Focusing in on PBC: Novel targets for future management

Michael Trauner

Medical University of Vienna, Austria

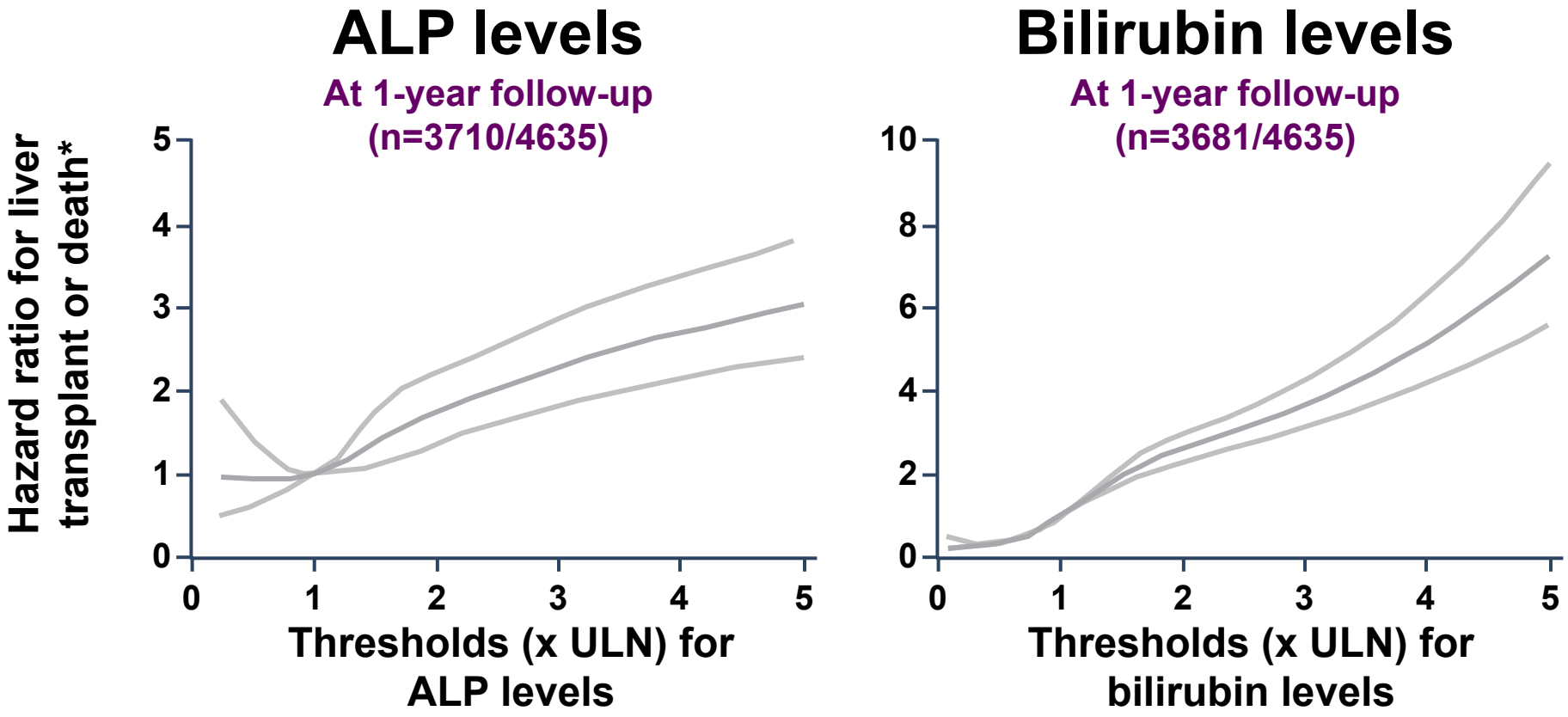
Note for keypad team: No correct answer, opinion poll question

How do you assess the prognosis of PBC patients in your daily clinical practice?

- Liver histology
- Fibroelastography
- Laboratory values
- None of the above

PBC, primary biliary cholangitis.

In PBC, elevated ALP and bilirubin values are associated with higher risk for liver transplant or death



*Estimated with cubic spline function.
ALP, alkaline phosphatase; PBC, primary biliary cholangitis; ULN, upper limit of normal.
Lammers WJ, *et al. Gastroenterology* 2014;147:1338–49.

Note to Prof Trauner: We have increased the font size of references to 12 pt (any larger causes interference with slide content).

Until 2016, UDCA was the only approved treatment for PBC[1–4]

The most recent guidelines for the treatment of PBC from 2009 recommend that patients with PBC should be treated with long-term UDCA[5]

2009 EASL recommendations for the treatment of PBC[5]
Patients with PBC, including those with asymptomatic disease, should be treated with UDCA (13–15 mg/kg/d) on a long-term basis
There is currently no consensus on how to treat patients with a suboptimal biochemical response to UDCA
Liver transplantation should be strongly considered in patients with advanced disease

EASL, European Association for the Study of the Liver; PBC, primary biliary cholangitis, UDCA, ursodeoxycholic acid.

1. FDA news release. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm503964.htm. Last accessed 11 April 2017; 2. Poupon R. *J Hepatol* 2010;52:745–58; 3. Intercept Press Release. Available at: http://ir.interceptpharma.com/releasedetail.cfm?ReleaseID=1004114. Last accessed 11 April 2017; 4. European Medicines Agency Press Release. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/10/news_detail_002618.jsp&mid=WC0b01ac058004d5c1. Last accessed 11 April 2017; 5. European Association for the Study of the Liver. *J Hepatol* 2009;237–67.

