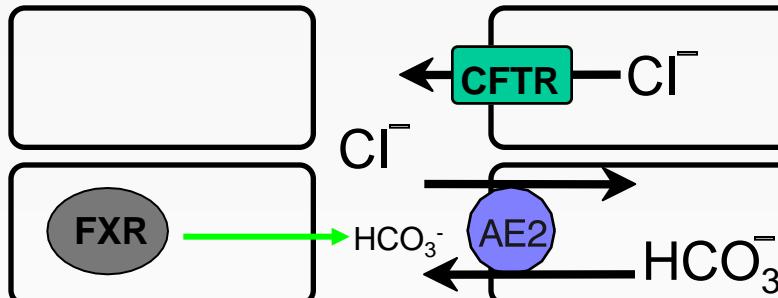
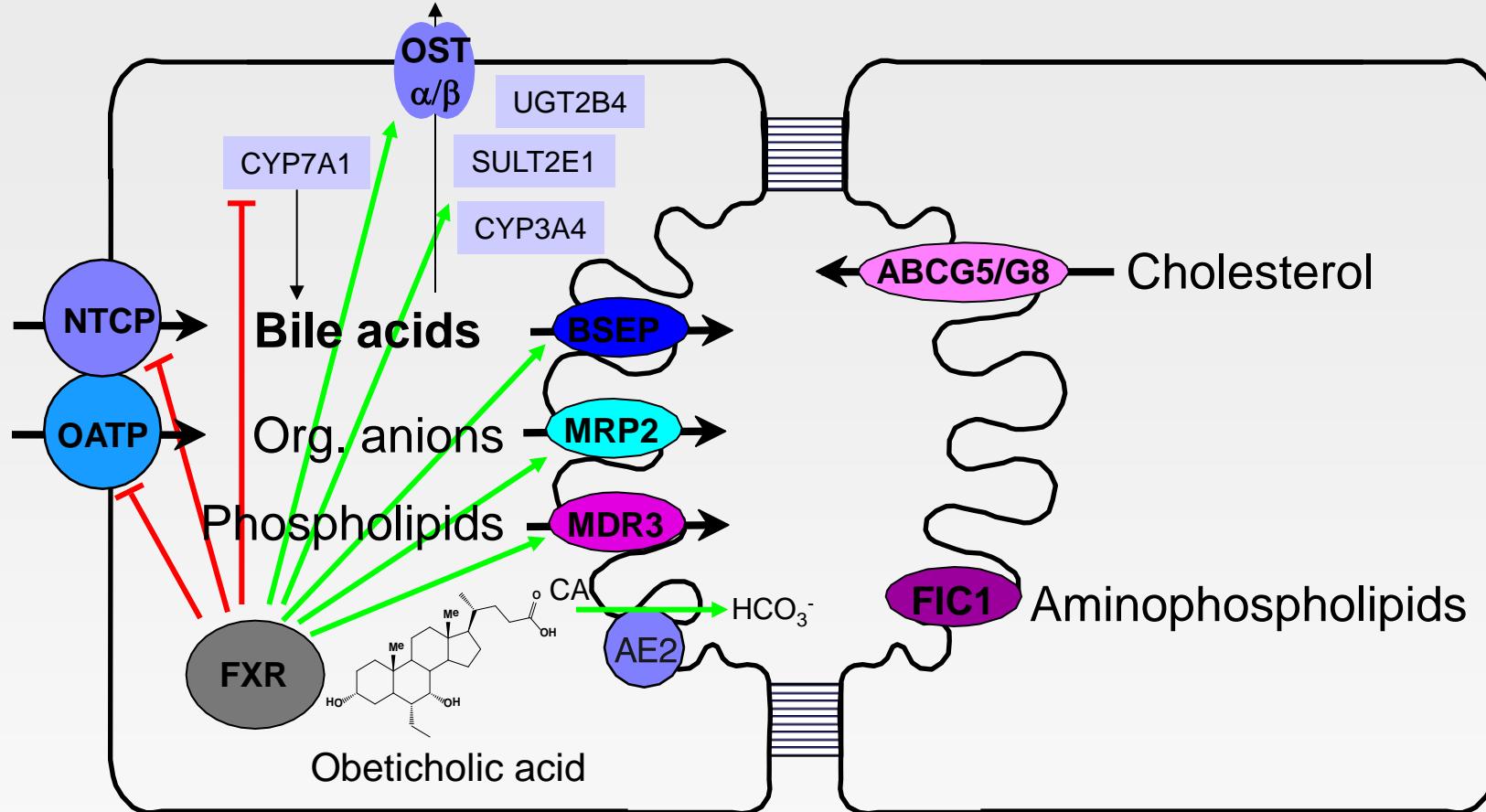


BSEP: ABCB11  
MRP2: ABCC2  
MDR3: ABCB4  
FIC1: ATP8B1

CA, Carboanhydrase

For details, see:  
Trauner et al., Hepatology 2017;65:1393

# The Farnesoid X receptor (FXR) protects against toxic effects of hydrophobic bile acids



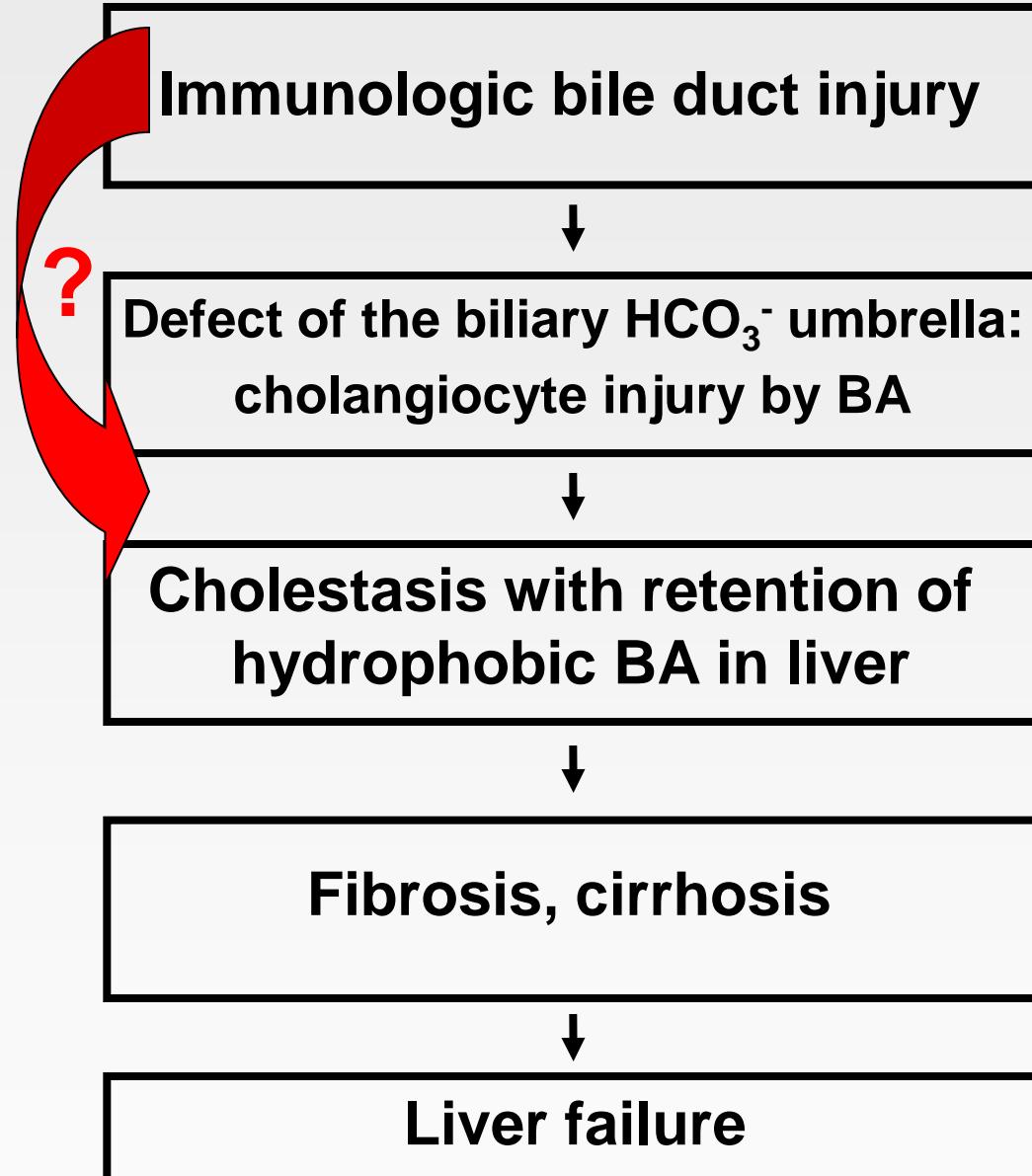
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# Primary biliary cholangitis:

Potentially new **Therapy**

## Potential pathogenetic mechanisms



**FXR agonist: Obeticholic acid**

Nevens et al., New Engl J Med 2016; 375: 631

**PPAR agonist: Bezafibrate**

Corpechot et al., New Engl J Med 2018;378:2171

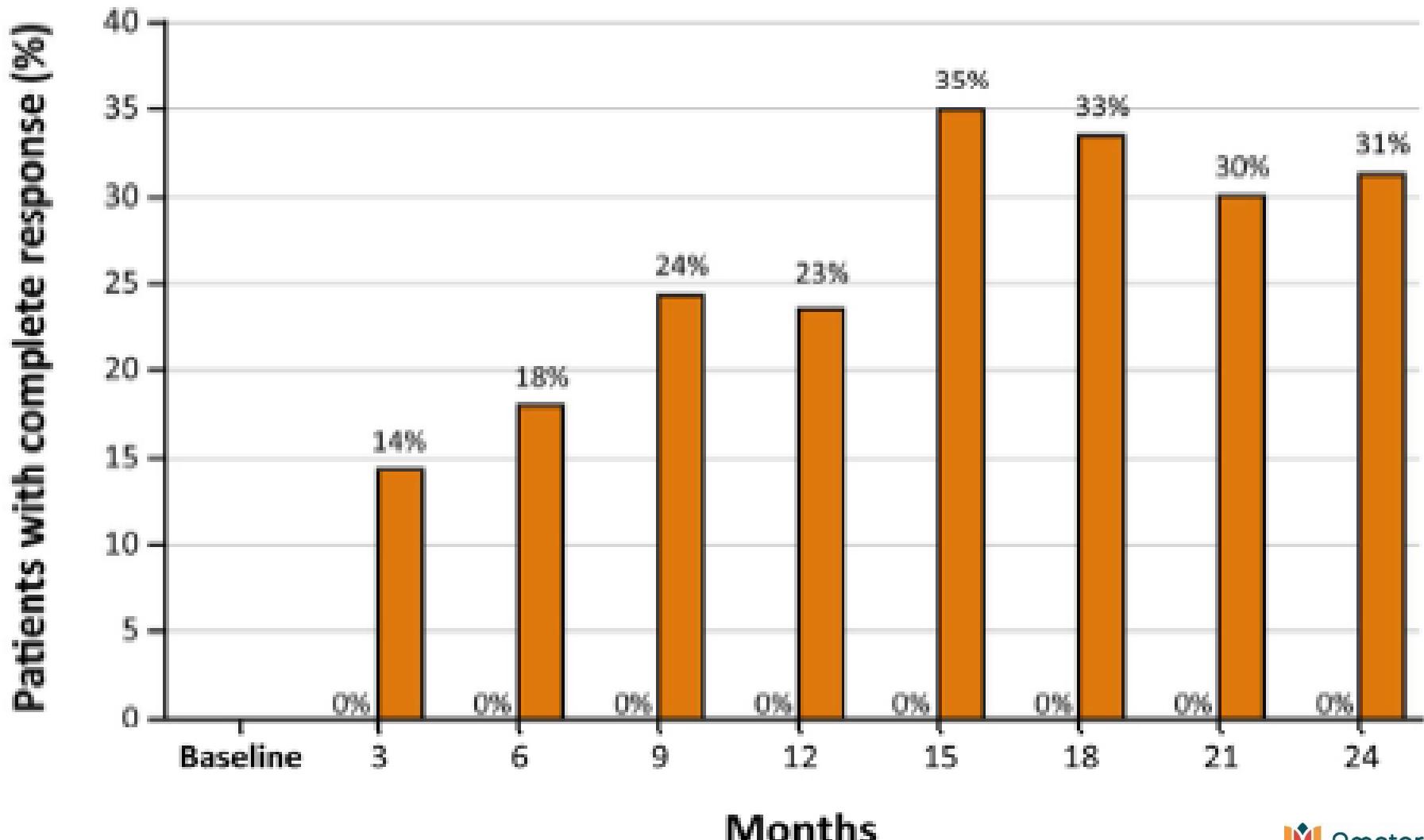
**Ursodeoxycholic acid  
(13-15 mg/kg/d)**

