Update on PSC Research

PSC Partners Seeking a Cure Conference
Pittsburgh, PA
April 8, 2006

David Rhodes

(father of Steven (20); PSC 07/03; UC 08/03)

PSC
PRIMARY SCLEROSING CHOLANGITIS

PSC
Partners Seeking a Cure

www.psc-literature.org **www.pscpartners.org**

Overview

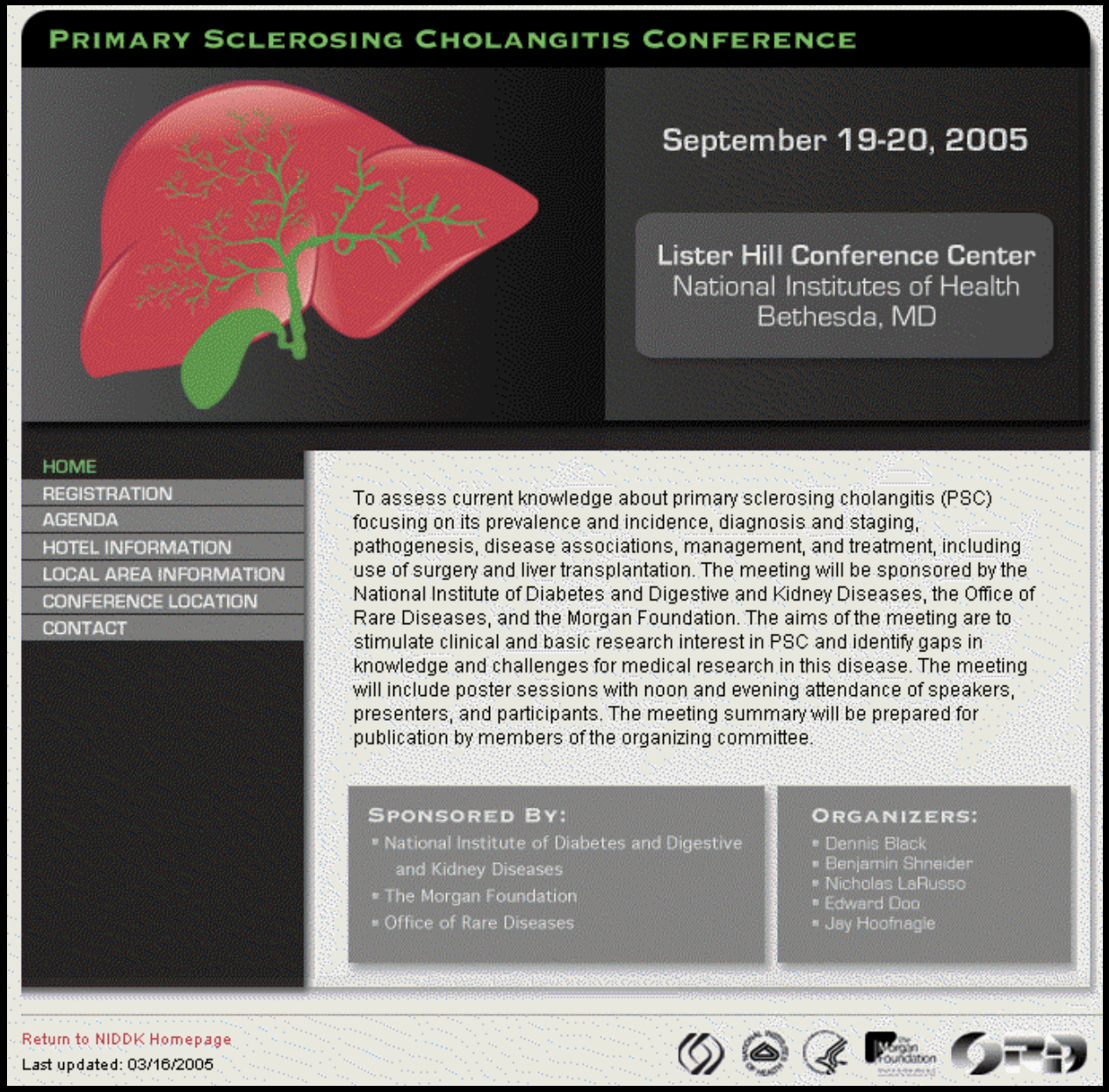
- Progress in understanding regulation of bile transport and metabolism

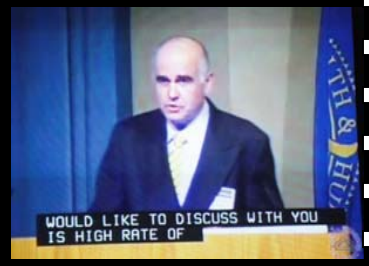
- Role of nuclear receptors in control of bile transport and metabolism

- Advances in understanding of how various medications are affecting nuclear receptors (and hence bile metabolism and transport)