Proposed mechanism of action of UDCA

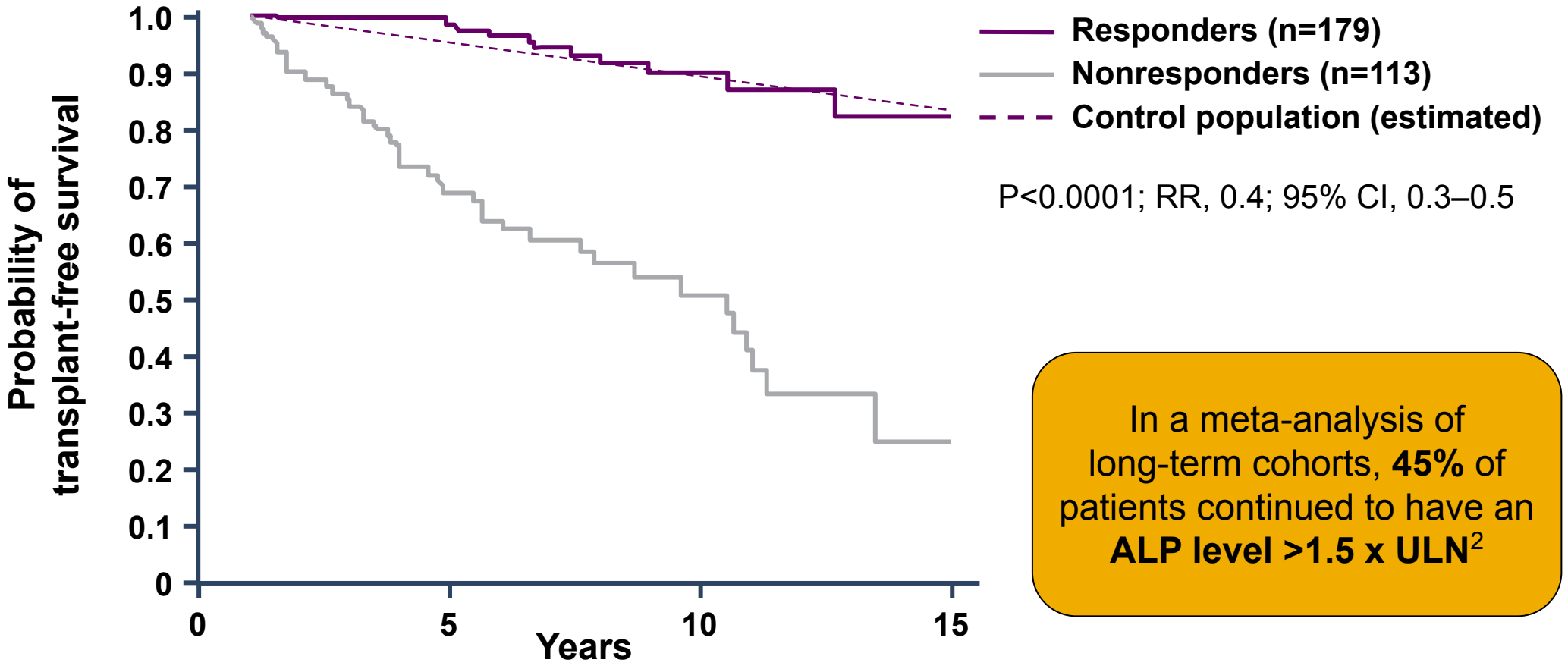
Although the exact mechanism of action has not been fully elucidated, experimental evidence suggests there are a number of mechanisms by which UDCA may carry out its effects

Primary mechanisms of action	
'Diluting' the BA pool	Reduces concentrations of hydrophobic BAs and becomes the major circulating BA, thereby reducing toxicity of circulating bile[1]
Increasing BA secretion	Stimulates secretion of BA from hepatocytes by increasing expression of BA transporters (via post-translational mechanisms)[1,2]
Cytoprotective	Stabilises hepatocyte membranes, protects against oxidative stress and may inhibit apoptosis induced by several agents[1,2]
Secondary mechanism of action	
Immune response effects	May interfere with basic mechanisms of autoimmunity and has anti-inflammatory properties[1,2]

BA, bile acid; UDCA, ursodeoxycholic acid.

1. Paumgartner G, Beuers U. *Hepatology* 2002;36:525–31; 2. Beuers U, *et al. J Hepatol* 2013;62(suppl1):S25–37.

Biochemical response to UDCA at 1 year predicts disease progression



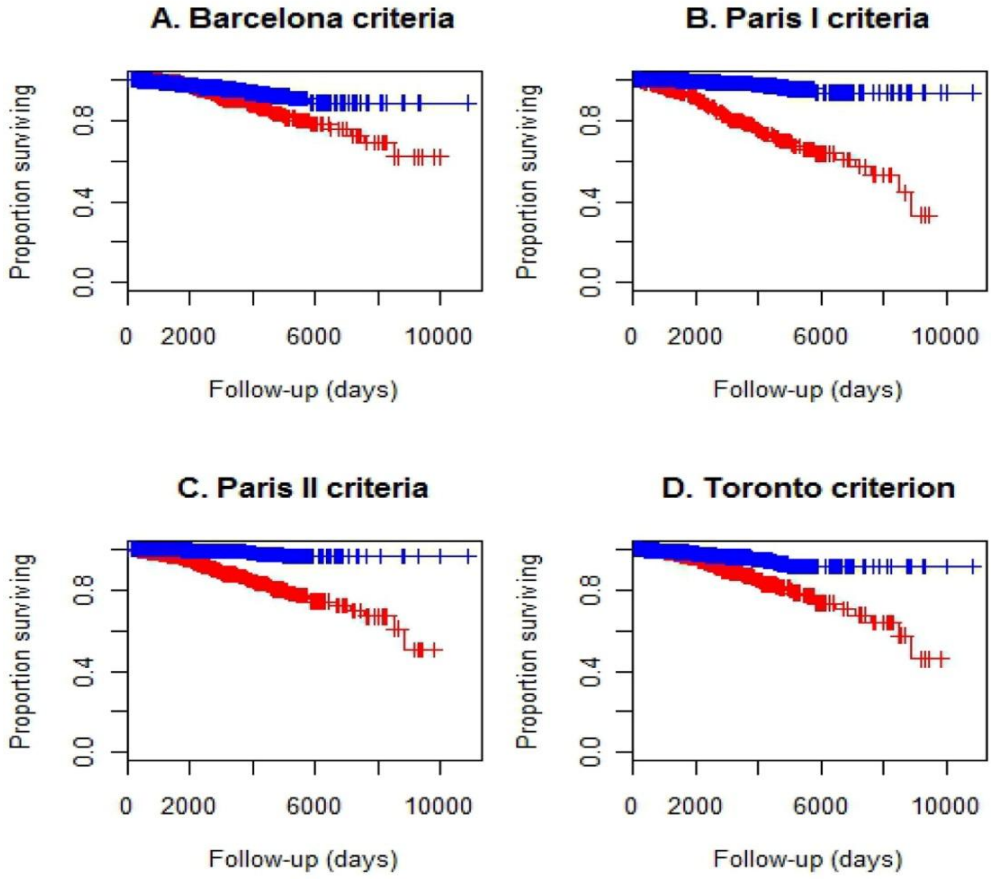
In a meta-analysis of long-term cohorts, **45%** of patients continued to have an **ALP level >1.5 x ULN**[2]

ALP, alkaline phosphatase; CI, confidence interval; RR, risk ratio; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

1. Corpechot C, *et al. Hepatology* 2008;48:871–7; 2. Lammers WJ, *et al. Gastroenterology* 2014;147:1338–49.

Defining response to UDCA

Survival curves for patients who did (blue) vs. did not (red) meet response criteria



Barcelona

- Decrease in ALP level >40% of baseline level or a normal level

Paris I (all criteria met)