# Bezafibrate normalizes serum liver tests in PBC patients with incomplete response to UDCA

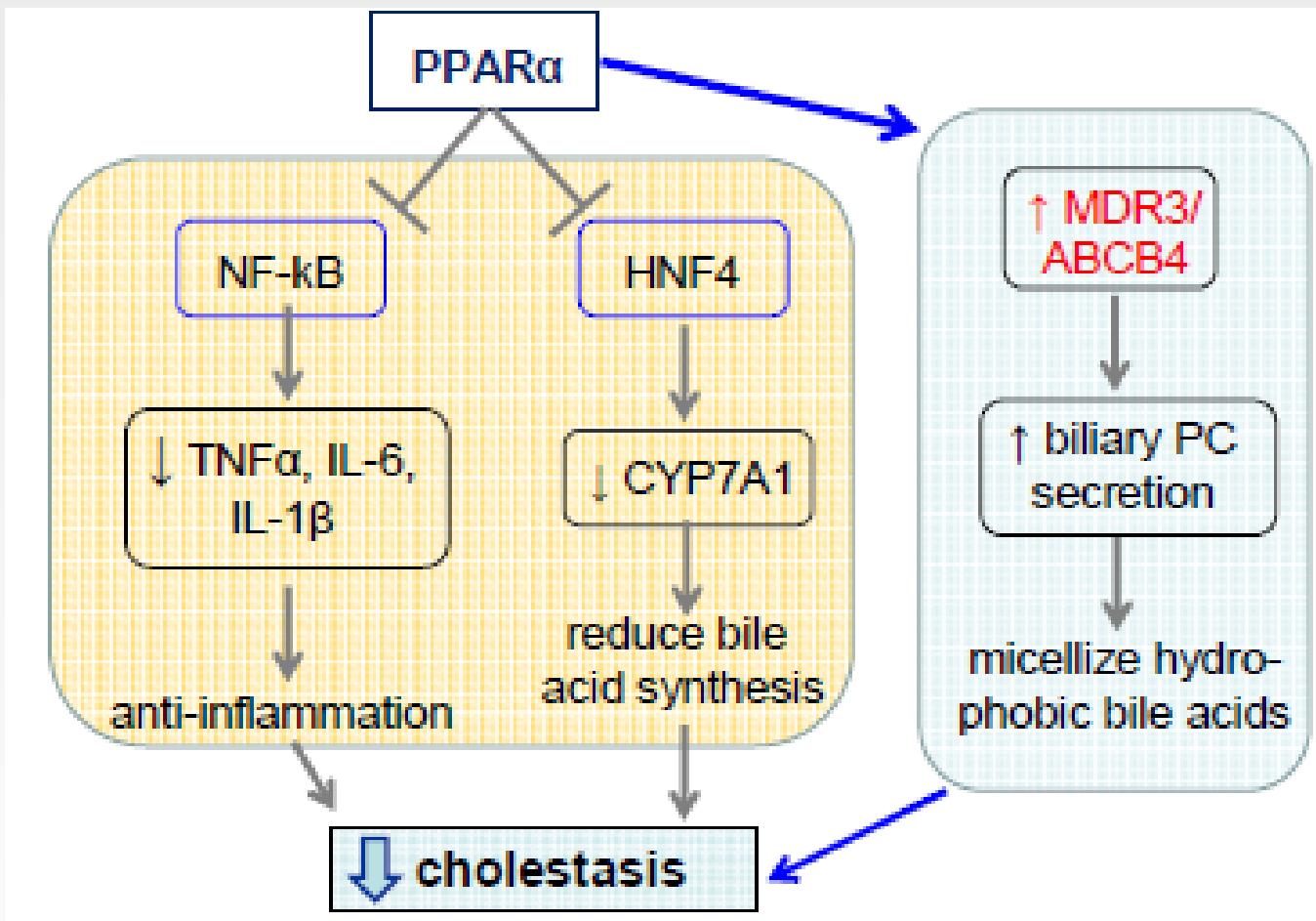
## Phase 3

Placebo

Bezafibrate



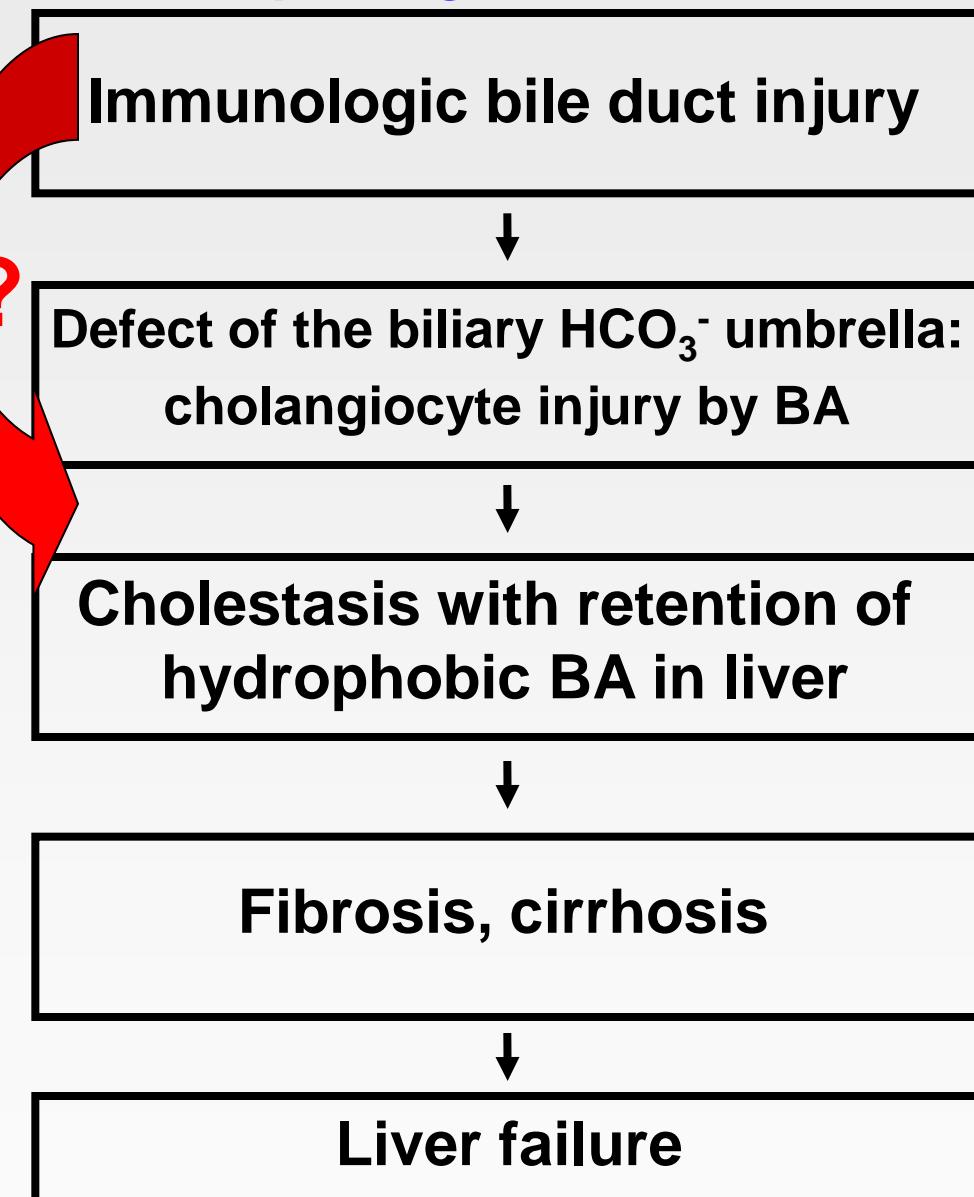
# Putative mechanisms of fibrate-induced reduction of cholestasis in the liver



# Primary biliary cholangitis:

Potentially new **Therapy**

## Potential pathogenetic mechanisms



**FXR agonist: Obeticholic acid**

Nevens et al., New Engl J Med 2016; 375: 631

**PPAR agonist: Bezafibrate**

Corpechot et al., New Engl J Med 2018;378:2171

**GR/PXR-Agonists: e.g., Budesonide?**

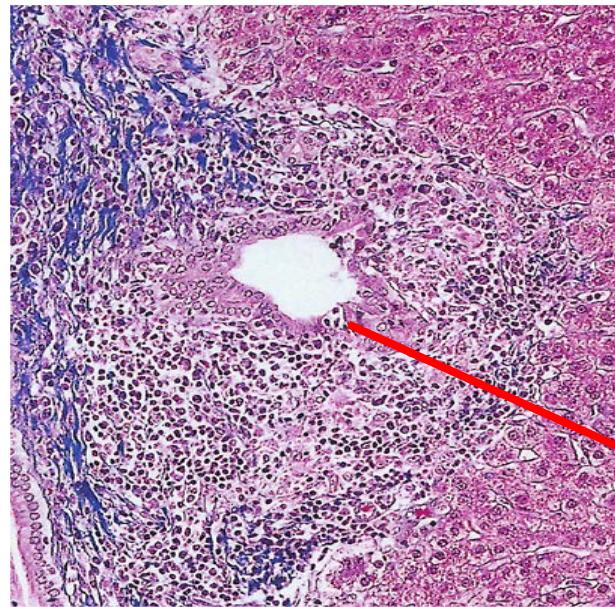
Hirschfield et al, in preparation

**Ursodeoxycholic acid  
(13-15 mg/kg/d)**

**Liver transplantation**

# Primary biliary cholangitis

## Characteristics



Florid, non-suppurative, destructive cholangitis

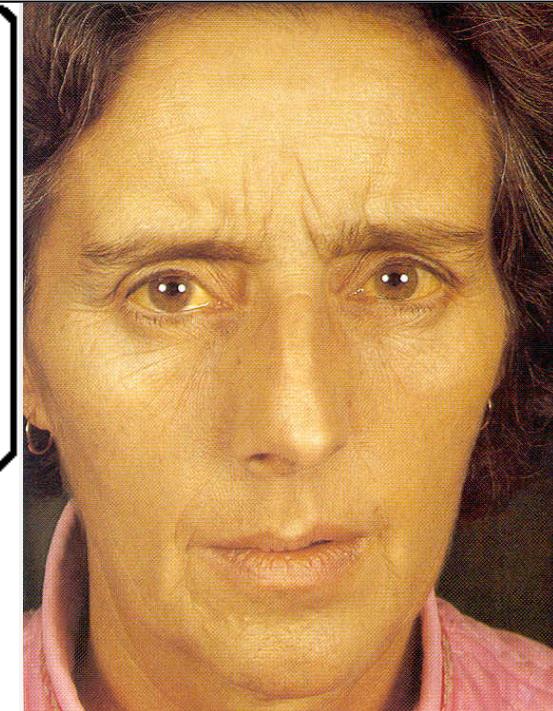
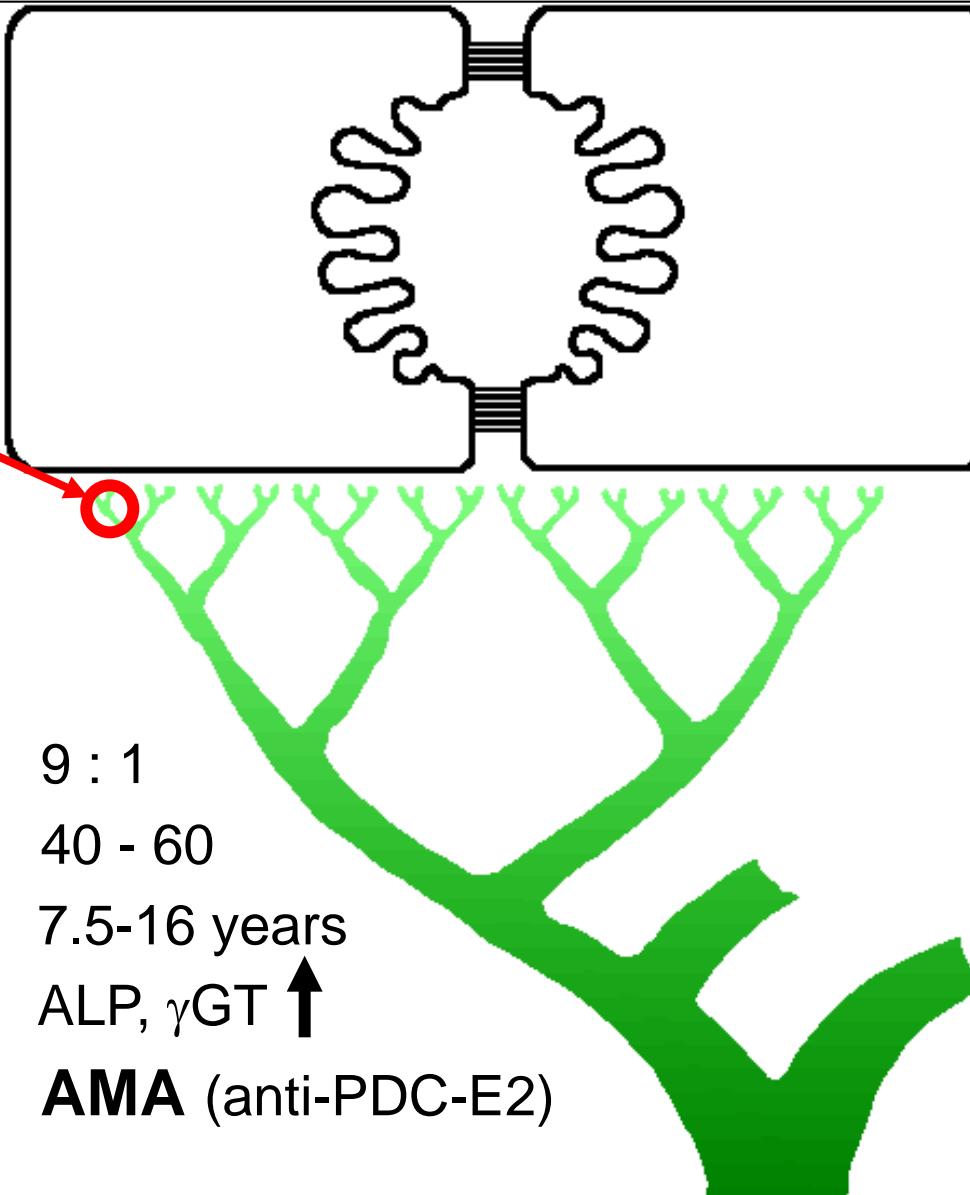
**Women : Men**