- Animal models of PSC

- Recent progress in IBD genetics and PSC genetics





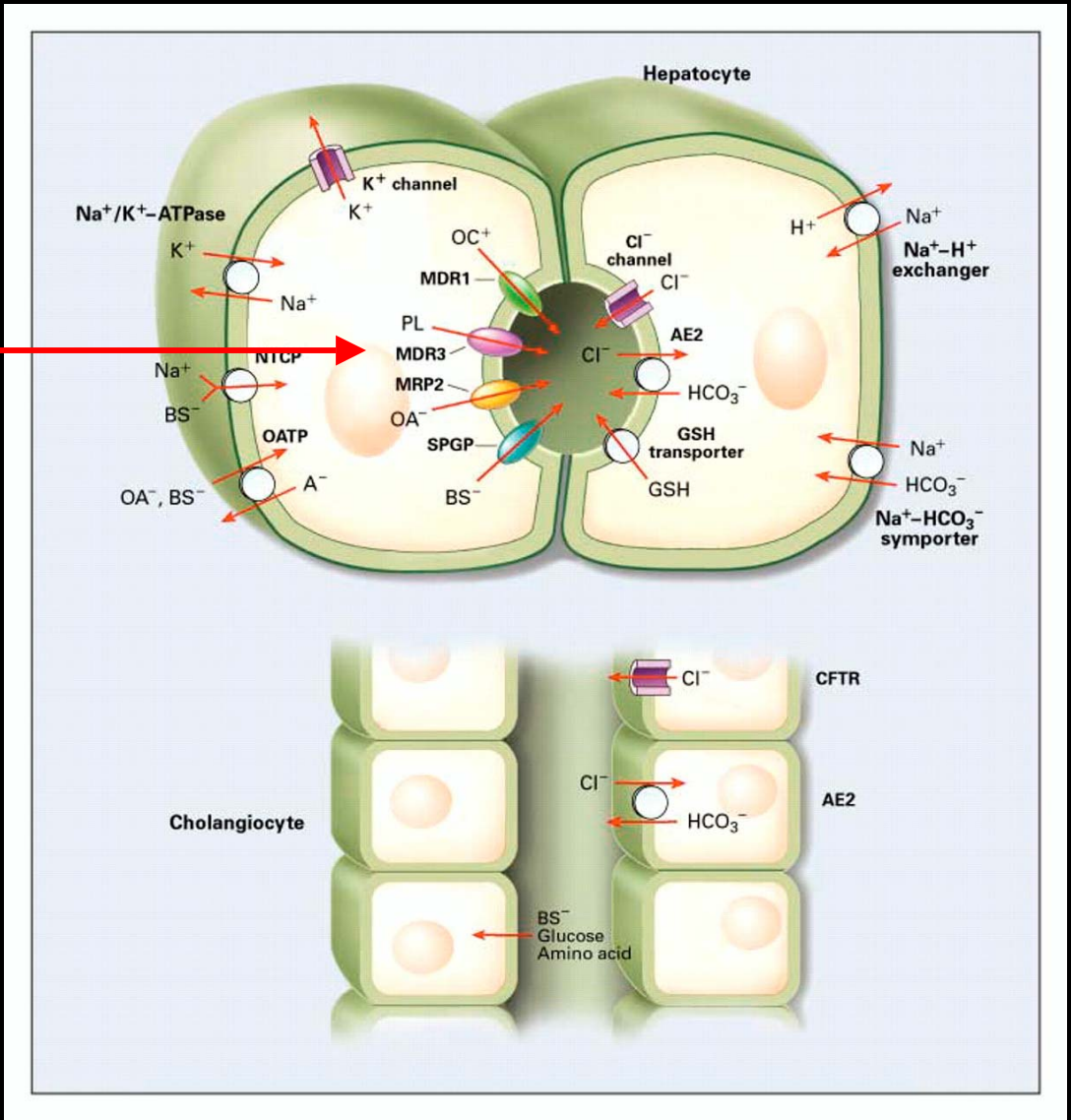
http://videocast.nih.gov/ram/niddk091905.ram
http://videocast.nih.gov/ram/niddk092005.ram

Transport Proteins of Hepatocytes and Bile-Duct Epithelial Cells (Cholangiocytes)

Multidrug Resistance 3

MDR3

Mice deficient in MDR3 (= Mdr2 in mice) develop sclerosing cholangitis



Trauner, M. et al. N Engl J Med 1998;339:1217-1227

The NEW ENGLAND JOURNAL of MEDICINE

Fickert P, Wagner M, Marschall HU, Fuchsbichler A, Zollner G, Tsybrovskyy O, Zatloukal K, Liu J, Waalkes MP, Cover C, Denk H, Hofmann AF, Jaeschke H, Trauner M 2006 24-*nor*Ursodeoxycholic acid is superior to ursodeoxycholic acid in the treatment of sclerosing cholangitis in Mdr2 (Abcb4) knockout mice. Gastroenterology 130: 465-481.

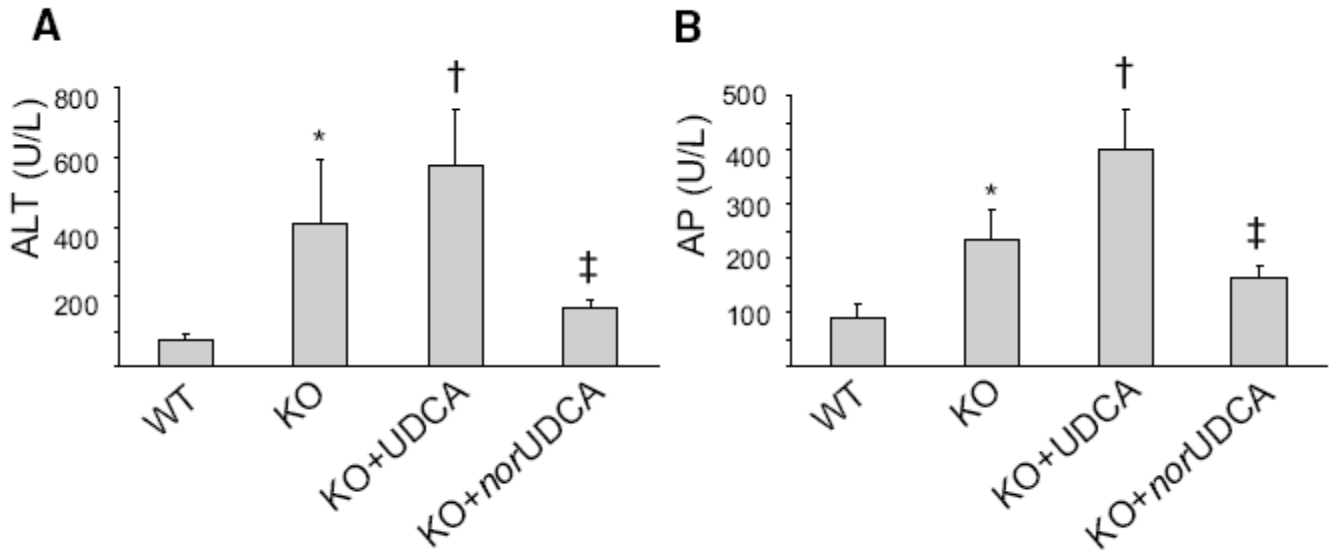


Figure 1. *nor*UDCA reduces serum alanine transaminase (ALT) and alkaline phosphatase (AP) levels, whereas UDCA significantly increases both enzymes in *Mdr2*$^{-/-}$ mice. Control diet–fed wild-type animals (WT), control diet–fed *Mdr2*$^{-/-}$ mice (KO), UDCA-fed *Mdr2*$^{-/-}$ mice (KO + UDCA), and *nor*UDCA-fed *Mdr2*$^{-/-}$ mice (KO + *nor*UDCA) are shown. Values are mean ± SD from 5 animals per group. $P < .05$: *WT vs KO, †KO vs KO + UDCA, ‡KO vs KO + *nor*UDCA.