- ALP level ≤3 X ULN
- AST level ≤2 X ULN
- Normal bilirubin level

Paris II (all criteria met)

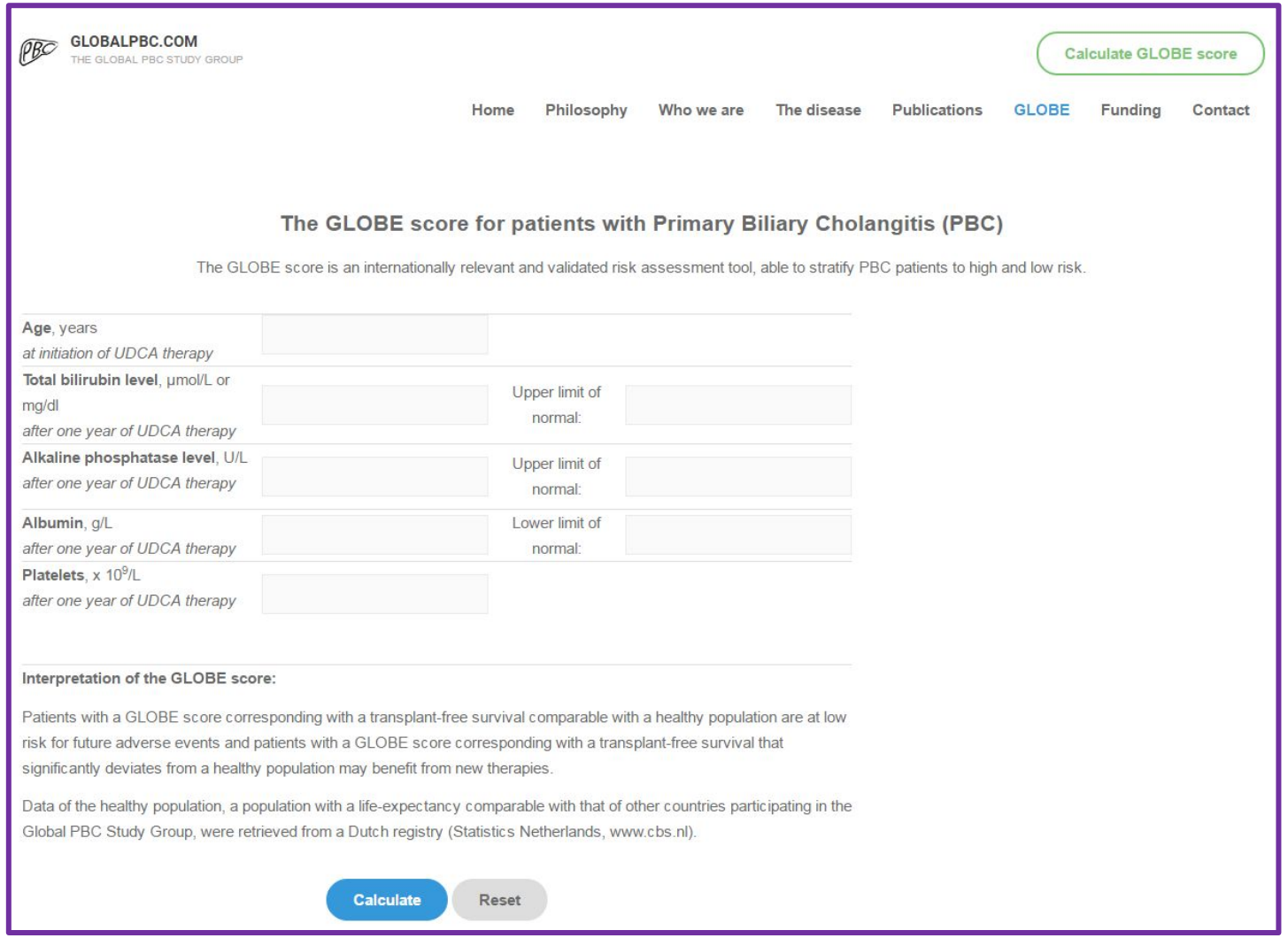
- ALP level ≤1.5 X ULN
- AST level ≤1.5 X ULN
- Normal bilirubin level

Toronto

- ALP level <1.76 X ULN*

*2-stage increase applied as per Kumagi T, *et al. Am J Gastroenterol* 2010;105:2186–94.
ALP, alkaline phosphatase; AST, aspartate aminotransferase; ULN, upper limit of normal; UDCA, ursodeoxycholic acid.
Carbone M, *et al. Gastroenterology* 2013;144:560–9.

GLOBE score online calculation



GlobalPBC.com. Available at: http://www.globalpbc.com/globe. Last accessed 11 April 2017; Lammers W, *et al. Gastroenterology* 2015;149:1804–12.