**Age at diagnosis**

**Survival** without treatment

**Cholestasis**

**Autoantibodies**



Sherlock and Summerfield, 1991

### Symptoms

- Fatigue
- **Pruritus**
- Sicca syndrome
- ...

# Therapeutic Targets in Pruritus of Cholestasis

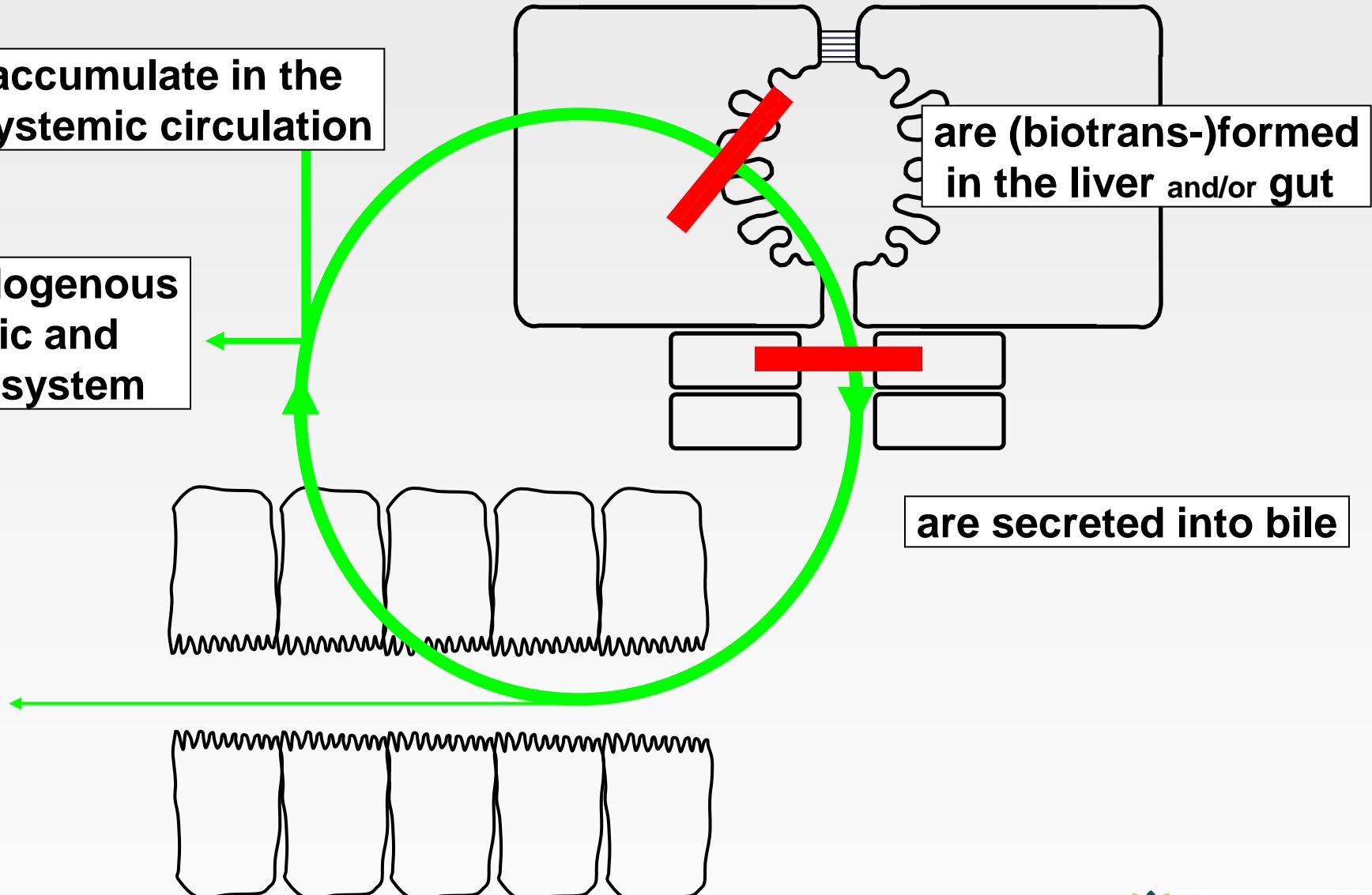
Pruritogens...

accumulate in the systemic circulation

affect the endogenous serotonergic and opioidergic system

are (biotrans-)formed in the liver and/or gut

are secreted into bile



# Therapeutic Targets in Pruritus of Cholestasis

Pruritogens...

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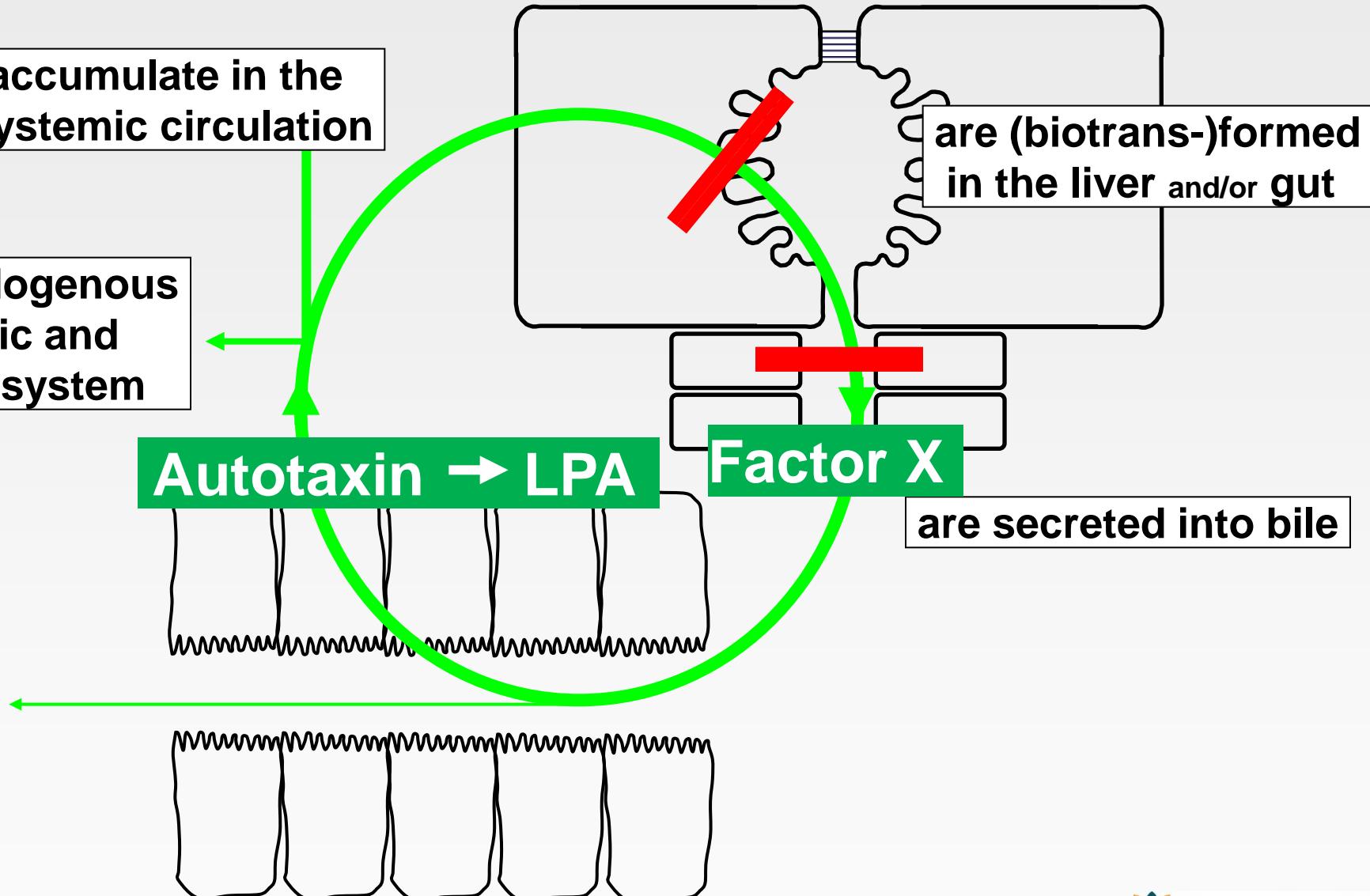
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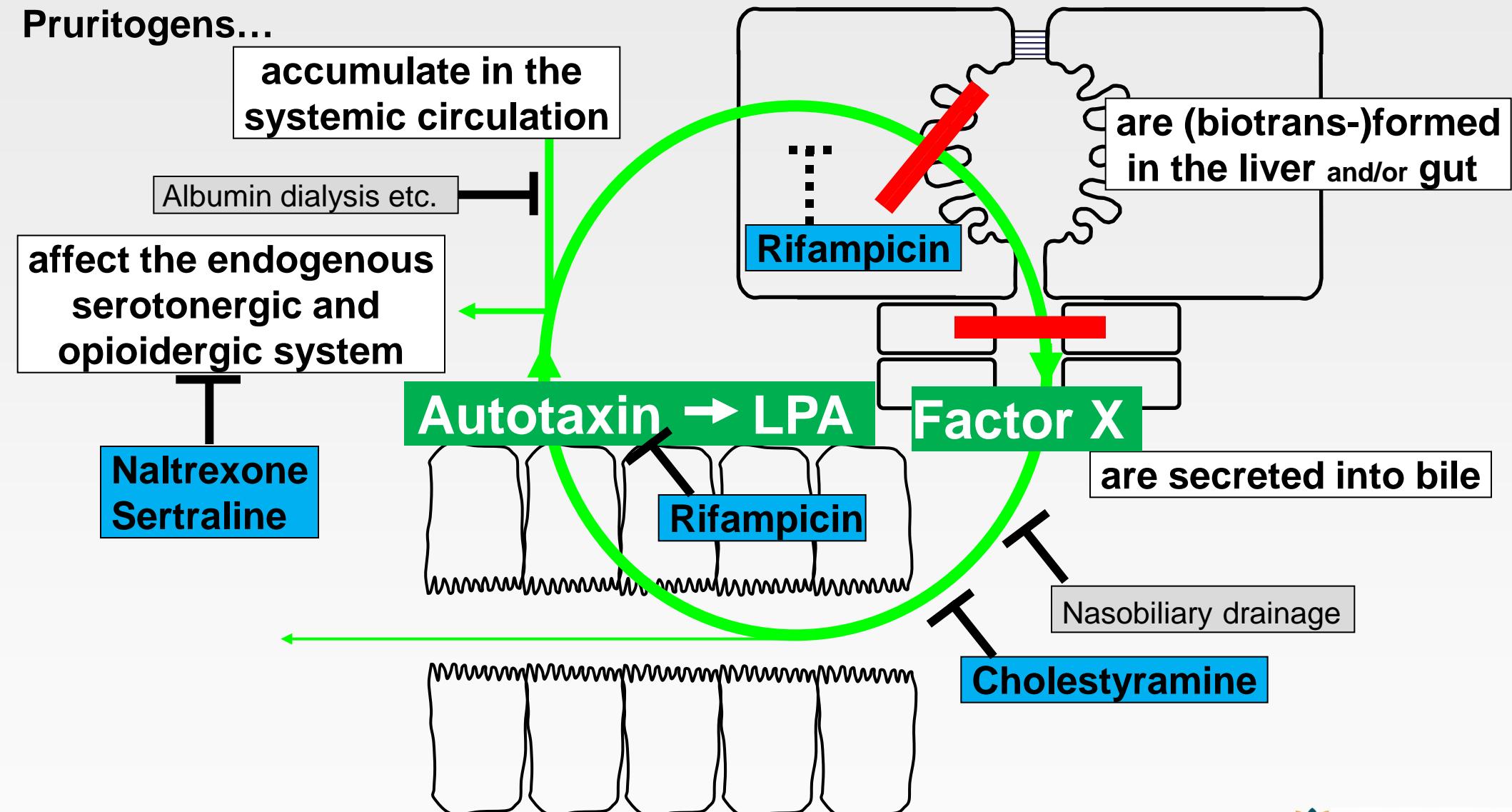
Autotaxin → LPA