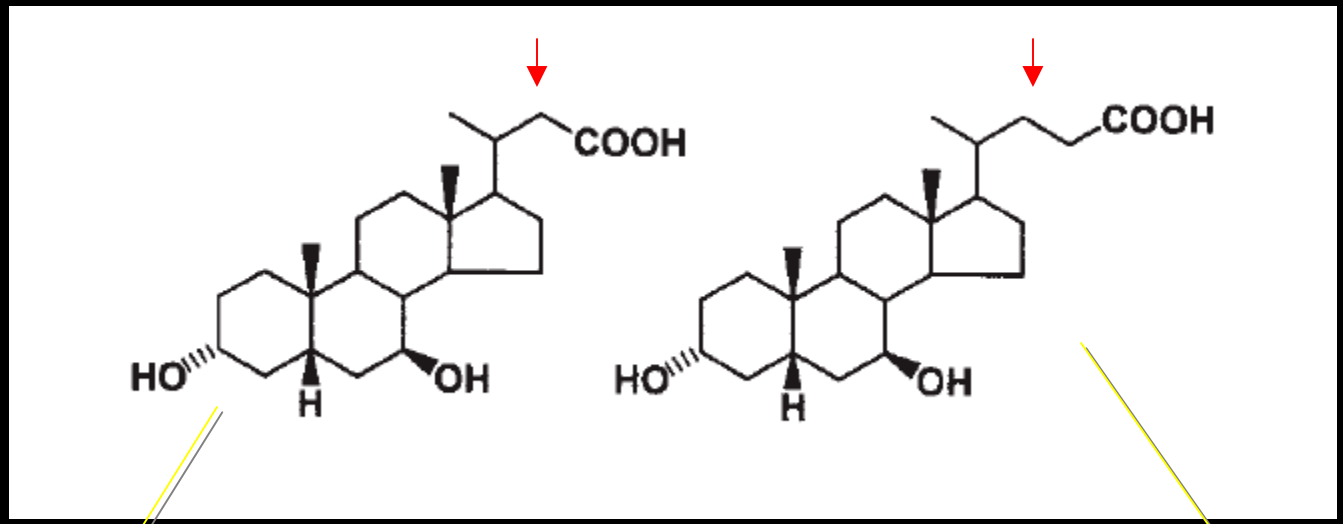
*nor*UDCA ameliorates sclerosing cholangitis in Mdr2-/- mice. Its therapeutic mechanisms involve:

(1) increasing the hydrophilicity of biliary bile acids,
(2) stimulating bile flow with flushing of injured bile ducts, and
(3) inducing detoxification and elimination routes for bile acids.

*nor*UDCA may be activating a receptor called the constitutive androstane receptor (CAR).

In contrast to UDCA, *nor*UDCA does not undergo significant conjugation with taurine or glycine in experimental animals but instead is secreted into bile in part in unchanged form and in part as trihydroxy derivatives, as well as sulfate and glucuronide conjugates. The secreted *nor*UDCA undergoes absorption by cholangiocytes, returns to the liver, and is resecreted into bile. Such cholehepatic shunting leads to a bicarbonate-rich hypercholeresis.

Hofmann AF, Zakko SF, Lira M, Clerici C, Hagey LR, Lambert KK, Steinbach JH, Schteingart CD, Olinga P, Groothuis GM 2005 Novel biotransformation and physiological properties of *nor*ursodeoxycholic acid in humans. Hepatology 42: 1391-1398.



*nor*UDCA

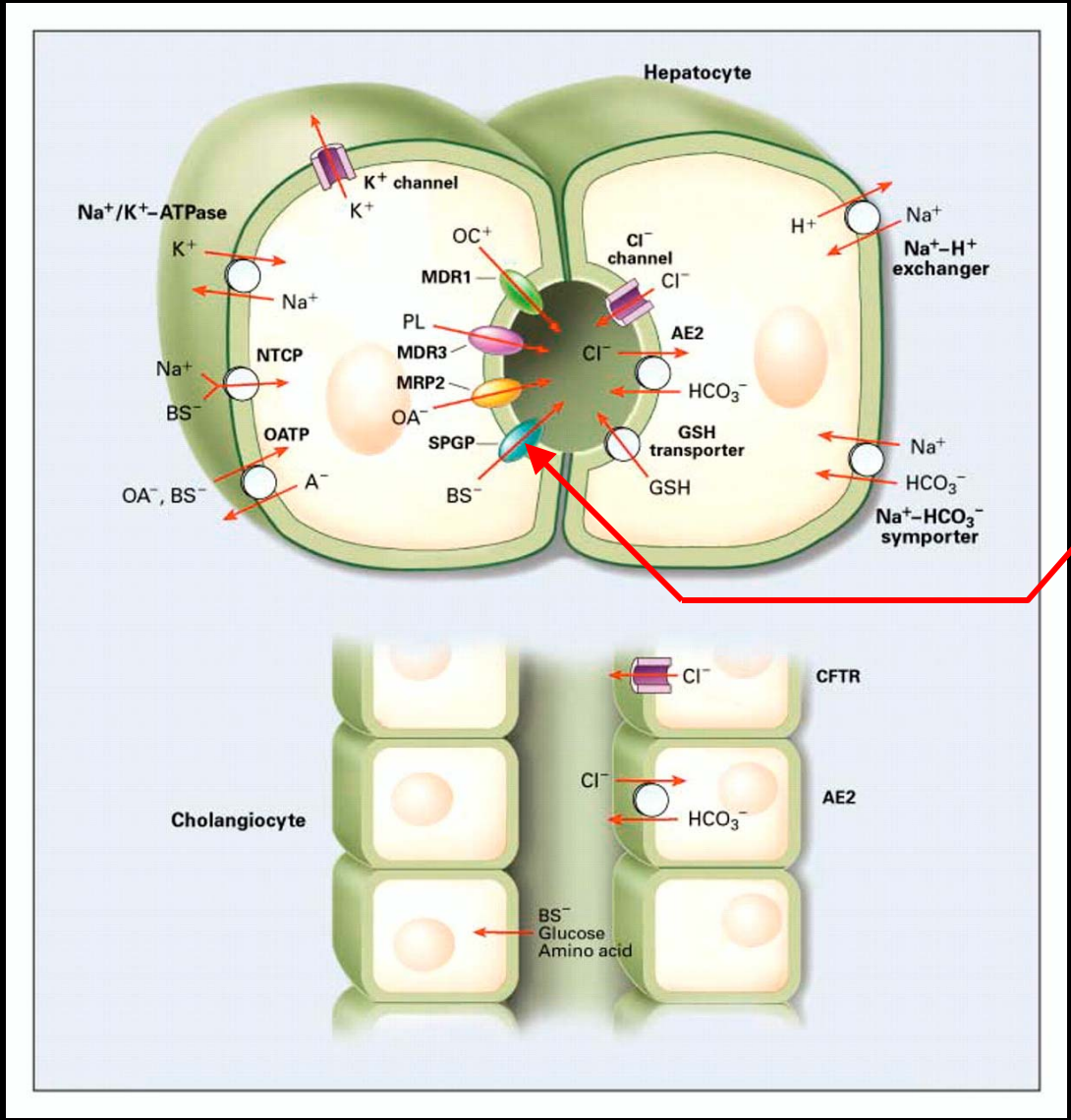
UDCA

Conjugated with glucuronic acid

Conjugated with glycine or taurine

Transport Proteins of Hepatocytes and Bile-Duct Epithelial Cells (Cholangiocytes)