Assessing the biochemical response to UDCA

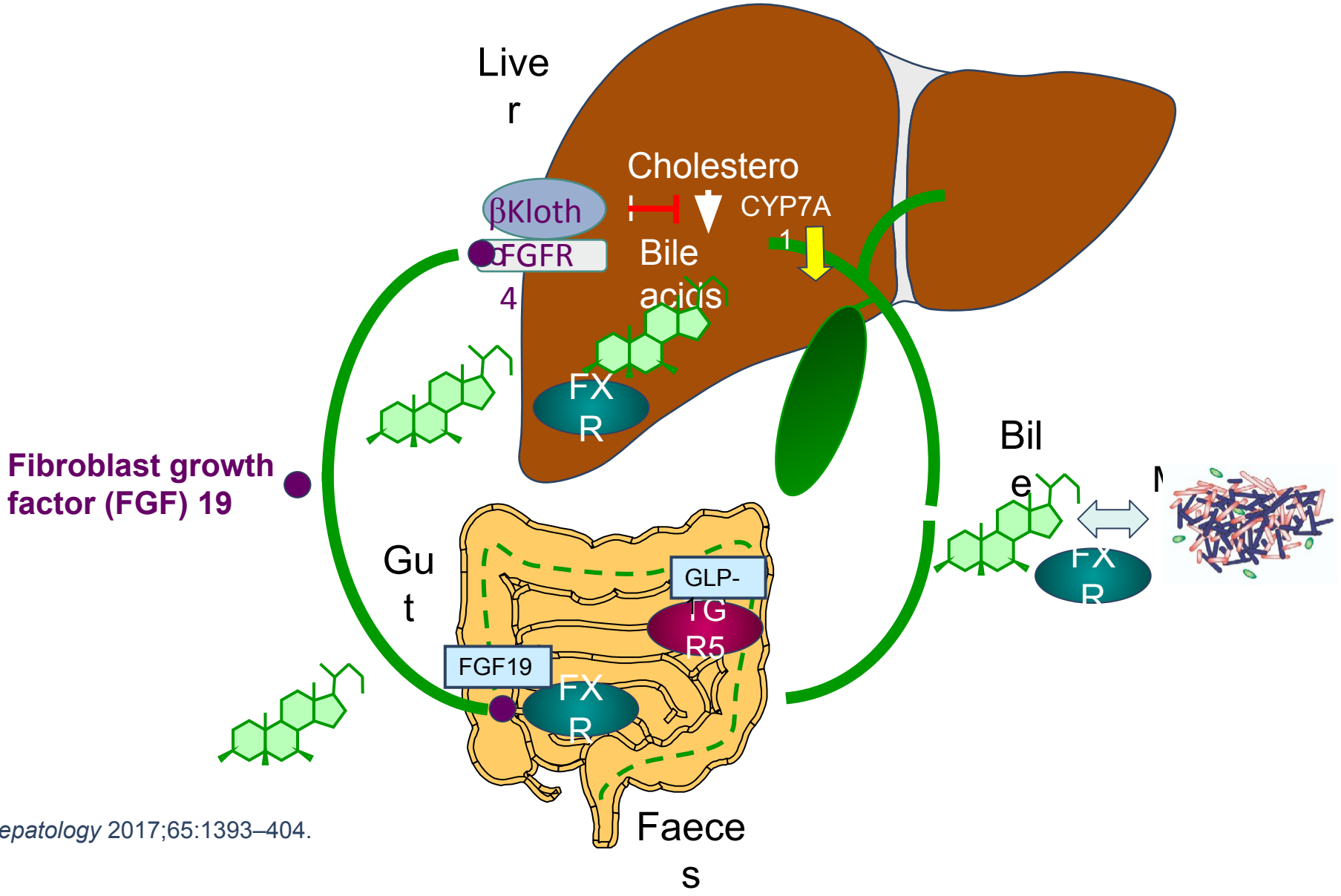
GLOBE Score	C-statistic = 0.81 (95% CI, 0.79–0.83)
Paris I	C-statistic = 0.69 (95% CI, 0.66–0.71)
Rotterdam	C-statistic = 0.69 (95% CI, 0.66–0.71)
Paris II	C-statistic = 0.63 (95% CI, 0.61–0.65)
Toronto	C-statistic = 0.61 (95% CI, 0.58–0.63)
Barcelona	C-statistic = 0.58 (95% CI, 0.55–0.61)

Derivation cohort (N=2488). CI, confidence index; UDCA, ursodeoxycholic acid.
Lammers W, *et al. Gastroenterology* 2015;149:1804–12.

What new targets are being investigated in PBC?

FGF, fibroblast growth factor; FXR, farnesoid X receptor; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor.
Trauner M, *et al. Hepatology* 2017;65:1393–404.

Bile acids as enterohepatic hormones



Trauner M, *et al. Hepatology* 2017;65:1393–404.

FGF19 via FGFR4 as a potential treatment for PBC

- FGF19 is an endocrine hormone released in the ileum that regulates hepatic bile acid, lipid, and carbohydrate metabolism[1]
  - FGF19 selectively binds to FGFR4
- It also has a role in regulating hepatic cell proliferation[1]
  - FGF19-FGFR4 signalling is associated with hepatocellular tumourigenesis
- An engineered FGF19 variant is capable of targeting bile acid homeostasis function, but not the proliferative function, by suppressing hepatic *CYP7A1* expression[1]
- In mouse PSC model, adeno-associated virus-mediated delivery of FGF19 improved liver injury, hepatic inflammation and fibrosis[2]
- Encouraging Phase II data in PBC[3]
  - Liver enzymes improved, pruritus not exacerbated

CYP7A1, cytochrome P450 7A1; FGF19, fibroblast growth factor 19; FGFR4, fibroblast growth factor receptor 4; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

1. Luo J, *et al. Sci Transl Med* 2014;6:247ra100; 2. Zhou M, *et al. Hepatology* 2016;63:914–29; 3. Mayo MJ, *et al. Hepatology* 2015;62(suppl 1):abstract 106.