Factor X



# Therapeutic Targets in Pruritus of Cholestasis

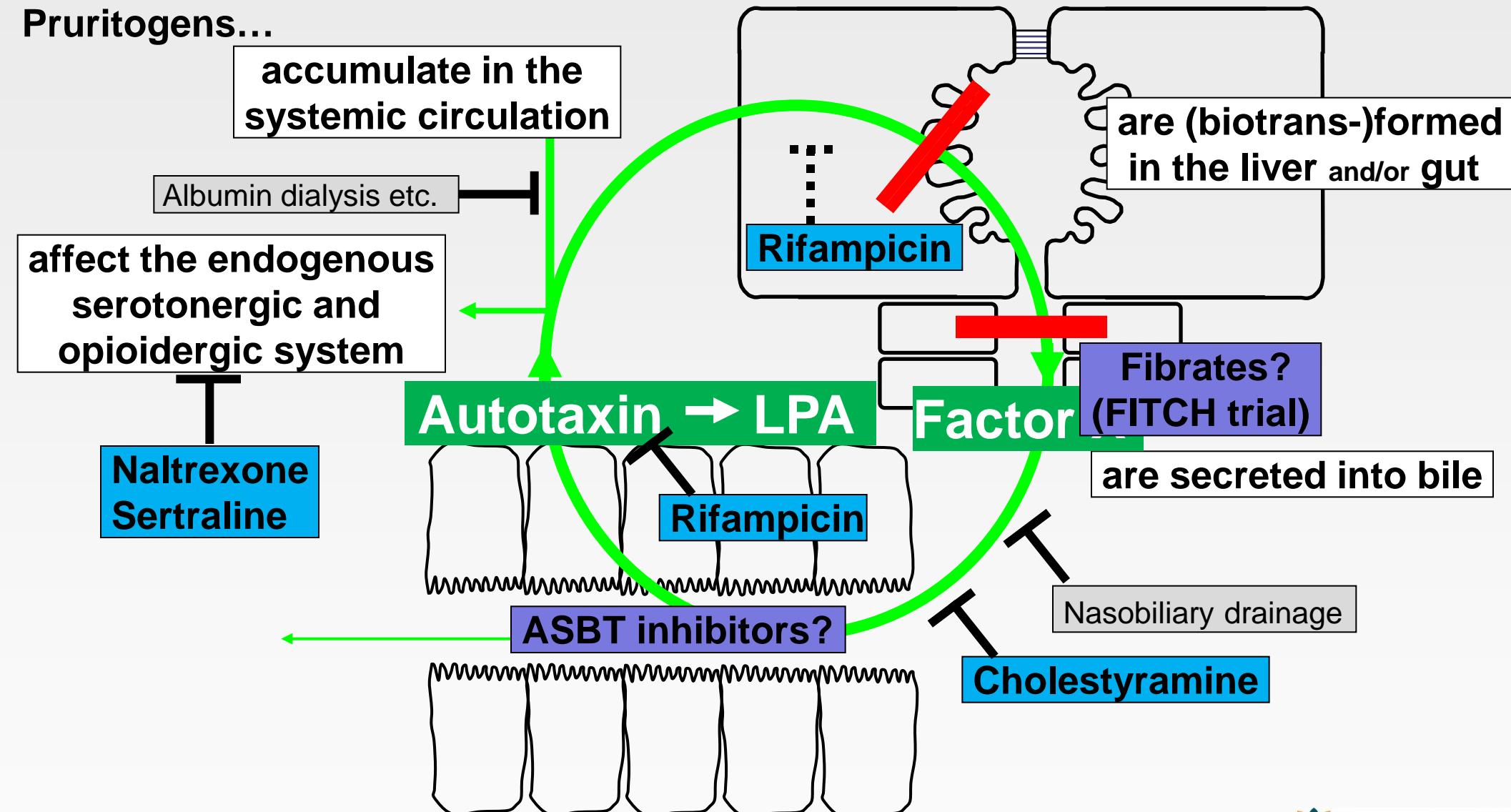
Pruritogens...



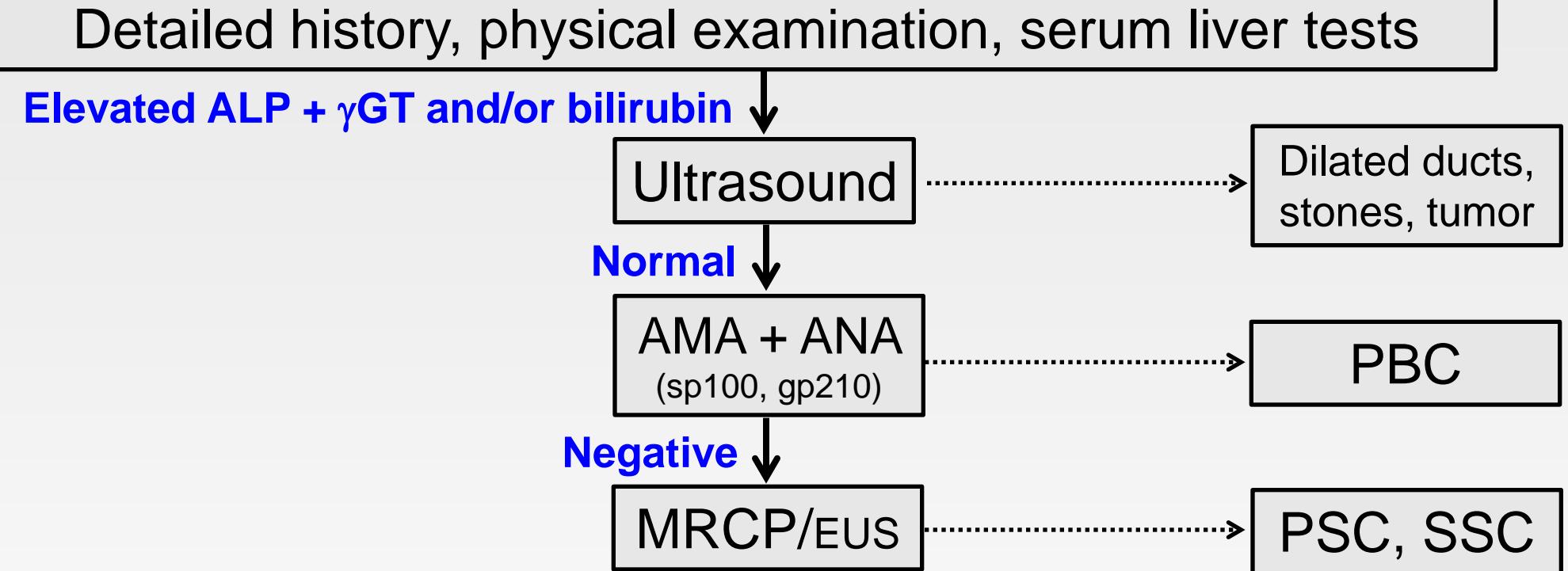
# Therapeutic Targets in Pruritus of Cholestasis

Present and future

Pruritogens...



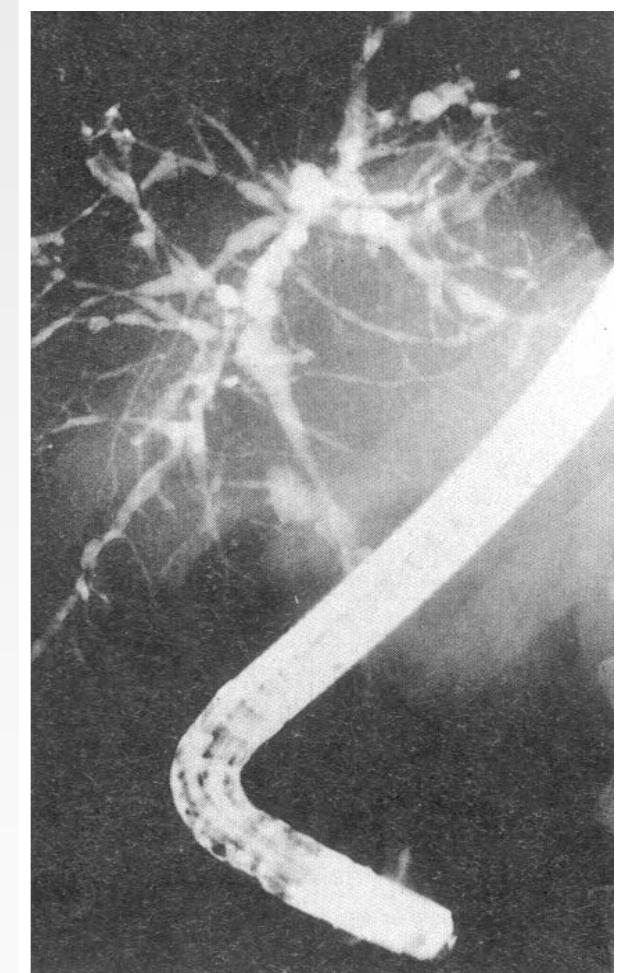
# Diagnostic approach to cholestasis



# Primary sclerosing cholangitis

## The typical patient in the Netherlands

Point prevalence (per 100.000)	6.0
Incidence (per 100.000/year)	0.5
Age at manifestation (yrs, mean)	38.9
Male gender	64%
Inflammatory bowel disease	68%
UDCA treatment	92%
LTx-free survival (yrs, mean)	<b>21.2</b>
(LTx-free survival of 450 patients at 3 LTx centres	13.2)
Cholangiocarcinoma	7%
Colorectal carcinoma	3%



m, 42 years

## *Pathogenetic model*

Immunologic bile duct injury  
(Cytokine-mediated)



Bile duct stenoses  
Aggravation of injury by BA



Cholestasis with retention of  
hydrophobic bile acids in liver



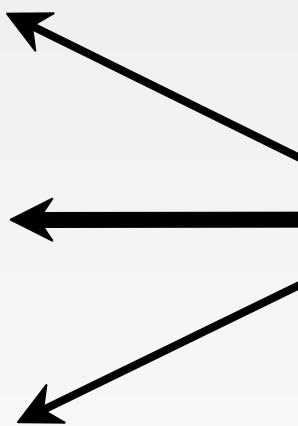
Fibrosis, cirrhosis



Liver failure

Ursodeoxycholic acid  
(15-20 mg/kg/d)

?