Ursodiol (UDCA) preserves BSEP activity; in part by activating a receptor called the farnesoid X receptor (FXR)



BSEP

Bile Salt Export Pump

Trauner, M. et al. N Engl J Med 1998;339:1217-1227

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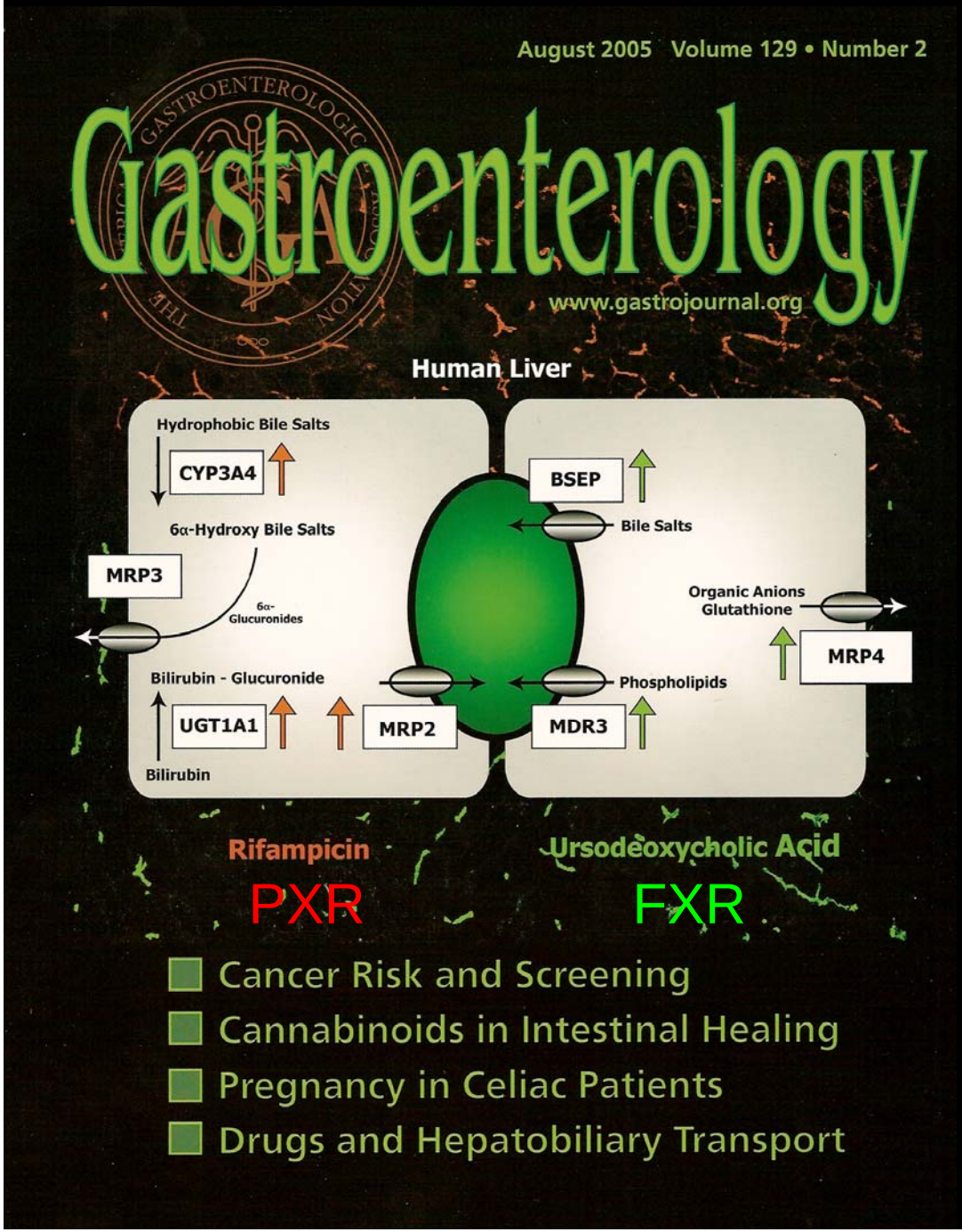
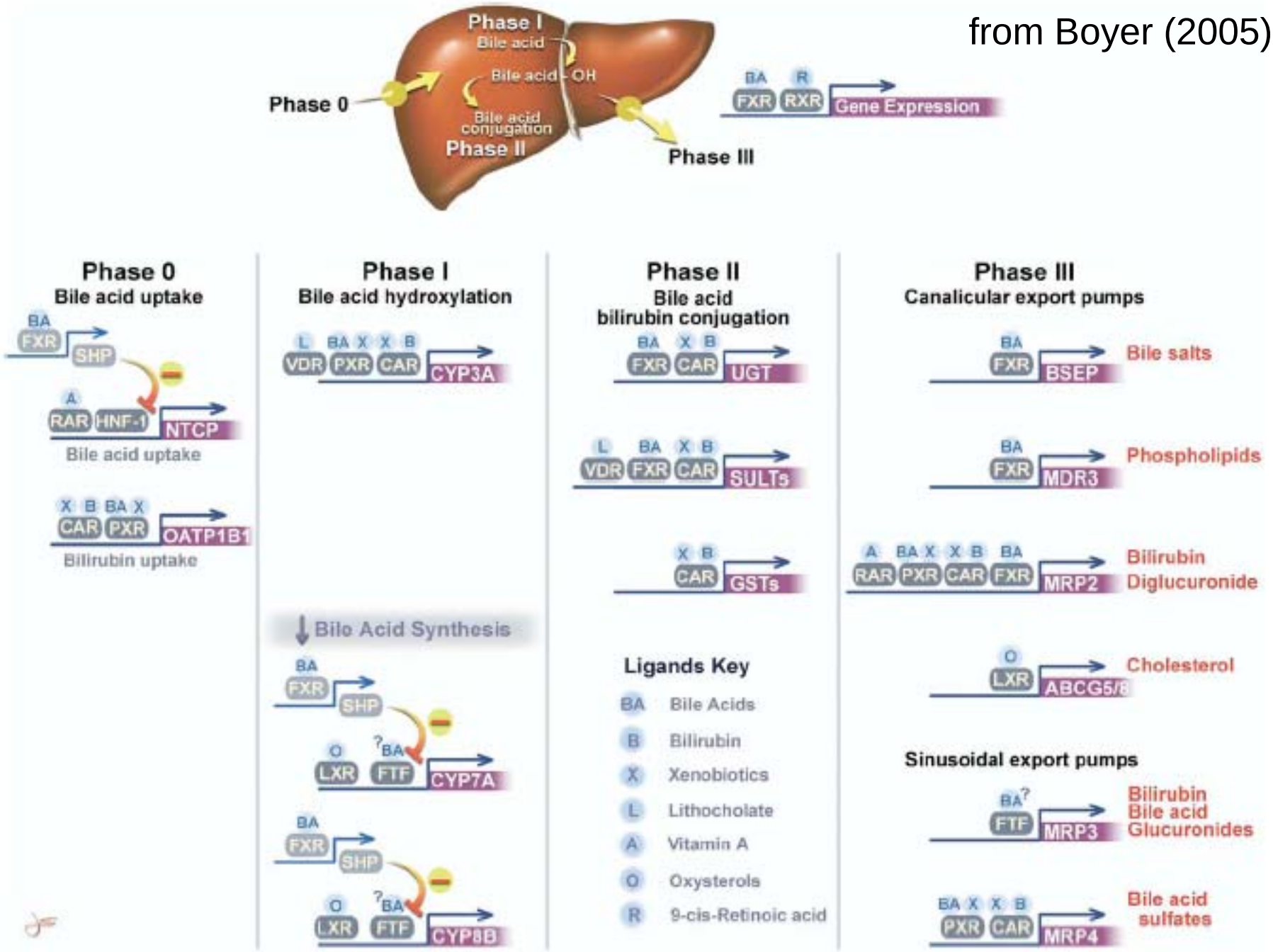