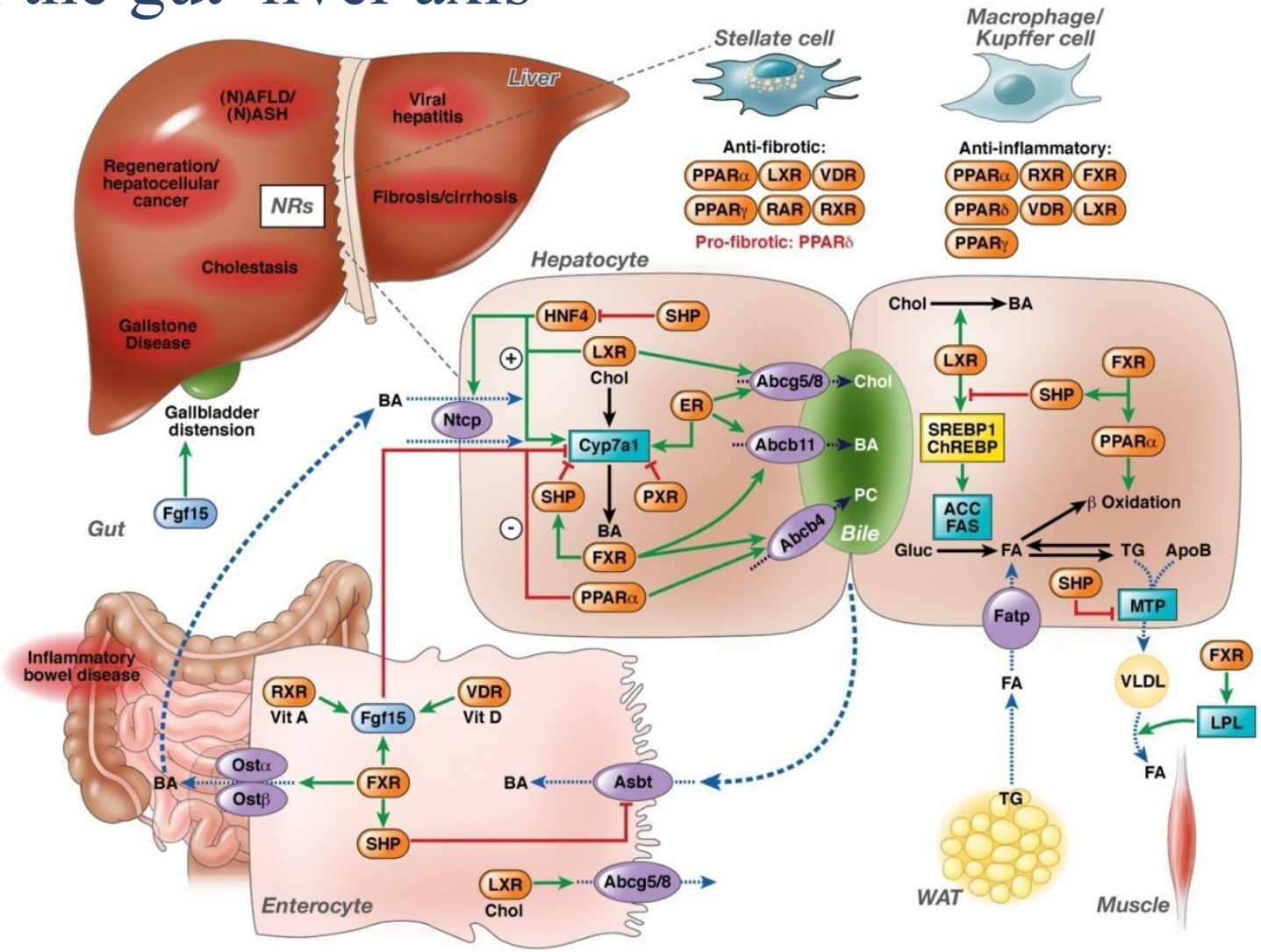
Biologic targets in PBC

- IL-12 and IL-23[1]
  - Pro-inflammatory effect implicated in pathogenesis of PBC
  - Produced by antigen presenting cells and promote Th1 and Th17 immune responses, respectively
  - Ustekinumab negative[2]
- CD40[3]
  - Activation of CD40 on BEC triggers activation of NF-κB and AP-1, leading to apoptosis and bile duct loss
  - Phase II (FFP104) ongoing (NCT02193360)[4]

AP-1, activator protein 1; BEC, biliary epithelial cell; IL, interleukin; NF-κB, nuclear factor kappa B; PBC, primary biliary cholangitis.

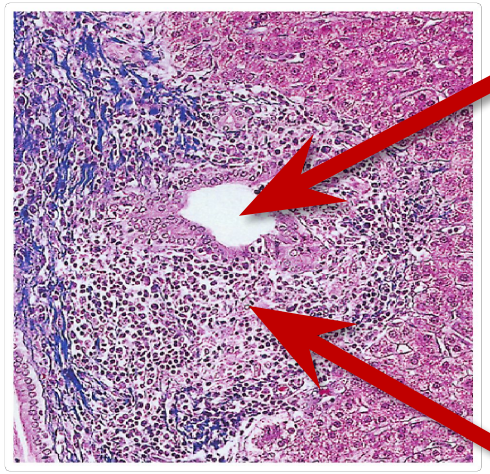
1. Yang CY, *et al. Hepatology* 2014;59:1944–53; 2. Hirschfield GM, *et al. Hepatology* 2016;64:189–99; 3. Afford SC, *et al. FASEB J* 2001;15:2345–54; 4. ClinicalTrials.gov identifier: NCT02193360. Available at https://clinicaltrials.gov/ct2/show/NCT02193360. Last accessed 11 April 2017.

Nuclear receptors such as PPAR and FXR are involved in regulation of the gut–liver axis



Trauner M, Halilbasic E. *Gastroenterology* 2011;140:1120–5.

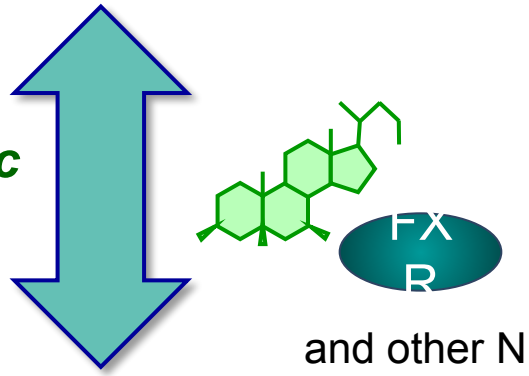
Two-pronged approach to nuclear receptors as therapeutic targets



Immune-mediated injury?
Autoimmune?

Protection/healing from **'inside'**
Target: Bile composition and homeostasis, cholangiocytes

Immunometabolic drugs?



and other NRs

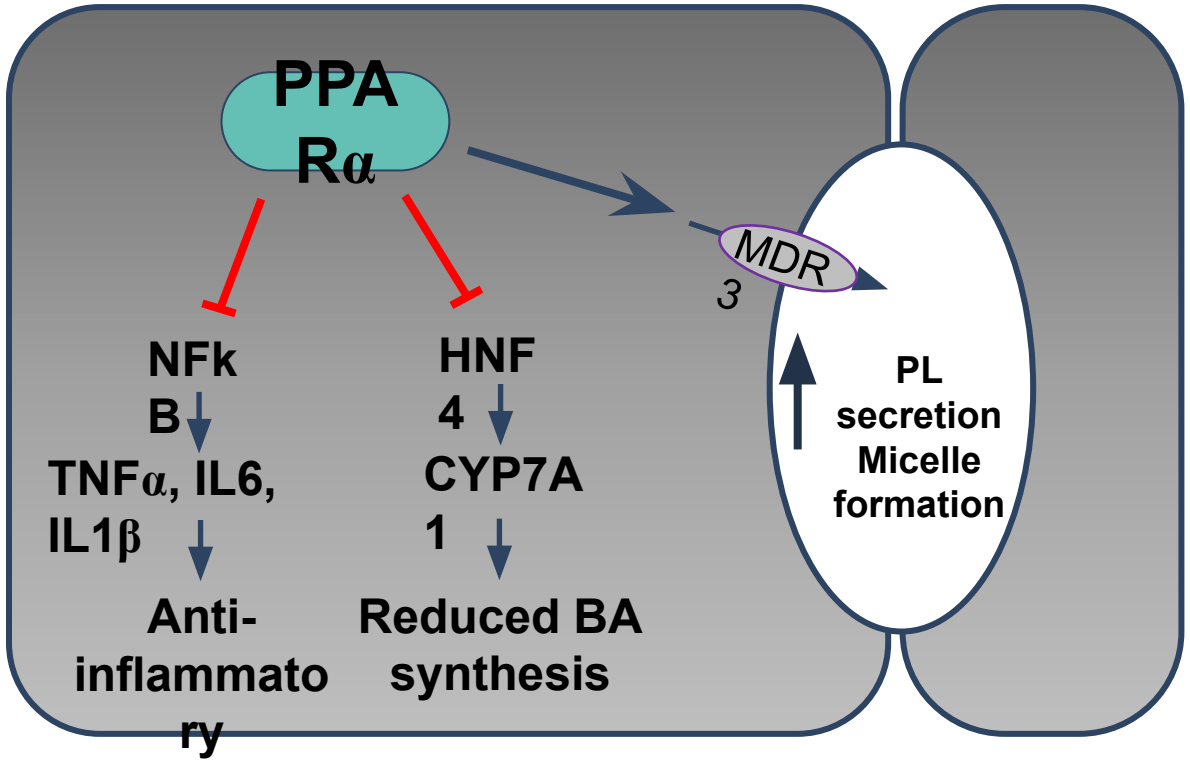
Protection/healing from **'outside'**
Target: Immune system and immune cells

FXR, farnesoid X receptor; NR, nuclear receptor.