Liver transplantation

## *Pathogenetic model*

Immunologic bile duct injury  
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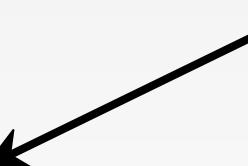


Liver failure



Endoscopic balloon dilatation

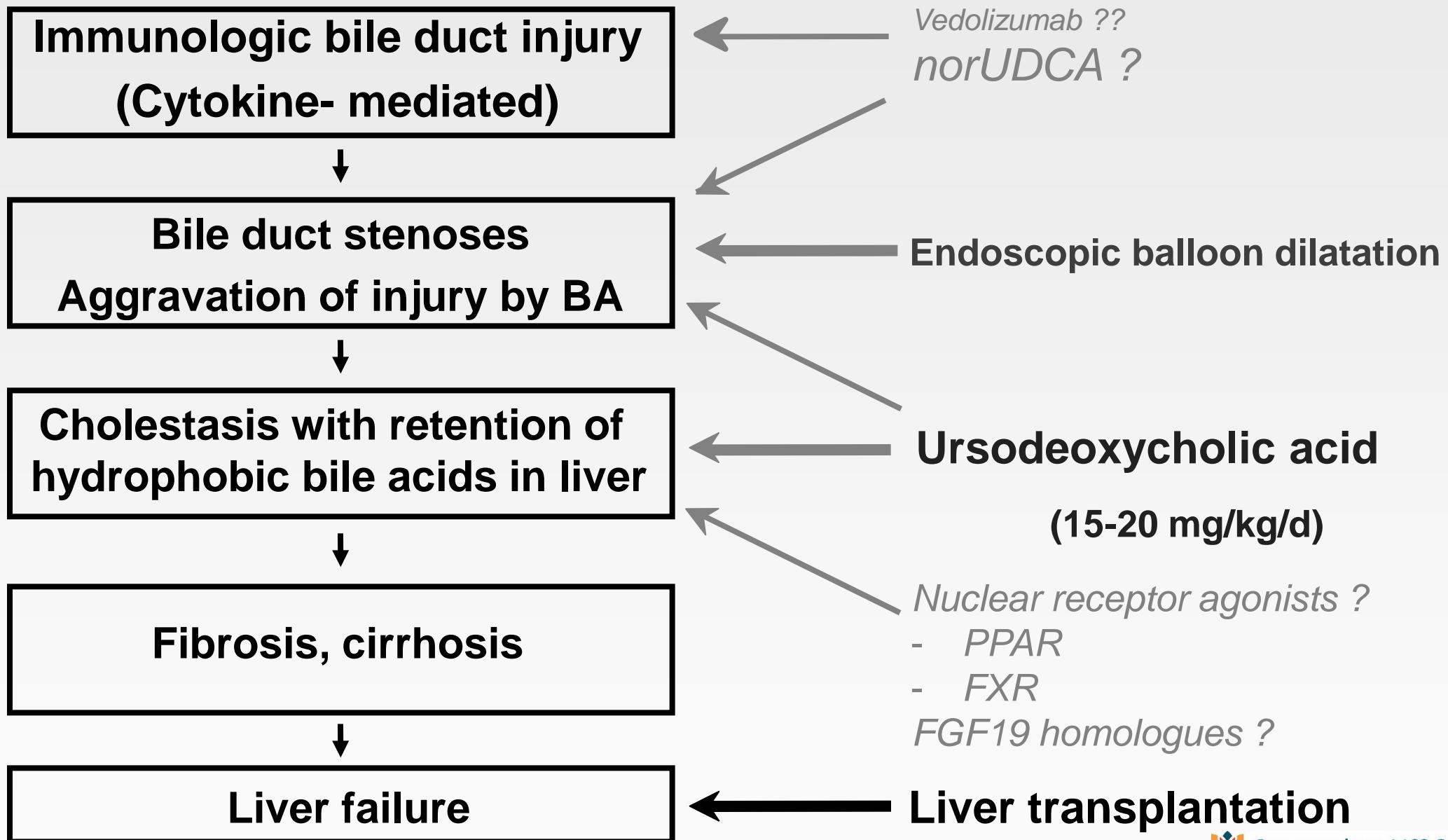
Ponsioen et al., Gastroenterology 2018;155:752



Ursodeoxycholic acid  
(15-20 mg/kg/d)

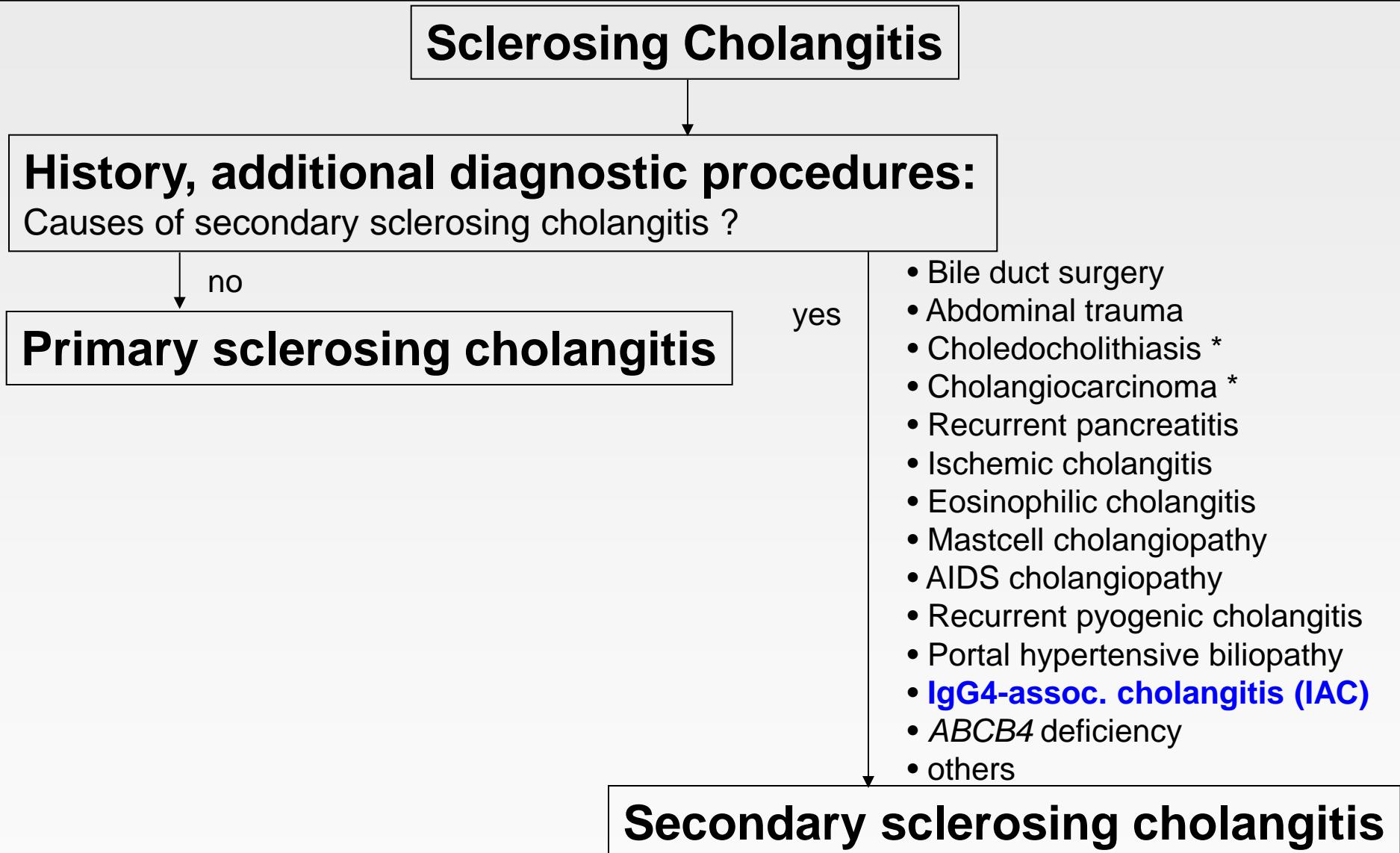


Liver transplantation



# The Patient with Sclerosing Cholangitis

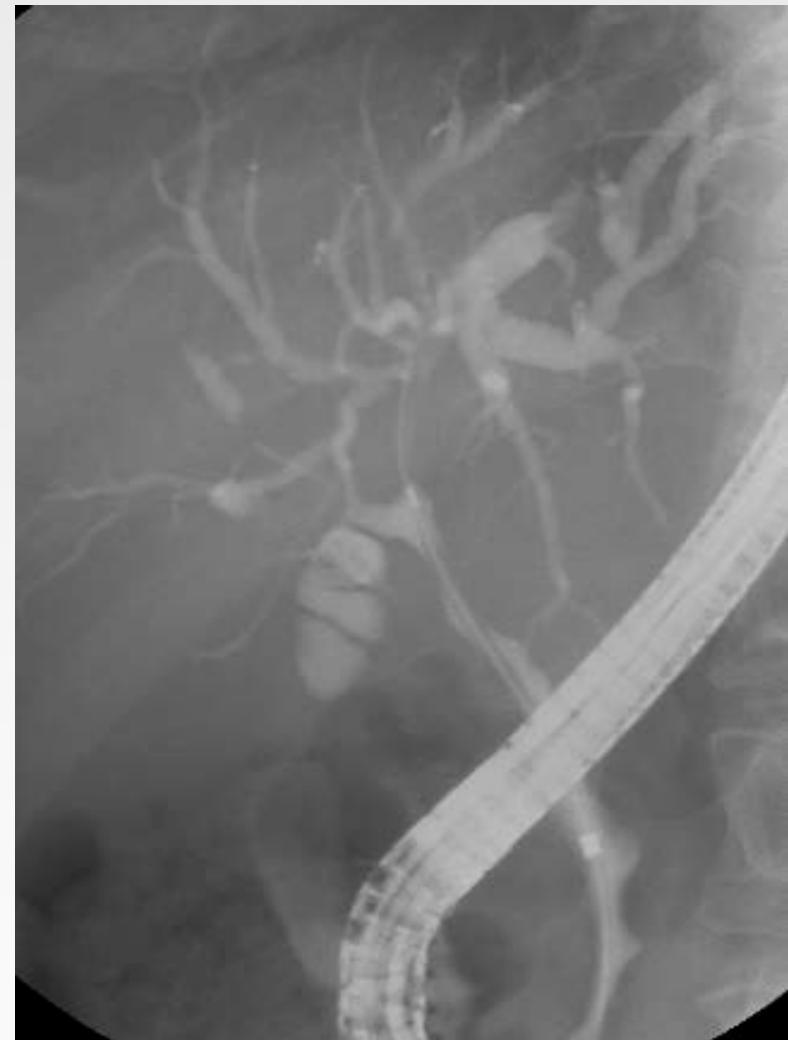
## Diagnostic Algorithm



\* may be consequence of PSC

# IgG4-associated cholangitis (IAC)

- Male (>80%)
- Middle aged / elderly (> 50 yrs)
- **Jaundice**, weight loss, abdominal pain
- Localized organ swelling / tumor
- Elevated serum / tissue IgG4
- Other organ manifestations of IgG4-RD



Stone et al N Engl J Med 2012;366:539  
Hubers et al. Clin Rev Allerg Immunol 2015;48:198

71 yrs, m; IgG4 11.9 g/L (n < 1.4)  
Alderlieste et al., Digestion 2009;79:220

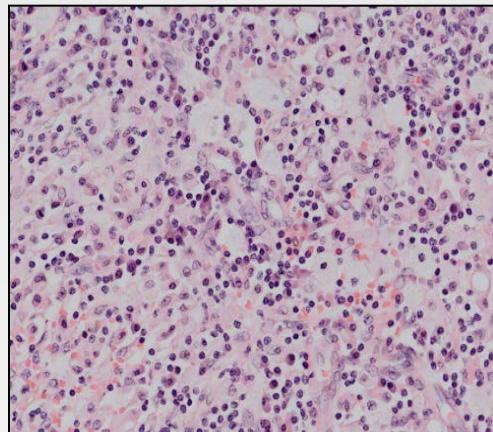
# IgG4-associated cholangitis

## HISORt Criteria

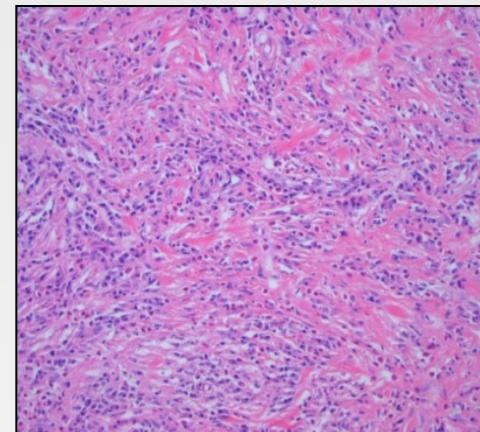
- **Histology** IgG4+ plasma cells, storiform fibrosis, obliterative phlebitis
- **Imaging** Organ swelling
- **Serology** Serum IgG4
- **Other organ involvement** Glands, others
- **Response to treatment** Corticosteroids