Marschall HU, Wagner M, Zollner G, Fickert P, Diczfalusy U, Gumhold J, Silbert D, Fuchsbichler A, Benthin L, Grundstrom R, Gustafsson U, Sahlin S, Einarsson C, Trauner M 2005 Complementary stimulation of hepatobiliary transport and detoxification systems by rifampicin and ursodeoxycholic acid in humans. Gastroenterology 129: 476-485.

Boyer JL 2005 Nuclear receptor ligands: rational and effective therapy for chronic cholestatic liver disease? Gastroenterology 129: 735-740.

from Boyer (2005)



Transport Proteins of Hepatocytes and Bile-Duct Epithelial Cells (Cholangiocytes)

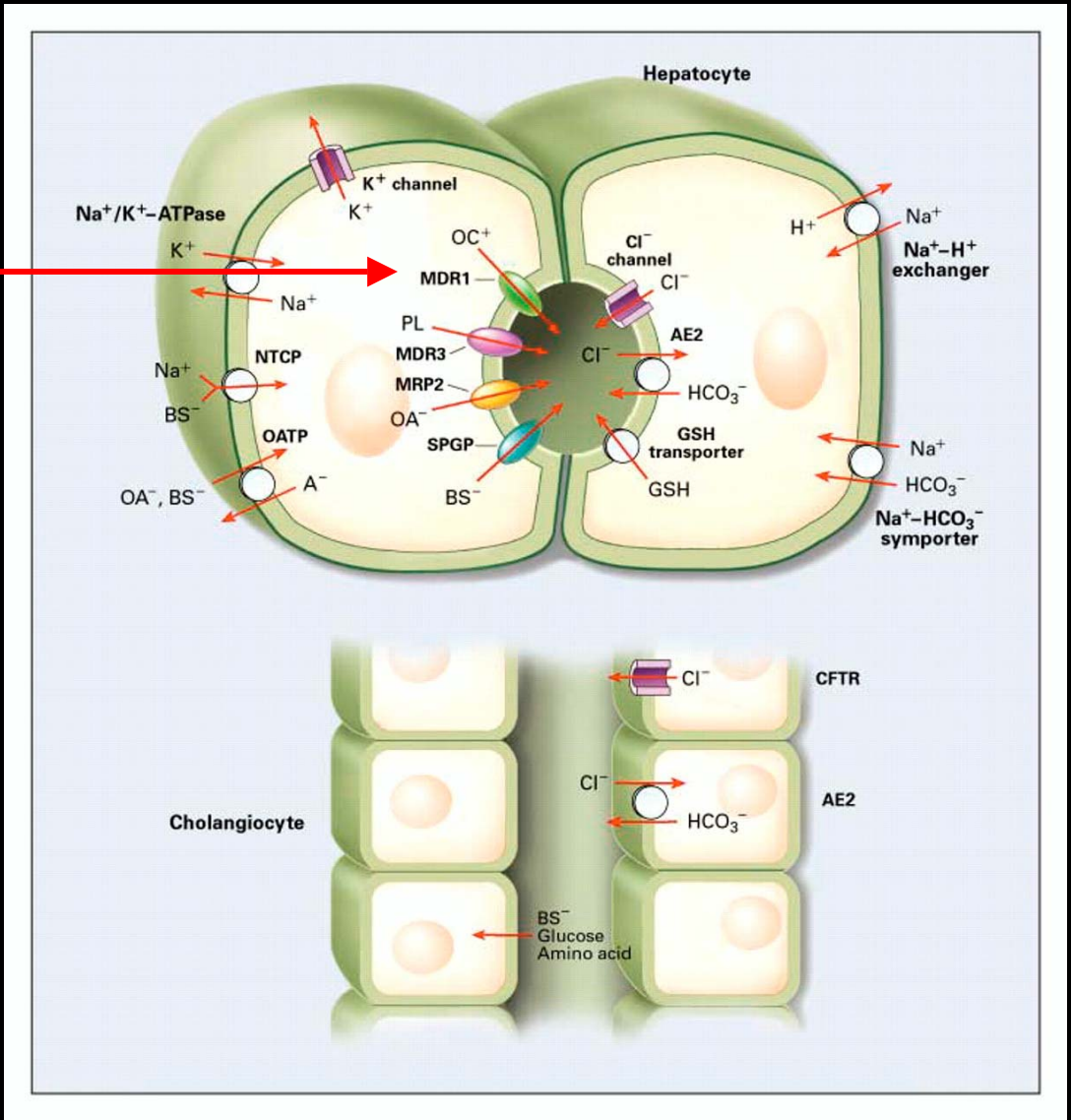
Multidrug Resistance 1

MDR1

decreased in UC due to decrease of PXR activity

PXR activated by rifampin

(also activates enzymes of bile metabolism)



MDR1 and PXR gene mutations linked to some cases of UC

Trauner, M. et al. N Engl J Med 1998;339:1217-1227

The NEW ENGLAND JOURNAL of MEDICINE

Langmann T, Moehle C, Mauerer R, Scharl M, Liebisch G, Zahn A, Stremmel W, Schmitz G 2004 Loss of detoxification in inflammatory bowel disease: dysregulation of pregnane X receptor target genes. Gastroenterology 127: 26-40.