Peroxisome proliferator-activated receptors (PPARs)

- Activated by fatty acids and derivatives[1]
- Key regulators of lipid/glucose metabolism and inflammation (co-regulation/dichotomy)[1,2]
- Three isoforms: α, β/δ, γ[1–3]
- Fibrates in PBC (& PSC): Improved liver measurements, due to metabolic and immune effects[1,3]
  - Fenofibrate → PPARα
  - Bezafibrate → slightly broader
  - Novel dual α/δ and δ ligands?

Anticholestatic and anti-inflammatory mechanisms of PPARα[4]



BA, bile acid; CYP7A1, cytochrome P450 7A1; HNF4, hepatocyte nuclear factor 4; IL, interleukin; NF-κB, nuclear factor-kappa B; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; PSC, primary sclerosing cholangitis; TNFα, tumour necrosis factor alpha.

1. Choi JM, Bothwell AL. *Mol Cells* 2012;33:217–22; 2. Pawlak M, *et al. J Hepatol* 2015;62:720–33; 3. Cuperus FJ, *et al. Curr Opin Gastroenterol* 2014;30:279–86; 4. Fuchs C, *et al. Clin Liver Dis* 2017;9:43–47.

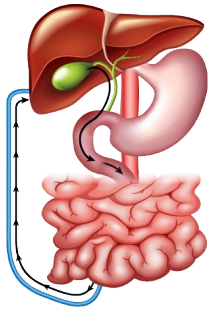
PPAR activity

Iso-form	Primary distribution	Anti-cholestatic mechanism
$\alpha^{1,2}$	Liver	• Regulates bile acid synthesis/detoxification • Modulates phospholipid secretion • Down-regulates hepatic proinflammatory genes • Broad anti-inflammatory effects
$\gamma^{1,2}$	Adipose tissue, immune system	• Regulates adipogenesis • Represses transactivation of inflammatory response genes • Anti-fibrotic effect on hepatic stellate cells
$\delta^{1,3}$	Ubiquitous	• Regulates target genes for lipid/glucose metabolism • Reduces liver fat • Antagonises inflammatory pathways

PPAR, peroxisome proliferator-activated receptor

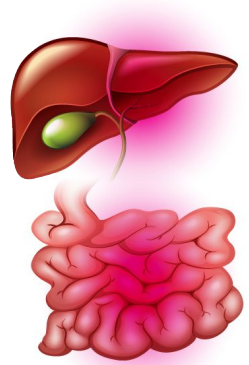
1. Cuperus FJ, *et al. Curr Opin Gastroenterol* 2014;30:279–86; 2. Zollner G, *et al. Br J Pharmacol* 2009;156:7–27;
3. Bays HE, *et al. J Clin Endocrinol Metab* 2011;96:2889–97.

FXR is predominantly expressed in the liver, intestine, and kidney, where it mediates its effects[1,2]



EFFECTS OF FXR ACTIVATION ON **BA HOMEOSTASIS**[3]

- ↓ BA synthesis
- ↑ BA secretion
- ↓ BA absorption/ reuptake



EFFECTS OF FXR ACTIVATION ON **INFLAMMATION**[4–6]

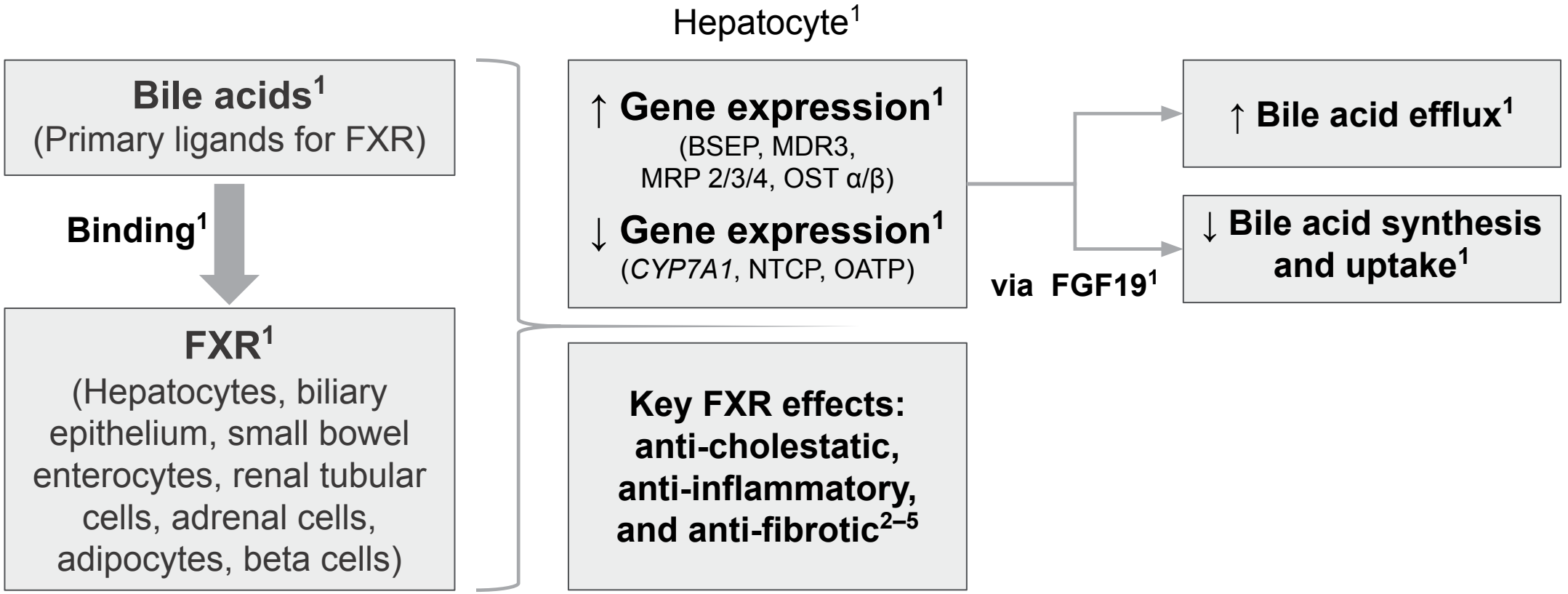
- ↓ Inflammation in the liver
- ↓ Inflammation in the intestine

Proposed roles based on *in vivo* and *in vitro* studies in multiple animal and cell models using different FXR agonists. *In vivo/in vitro* studies do not necessarily correlate with clinical response, and not all FXR agonists may produce the same effects.