# Consensus criteria: Histology of IgG4-related disease

2 of 3 major histological features



Lymphoplasmacytic infiltrate

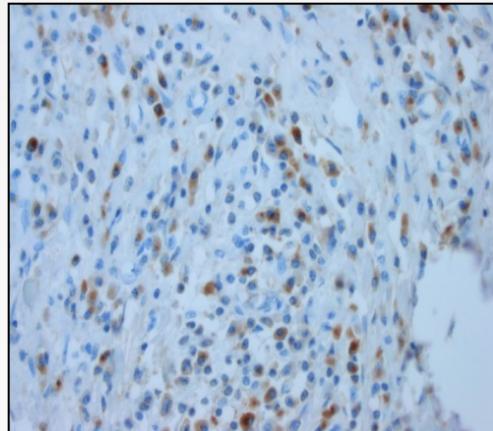


Storiform fibrosis



Obliterative phlebitis

>50 IgG4+ plasma cells  
(resection specimen)

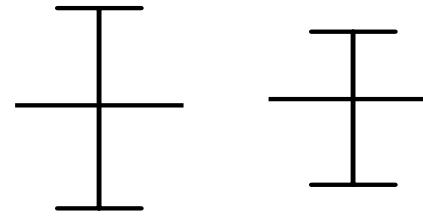


Deshpande et al. Mod Pathol 2012;25:1181

Courtesy of J. Verheij

# Diagnostic value of serum IgG4 is limited for IgG4-RD

1.4

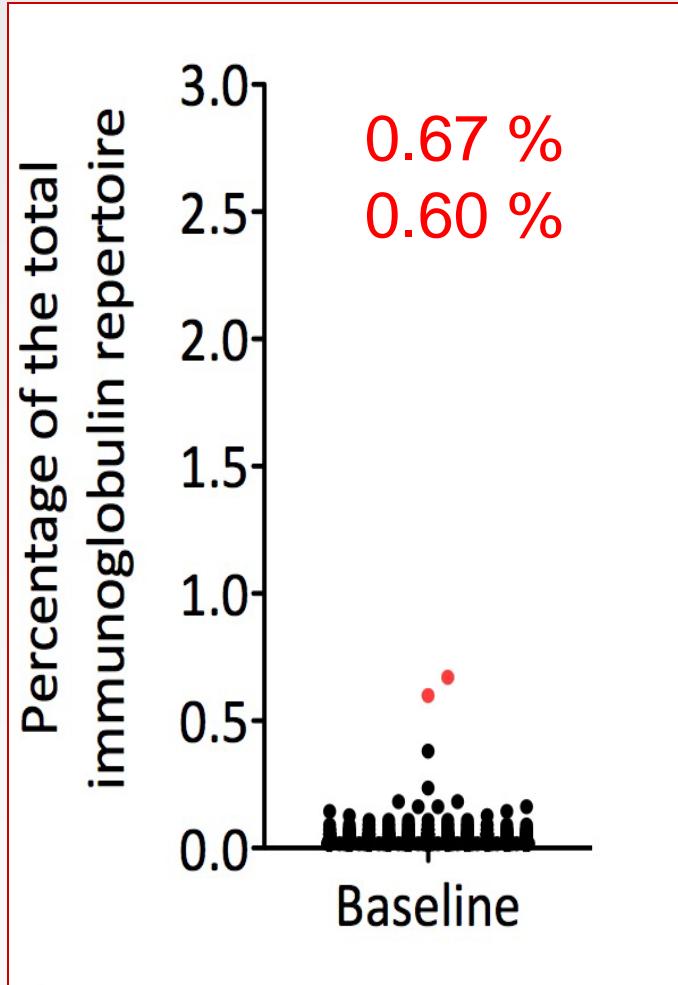


Sensitivity = 86%  
Specificity = 75%

# IgG4-associated cholangitis

## B-cell receptor sequencing

Patient #1



- Two highly expanded IgG4<sup>+</sup> B cell clones

### B-cell receptor (BCR) sequencing protocol

- Isolation of B-cell mRNA
- Amplification of BCR heavy chains
- Next generation sequencing
- Customized bioinformatics algorithms

➔ Specific B-cell responses may be relevant  
in the pathogenesis of IgG4-related disease

# IgG4-associated cholangitis: B cell receptor sequencing

The most prominent IgG4+ BCR clone ranks higher in IgG4-RD than control

Ranking of the  
most prominent  
IgG4+ BCR  
clone

among all IgG clones

IAC

HC

DC

IAC  
4 weeks

IAC  
8 weeks  
prednisolone

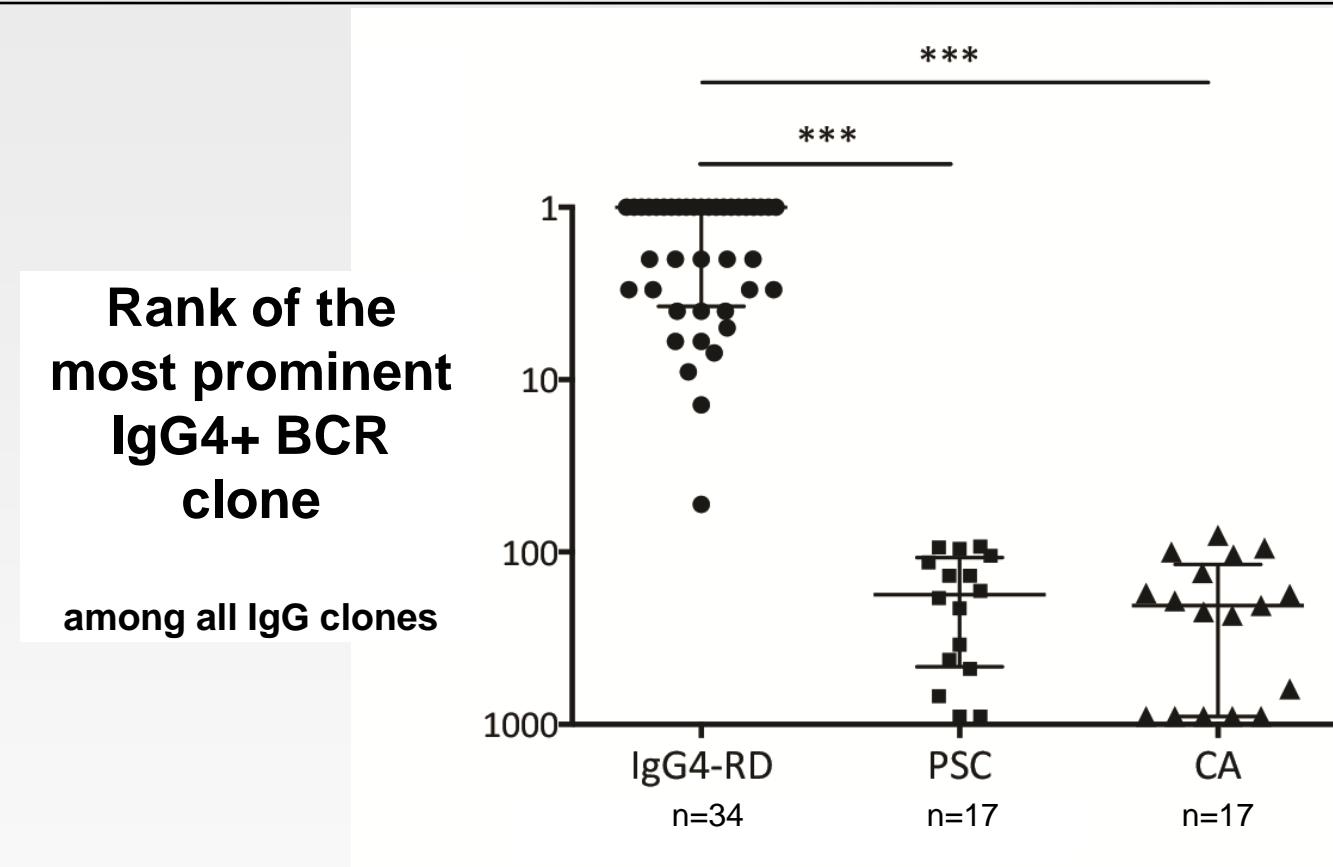
IAC: IgG4 cholangiopathy

HC: Healthy control

DC: Disease control

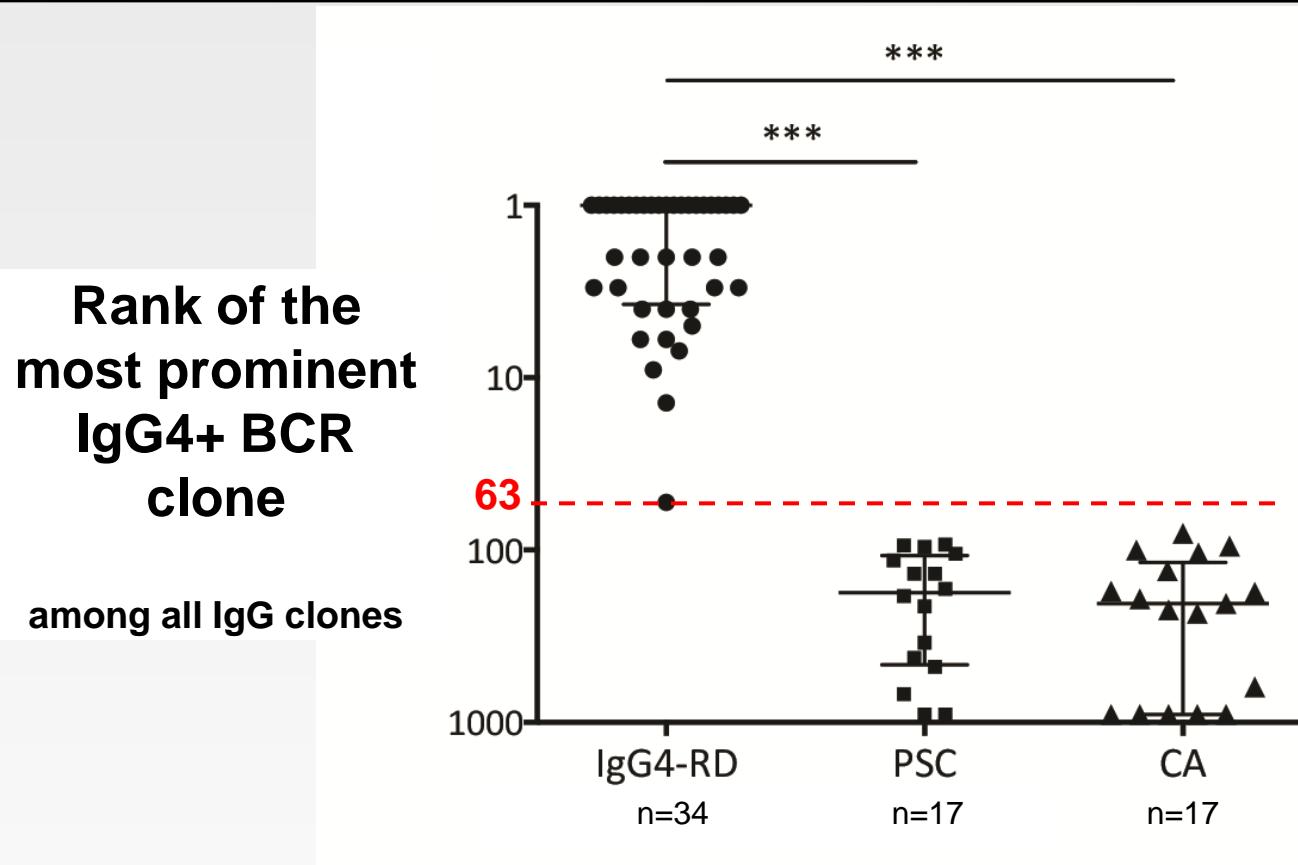
# Diagnosis of IgG4-associated cholangitis