Ho GT, Nimmo ER, Tenesa A, Fennell J, Drummond H, Mowat C, Arnott ID, Satsangi J 2005 Allelic variations of the multidrug resistance gene determine susceptibility and disease behavior in ulcerative colitis. Gastroenterology 128: 288-296.

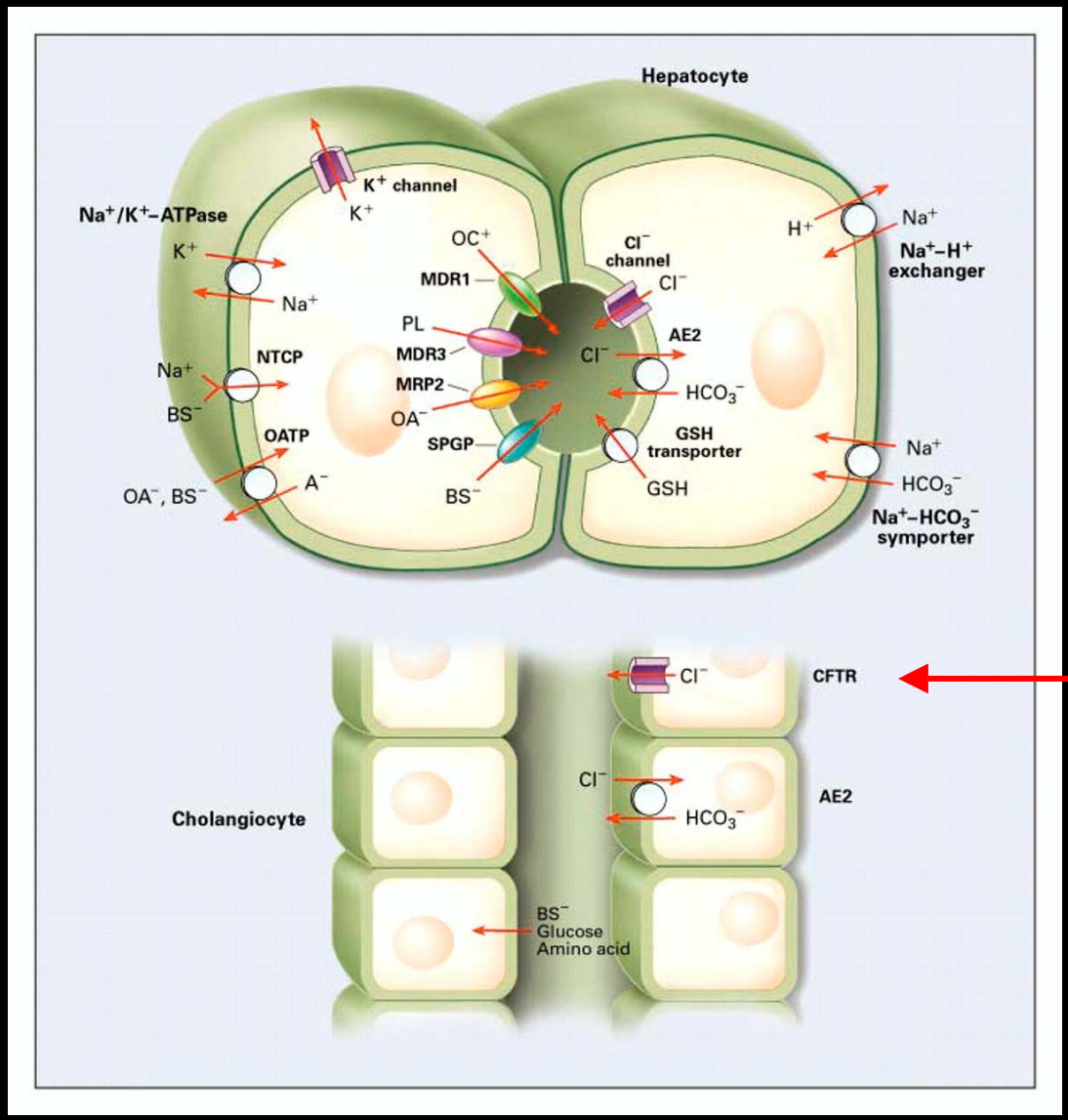
Dring MM, Goulding CA, Trimble VI, Keegan D, Ryan AW, Brophy KM, Smyth CM, Keeling PWN, O'Donoghue D, O'Sullivan M, O'Morain C, Mahmud N, Wikstrom AC, Kelleher D, McManus R 2006 The pregnane X receptor locus is associated with susceptibility to inflammatory bowel disease. Gastroenterology 130: 341-348.

Transport Proteins of Hepatocytes and Bile-Duct Epithelial Cells (Cholangiocytes)

CFTR-deficient mice (cftr (-/-)) develop sclerosing cholangitis when given colitis.

DHA protects against bile duct injury.