BA, bile acid; FXR, farnesoid X receptor.

1. Forman BM, *et al. Cell* 1995;81:687–93; 2. de Aguiar Vallim TQ, *et al. Cell Metab* 2013;17:657–69; 3. Modica S, *et al. Nucl Recept Signal* 2010;8:e005; 4. Wang YD, *et al. Hepatology* 2008;48:1632–43; 5. Vavassori P, *et al. J Immunol* 2009;183:6251–61; 6. Gadaleta RM, *et al. Gut* 2011;60:463–72.

Role of FXR signalling in bile acid homeostasis

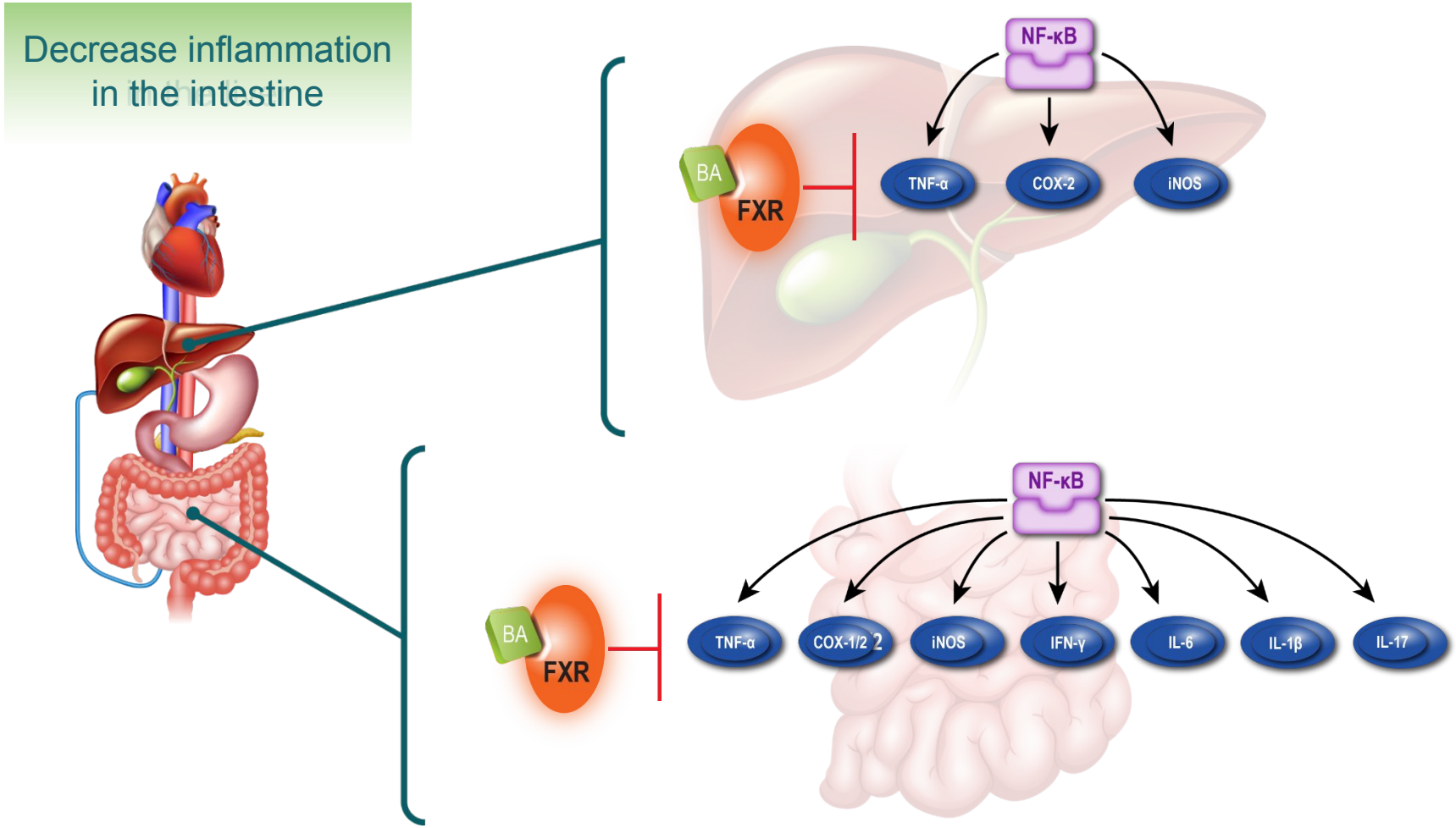


BSEP, bile salt export pump; FGF, fibroblast growth factor; FXR, farnesoid X receptor; MRP 2/3/4, multidrug resistant protein 2/3/4; NTCP, sodium/taurocholate co-transporting polypeptide; OATP, organic anion transporting polypeptide; OST α/β, organic soluble transporter α/β.

1. Neuschwander-Tetri BA. *Curr Gastroenterol Rep* 2012;14:55–62; 2. Adorini L, *et al. Drug Discov Today* 2012;17:988–97; 3. Pellicciari R, *et al. J Med Chem* 2002;45:3569–72; 4. Verbeke L, *et al. Sci Rep* 2016;6:33453; 5. Baghdasaryan A, *et al. Hepatology* 2011;54:1303–12.

Note to Prof Trauner: We had to reduce the font size of the references here so the images could fit on the slide

Possible mechanisms by which FXR may regulate inflammation



NF-κB expression itself was not directly altered. Proposed pathways based on *in vitro* studies in mouse and human macrophages and *in vivo* studies in murine colitis models. *In vivo/in vitro* studies do not necessarily correlate with clinical response, and not all FXR agonists may produce the same effects.
BA, bile acid; FXR, farnesoid X receptor; NF-κB, nuclear factor-kappa B.
Wang YD, *et al. Hepatology* 2008;48:1632–43; Vavassori P, *et al. J Immunol* 2009;183:6251–61; Gadaleta RM, *et al. Gut* 2011;60:463–72.