The most prominent IgG4+ BCR clone ranks higher in IgG4-RD than control



# Diagnosis of IgG4-associated cholangitis

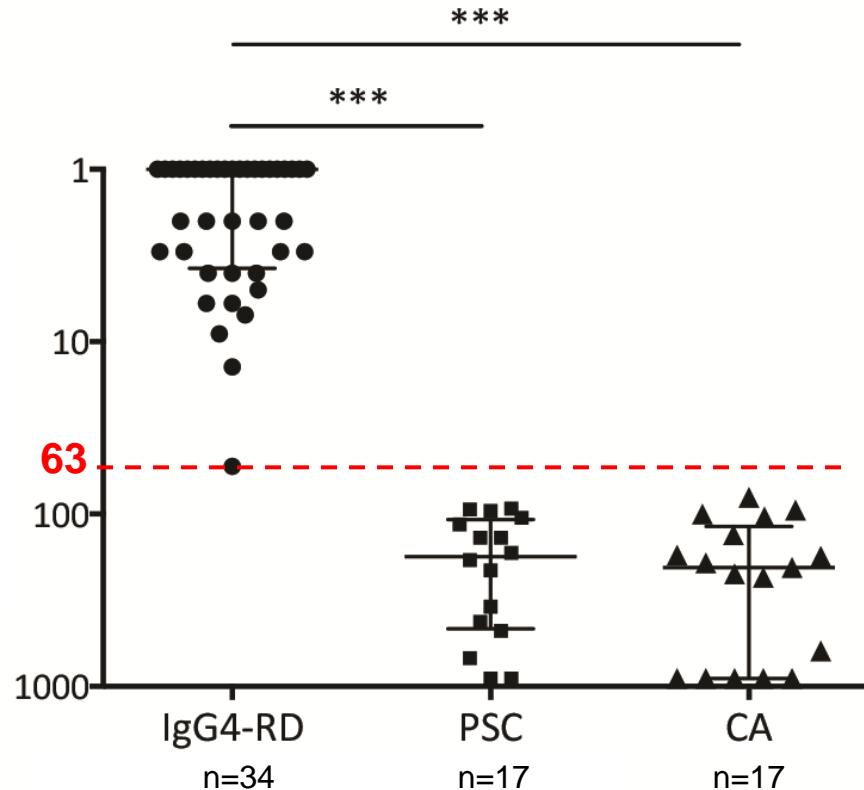
The most prominent IgG4+ BCR clone ranks higher in IgG4-RD than control



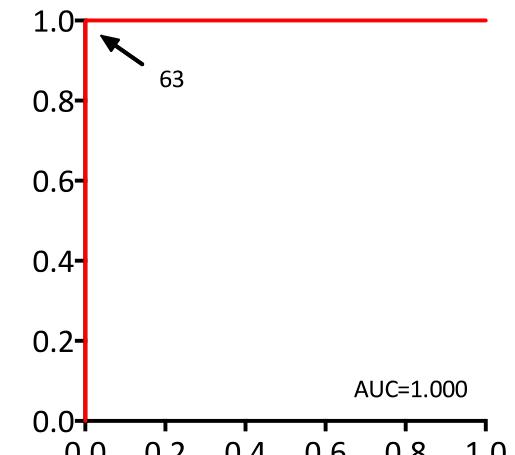
# Diagnosis of IgG4-associated cholangitis

The most prominent IgG4+ BCR clone ranks higher in IgG4-RD than control

Rank of the  
most prominent  
IgG4+ BCR  
clone  
among all IgG clones



Sensitivity = 100%  
Specificity = 100%



# Chronic Exposure to Occupational Antigens May Play a Key Role in the Initiation and/or Maintenance of IgG4-Related Disease



**“Blue collar” work**

(> 1 year, mostly lifelong)

IAC/AIP (n=25 and 44, resp.)

PSC (n=21 and 22, resp.)

Amsterdam

88 %

16 %

Oxford

61 %

22 %

# Treatment of IgG4-associated cholangitis

## 1. Initial treatment:

- 40 mg\* predniso(lo)ne / day for 4 weeks
- Tapering of daily predniso(lo)ne: 5 mg/week
- Total treatment duration: 11 weeks

\* (10-)20 mg predniso(lo)n / day may be sufficient

Buijs et al. Pancreas 2014;43:261

## 2. Long-term maintenance treatment (incomplete responders):

- 5(-10) mg/d Predniso(lo)ne
- $\leq$  2 mg/kg/d Azathioprine

3. Experimental (corticosteroid-refractory patients): Rituximab; Tacrolimus

# Diagnostic approach to cholestasis

♀ 34 yrs

Detailed history, physical examination, serum liver tests

Elevated ALP +  $\gamma$ GT and/or bilirubin

Ultrasound

Dilated ducts,  
stones, tumor

Normal

AMA + ANA  
(sp100, gp210)

PBC

Negative

MRCP/EUS

PSC, SSC

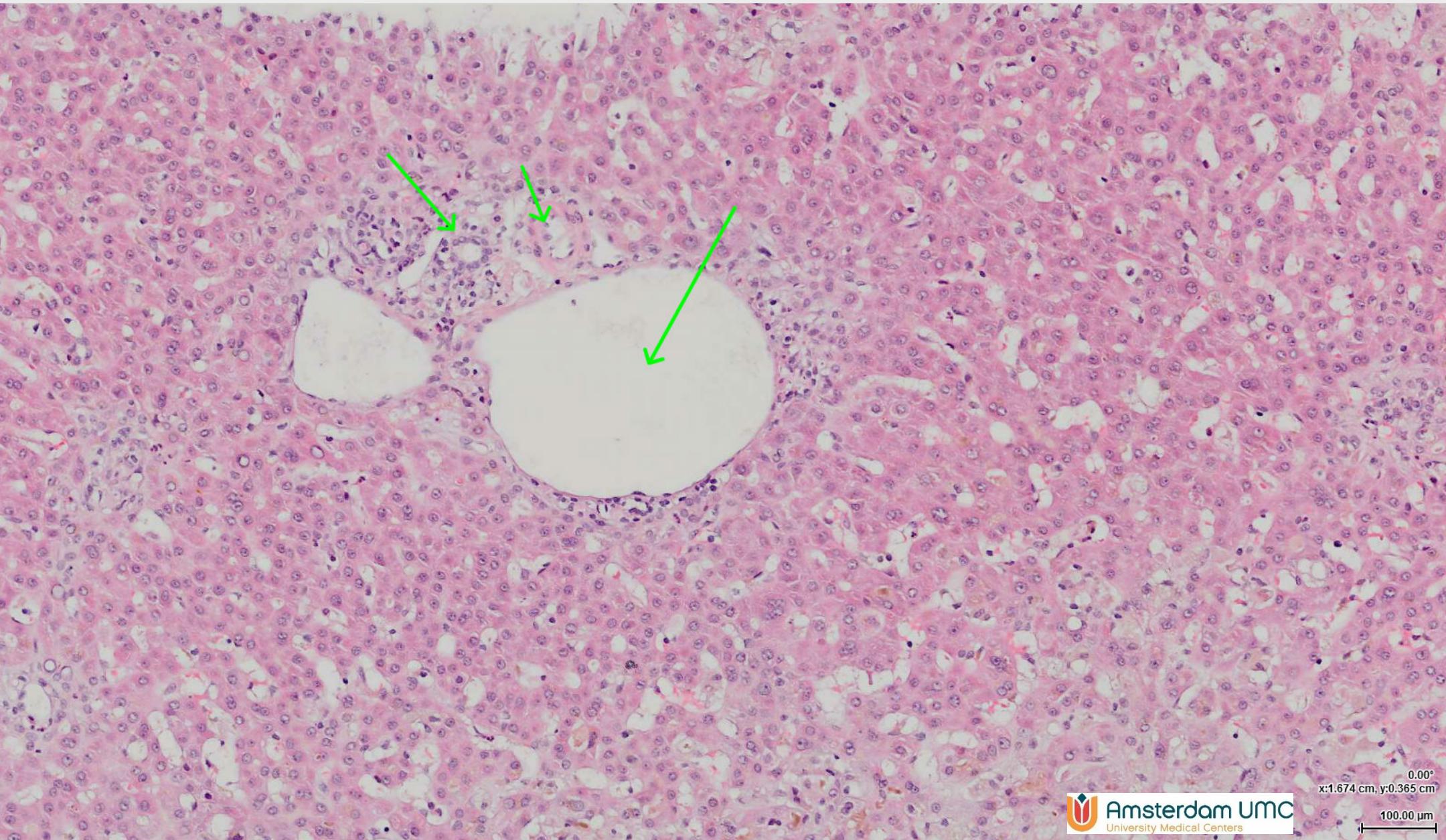
ERCP ?

Negative

Liver biopsy

Parenchymal  
disease

# Liver biopsy



# Diagnostic approach to cholestasis

♀ 34 yrs

Detailed history, physical examination, serum liver tests

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Liver biopsy

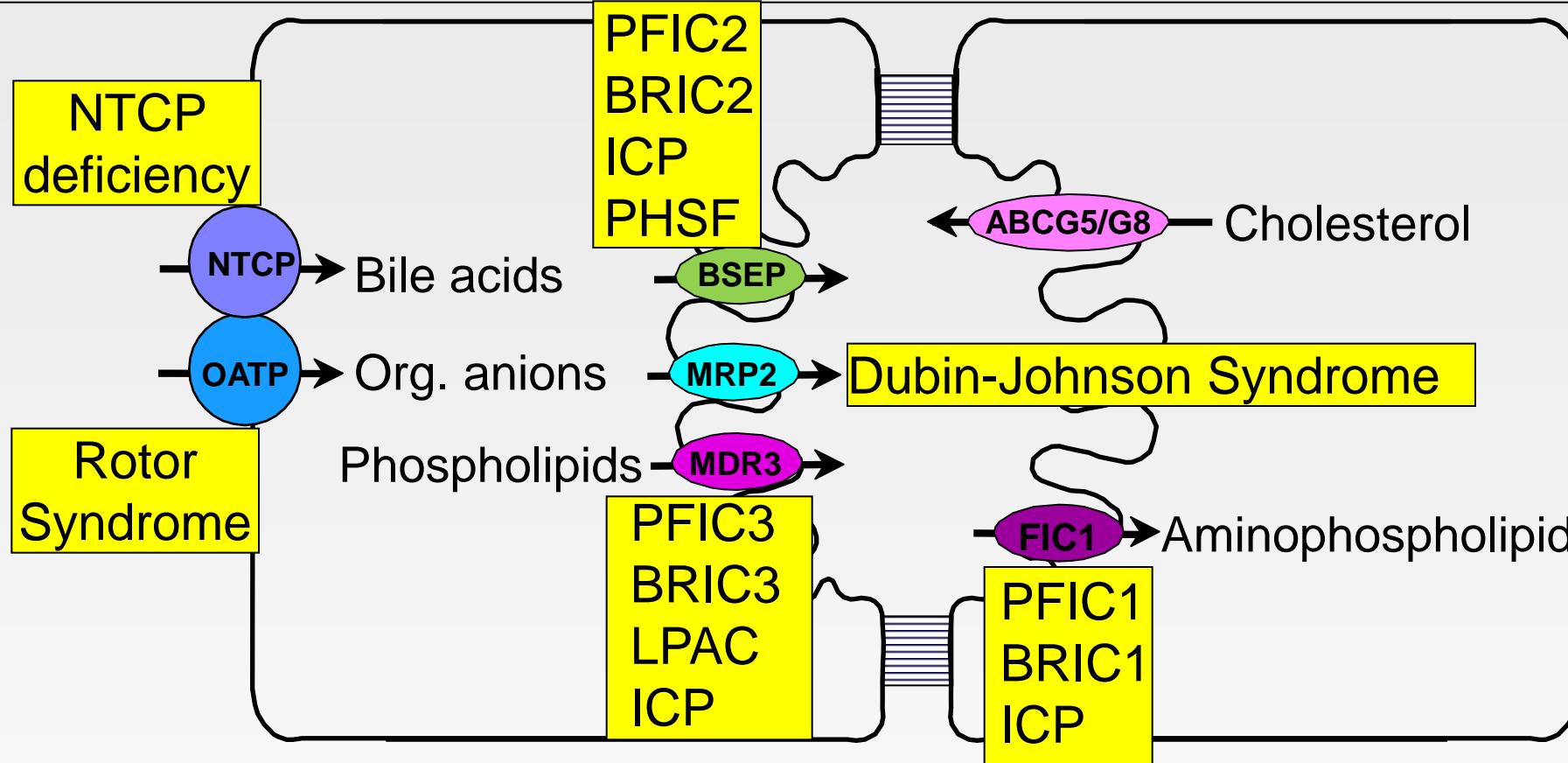
Parenchymal  
disease

Negative

Genetic analysis

ABCB4 def.,  
(ABCB11, ATP8B1, etc)