DHA = docosahexaenoic acid



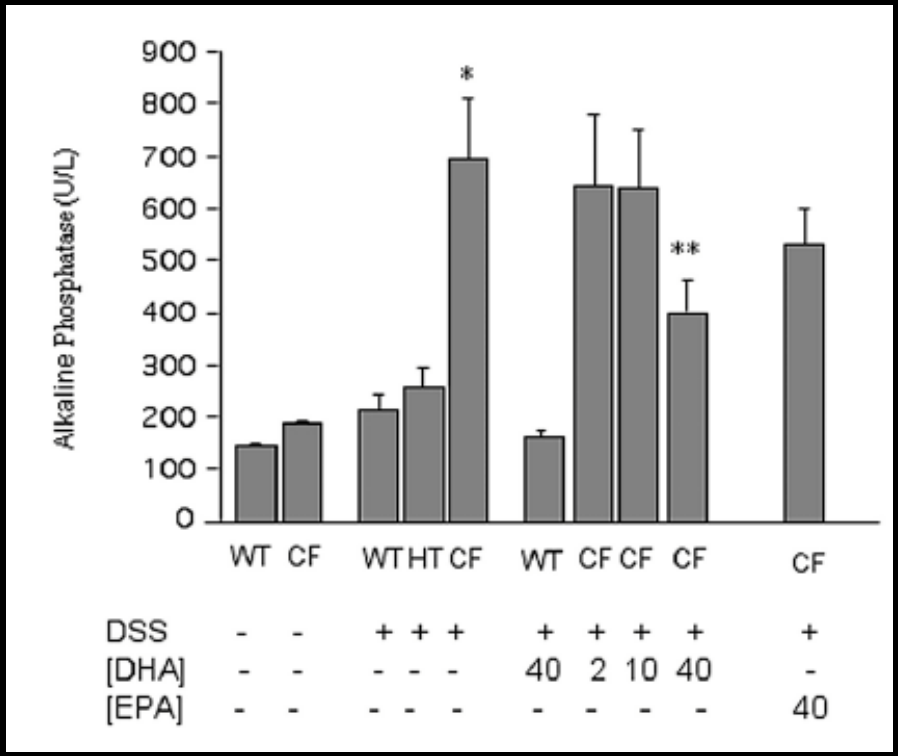
CFTR

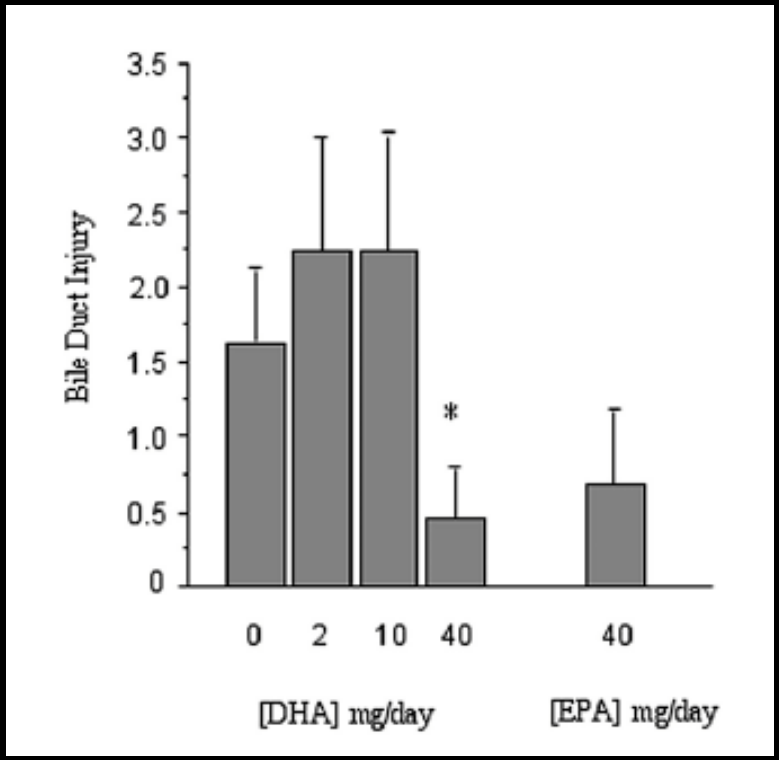
Trauner, M. et al. N Engl J Med 1998;339:1217-1227

The NEW ENGLAND JOURNAL of MEDICINE

Sheth S, Shea JC, Bishop MD, Chopra S, Regan MM, Malmberg E, Walker C, Ricci R, Tsui LC, Durie PR, Zielenski J, Freedman SD 2003 Increased prevalence of CFTR mutations and variants and decreased chloride secretion in primary sclerosing cholangitis. Hum. Genet. 113: 286-292.

Blanco PG, Zaman MM, Junaidi O, Sheth S, Yantiss RK, Nasser IA, Freedman SD 2004 Induction of colitis in cftr-/- mice results in bile duct injury. Am. J. Physiol. Gastrointest. Liver Physiol. 287: G491-G496.





Pall H, Zaman MM, Andersson C, Freedman SD 2006 Decreased peroxisome proliferator activated receptor alpha (PPARa) is associated with bile duct injury in cystic fibrosis transmembrane conductance regulator (-/-) mice. J. Pediatr. Gastroenterol. Nutr. 42: 275-281.

Dextran sodium sulfate (DSS) induced bile duct injury in cftr (-/-) mice is associated with a defect in PPARa expression, which is reversed by DHA.

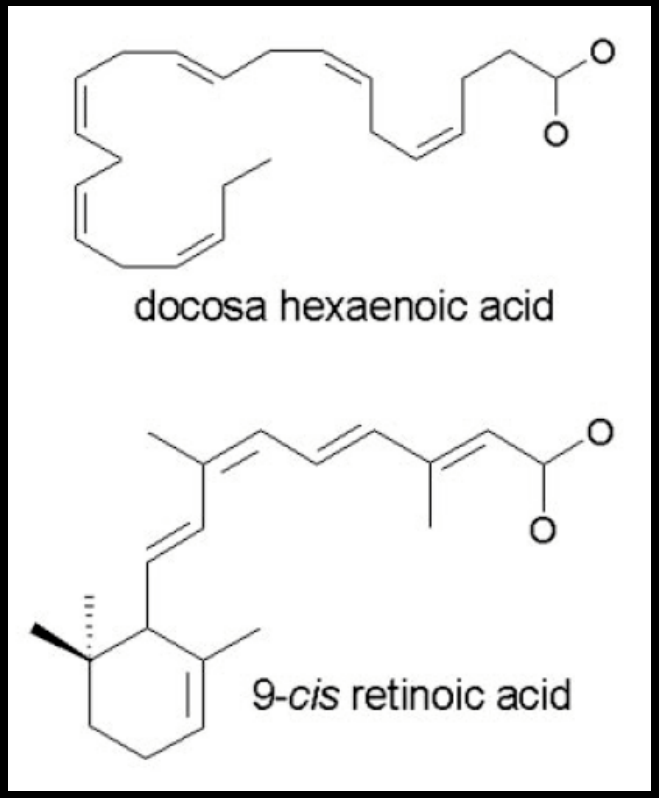
DHA induces the expression of PPARa, a receptor that controls expression of MDR3, and is known to be involved in the control of inflammation.

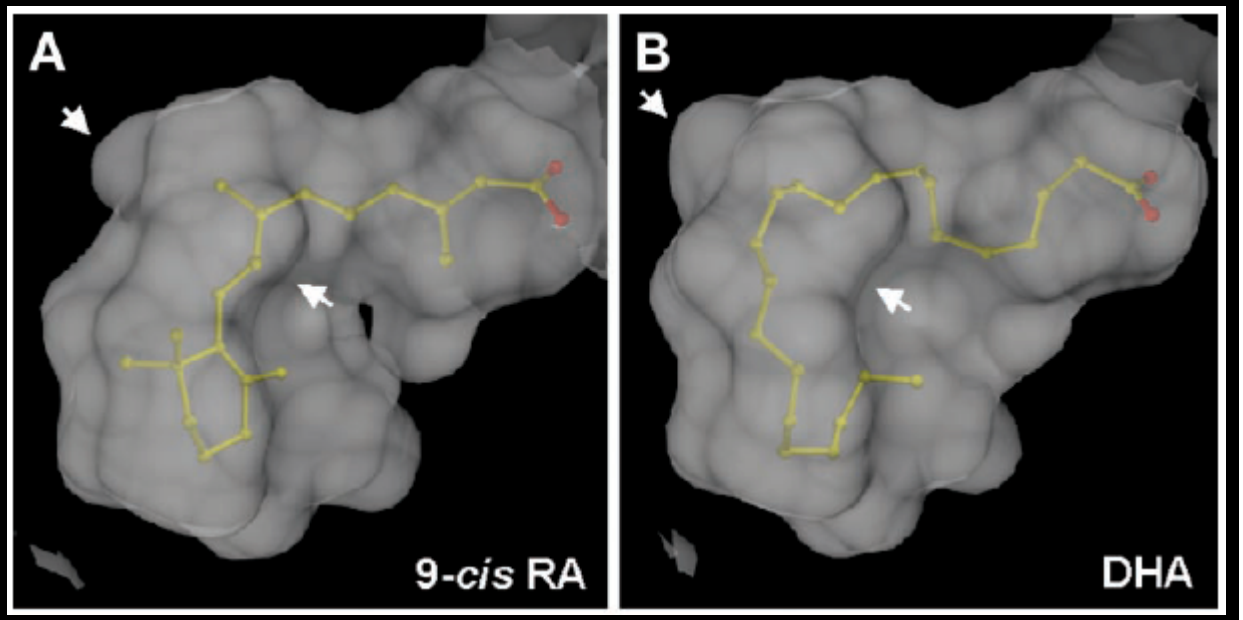
Dr. Steven Freedman currently has a trial to test the efficacy of DHA in PSC (funded by the Morgan Foundation).