Note to Prof Trauner: We were unable to find the information in the Baghdasaryan reference which states the effect of INT-767 on MCP-1 expression so we have removed this here

FXR activation may modulate the course of cholestatic liver disease in mouse models of cholangitis

- Activation of FXR by INT-767 reverses cholestatic liver and bile duct injury in *Mdr2 (Abcb4)*$^{-/-}$ mice[1]
- INT-767 led to:[1]
  - Reductions in:
    - COL1a1 expression by fibroblasts
    - TNF-α and IL-1β expression by inflammatory cells
    - VCAM-1 expression by cholangiocytes
  - Increases in HCO_3^- secretion

  ⇨ Reduced toxicity of bile

FXR, farnesoid X receptor.

1. Baghdasaryan A, *et al. Hepatology* 2011;54:1303–12.

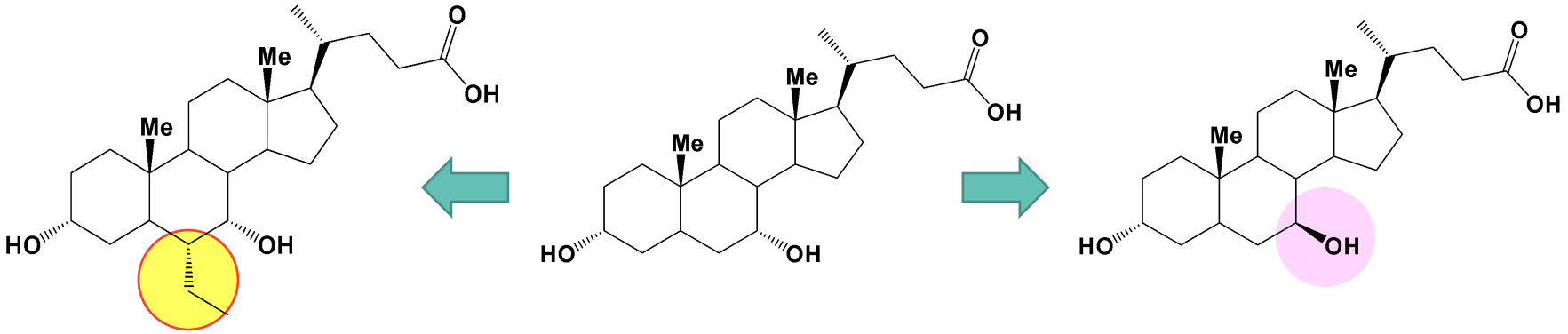
Note to Prof Trauner: The Pellicciari reference does include the images of the molecular structures

Obeticholic acid (OCA) is a potent and selective steroidal FXR agonist

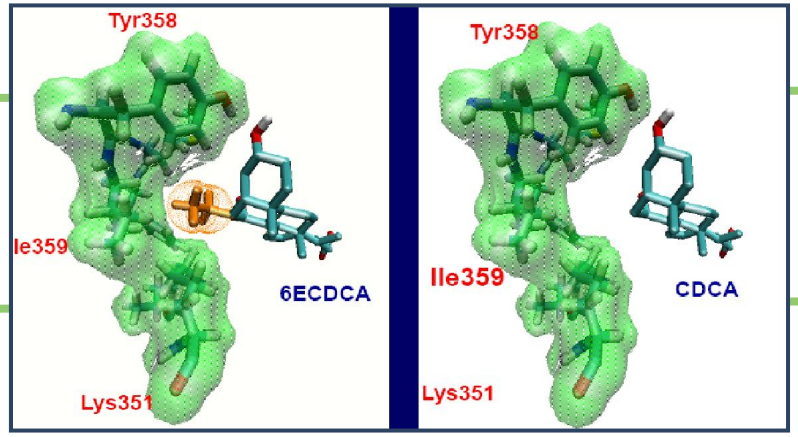
OCA
6a-ethyl chenodeoxycholic acid

CDCA
chenodeoxycholic acid

UDCA
ursodeoxycholic acid



FXR EC_{50} (agonist)



No activity (acts via PKC)
UDCA as FXR-antagonist?*

CDCA, chenodeoxycholic acid; EC_{50}, half maximal effective concentration; FXR, farnesoid X receptor; OCA, obeticholic acid; PKC, protein kinase C; UDCA, ursodeoxycholic acid.

Pellicciari R, *et al. J Med Chem* 2002;45:3569–72; *Müller M, *et al. J Hepatol* 2015;62:1398–404.

Note for keypad team: No correct answer, opinion poll question

In your opinion, FXR ligands exert beneficial effects in cholestatic liver injury by:

- Repression of bile acid synthesis
- Promotion of biliary secretion (bile acids, phospholipids, HCO_3^-)
- Mediating anti-inflammatory effects
- All of the above

FXR, farnesoid X receptor.

Summary

- In PBC, elevated ALP and bilirubin values are associated with higher risk for liver transplant or death[1]
- Until 2016, UDCA was the only approved treatment for PBC[2–5]
  - Early treatment with UDCA is associated with improved long-term outcomes[6]
- Biochemical response after one year of UDCA treatment is predictive of disease outcomes but 45% of patients continue to have ALP >1.5 x ULN[7,8]
- New therapeutic targets under investigation for PBC include FXR, PPARs, FGF19 and biologics (anti-IL-12, IL-23 and CD40)
- FXR activation is associated, *in vitro* and *in vivo*, with reduced bile acid secretion and absorption/reuptake as well as reduced inflammation of the liver*[8–13]
- Obeticholic acid, a potent and selective steroidal FXR agonist,[14] presents a new targeted therapeutic option in PBC

**In vivo/in vitro* studies do not necessarily correlate with clinical response, and not all FXR agonists may produce the same effects.

ALP, alkaline phosphatase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; IL, interleukin; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

1. Lammers WJ, *et al. Gastroenterology* 2014;147:1338–49; 2. FDA news release. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm503964.htm. Last accessed 11 April 2017; 3. Poupon R. *J Hepatol* 2010;52:745–58; 4. Intercept Press Release. Available at: http://ir.interceptpharma.com/releasedetail.cfm?ReleaseID=1004114. Last accessed 11 April 2017; 5. European Medicines Agency Press Release. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/10/news_detail_002618.jsp&mid=WC0b01ac058004d5c1. Last accessed 11 April 2017; 6. Poupon RE, *et al. Gastroenterology* 1997;113:884–90; 7. Corpechot C, *et al. Hepatology* 2008;48:871–5; 8. Forman BM, *et al. Cell* 1995;81:687–93; 9. de Aguiar Vallim TQ, *et al. Cell Metab* 2013;17:657–69; 10. Modica S, *et al. Nucl Recept Signal* 2010;8:e005; 11. Wang YD, *et al. Hepatology* 2008;48:1632–43; 12. Vavassori P, *et al. J Immunol* 2009;183:6251–61; 13. Gadaleta RM, *et al. Gut* 2011;60:463–72; 14. Pellicciari R, *et al. J Med Chem* 2002;45:3569–72.