# Consequences of transporter defects



Transporter	Gene
FIC1	<i>ATP8B1</i>
BSEP	<i>ABCB11</i>
MDR3	<i>ABCB4</i>

**PFIC:** Progressive familial intrahepatic cholestasis

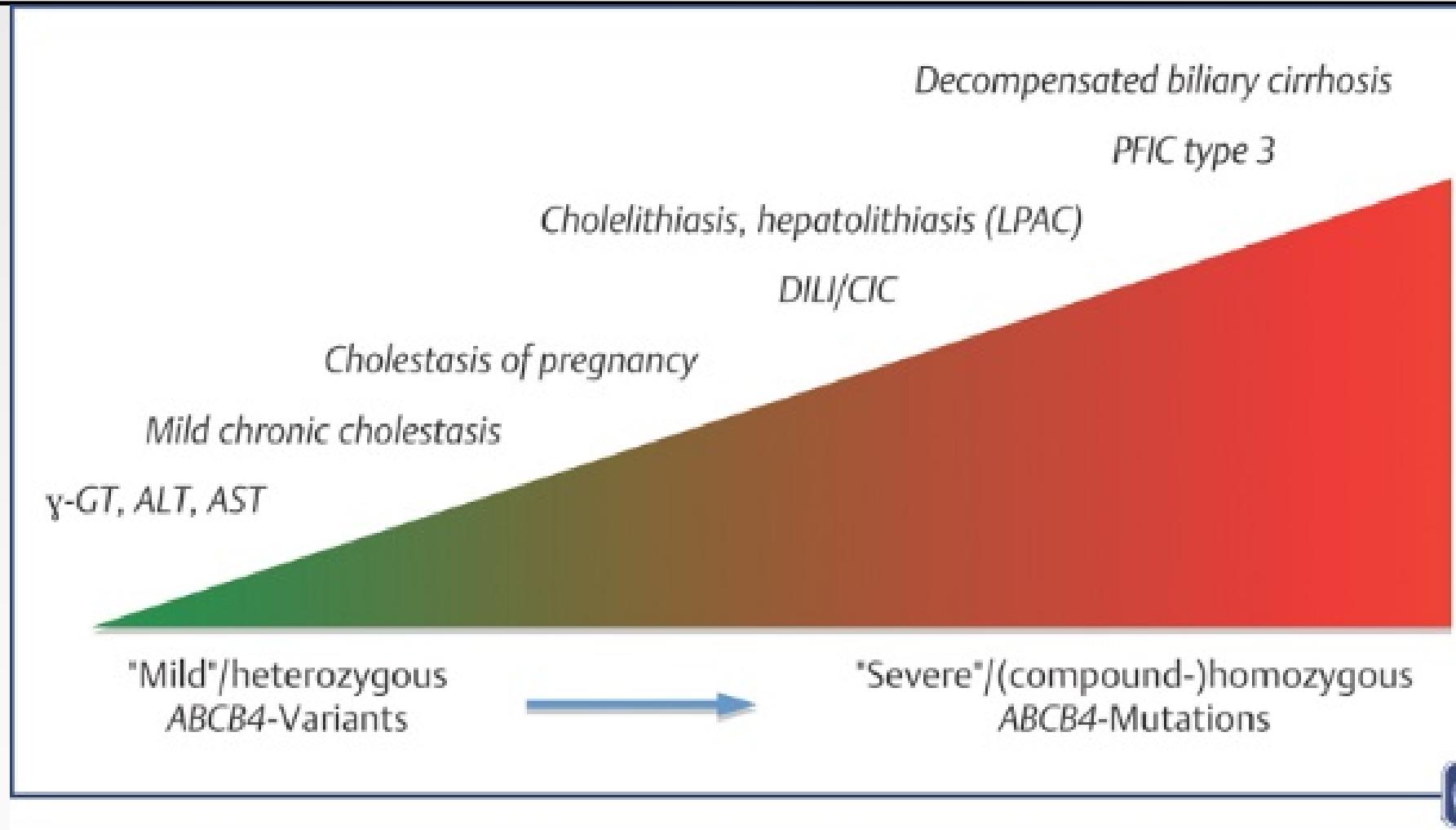
**LPAC:** Low phospholipid associated cholelithiasis

**BRIC:** Benign recurrent intrahepatic cholestasis

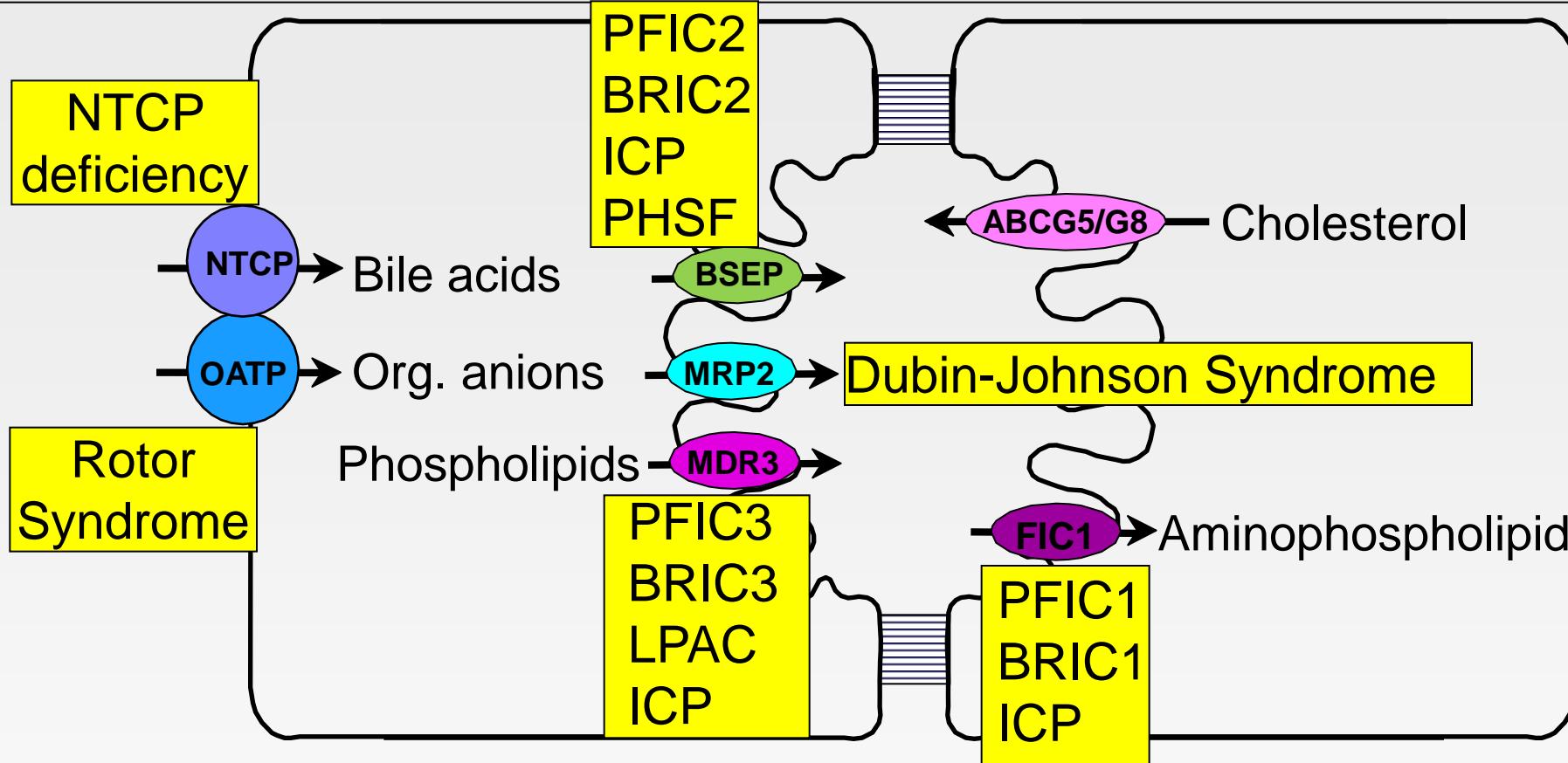
**ICP:** Intrahepatic cholestasis of pregnancy

**PHSF:** Persistent hepatocellular secretory failure

# ABCB4 Deficiency



# Consequences of transporter defects



Transporter	Gene
FIC1	<i>ATP8B1</i>
BSEP	<i>ABCB11</i>
MDR3	<i>ABCB4</i>

**PFIC:** Progressive familial intrahepatic cholestasis

**LPAC:** Low phospholipid associated cholelithiasis

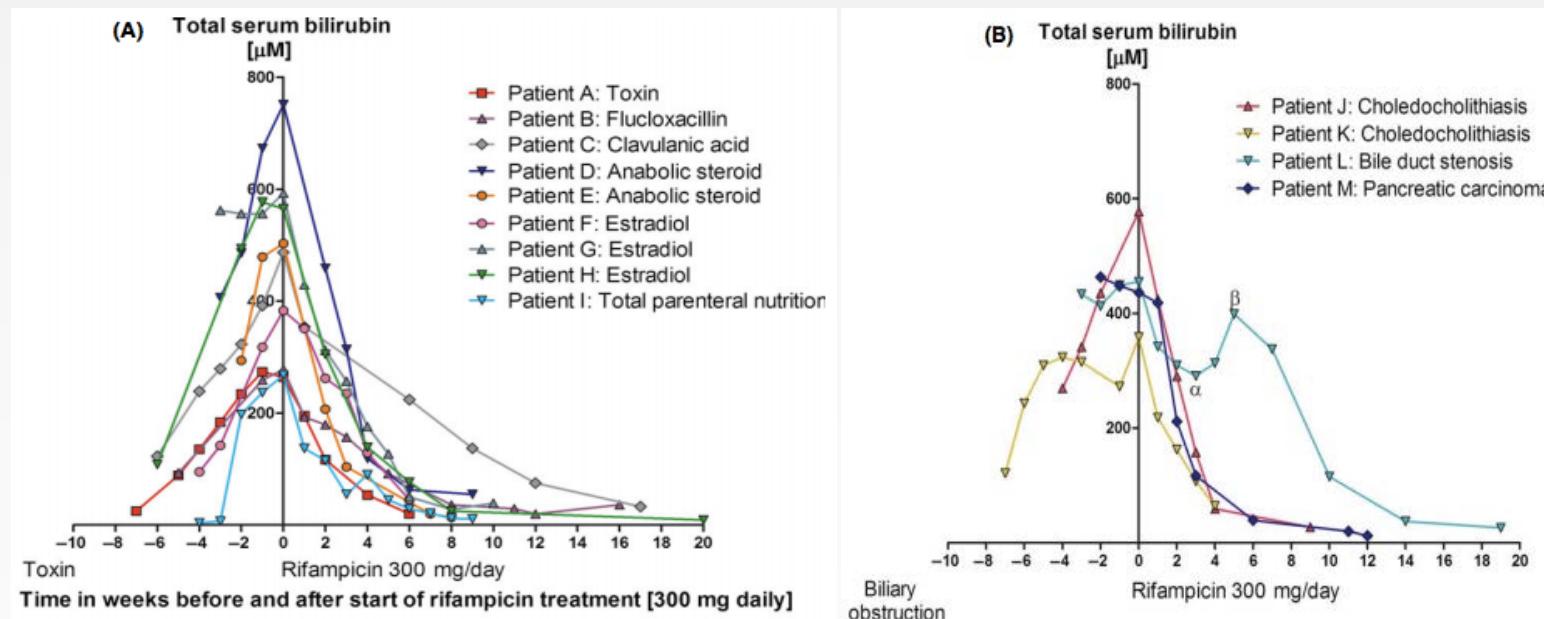
**BRIC:** Benign recurrent intrahepatic cholestasis

**ICP:** Intrahepatic cholestasis of pregnancy

**PHSF:** Persistent hepatocellular secretory failure

# Persistent hepatocellular secretory failure (PHSF)

- Serum bilirubin >255 µmol/L (>15 mg/dL)
- Persistently elevated bilirubin (>1 week) after removal of the underlying cause (medication, toxin, transient mechanical obstruction)
- Exclusion of bile duct obstruction by imaging
- No underlying liver disease
- Rapid response to rifampicine



# Management of cholestatic liver diseases 2019