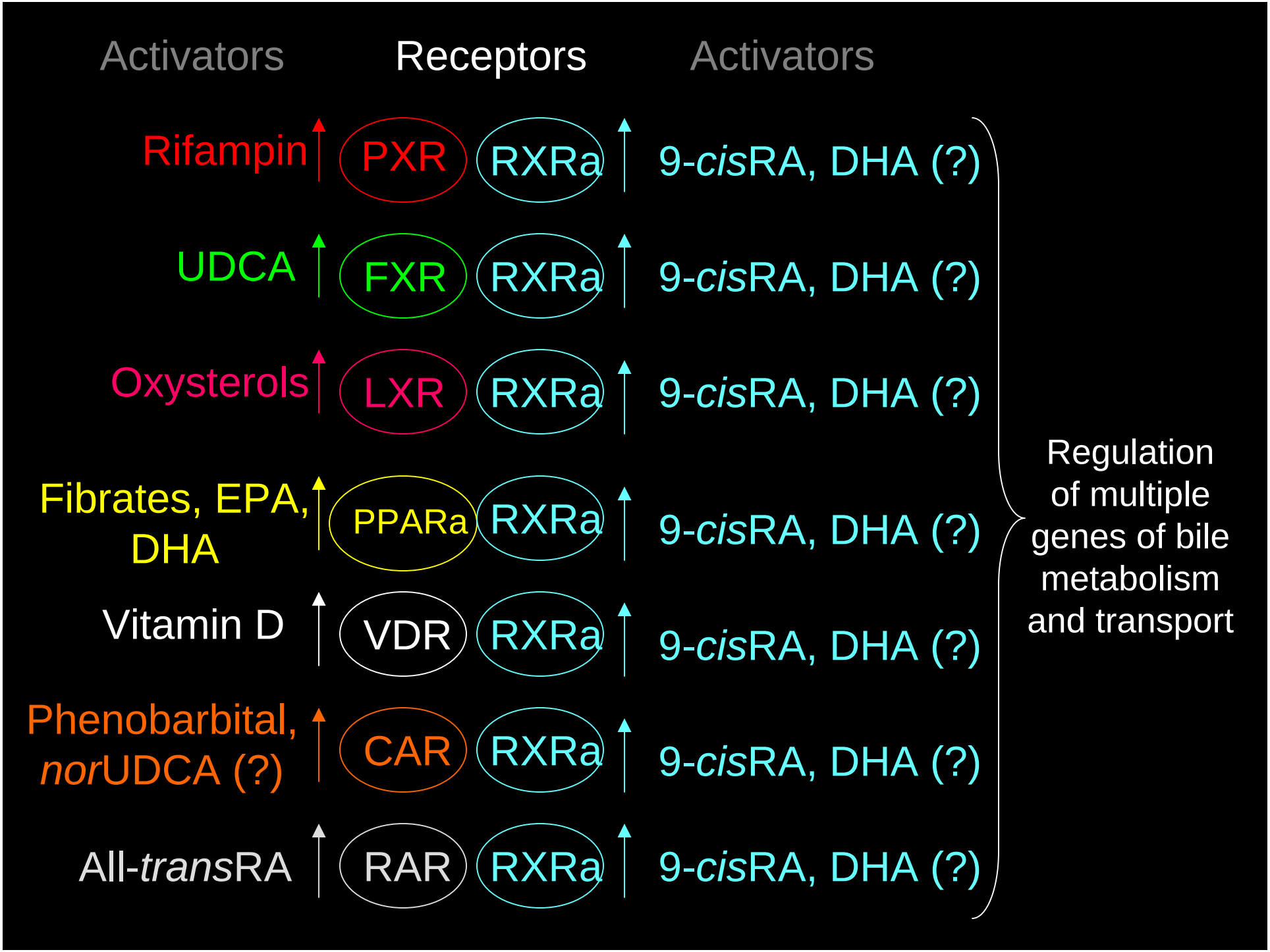
DHA might also be binding to (and activating) the retinoid X receptor alpha (RXRa).

DHA structurally resembles 9-*cis* retinoic acid, and binds to the RXRa active site:

Egea PF, Mitschler A, Moras D 2002 Molecular recognition of agonist ligands by RXRs. Mol. Endocrinol. 16: 987-997.






Activators
Receptors
Activators
Rifampin
PXR
RXRa
9-*cis*RA, DHA (?)
UDCA
FXR
RXRa
9-*cis*RA, DHA (?)
Oxysterols
LXR
RXRa
9-*cis*RA, DHA (?)
Fibrates, EPA, DHA
PPARa
RXRa
9-*cis*RA, DHA (?)
Vitamin D
VDR
RXRa
9-*cis*RA, DHA (?)
Phenobarbital, *nor*UDCA (?)
CAR
RXRa
9-*cis*RA, DHA (?)
All-*trans*RA
RAR
RXRa
9-*cis*RA, DHA (?)
Regulation of multiple genes of bile metabolism and transport

PSC genetics research in the U.S.A. is currently underway at:

- Mayo Clinic: Unraveling the Genetic Predilection to Primary Sclerosing Cholangitis (PSC).
  http://clinicaltrials.mayo.edu/clinicaltrialdetails.cfm?trial_id=100124

- UC Davis: The UC Davis group is establishing a PSC Patient Registry and DNA/Serum Bank.
  http://www.psc-literature.org/PSC_research_at_UC_Davis.pdf

- Beth Israel Deaconess Medical Center Children's Hospital, Boston: focused on CFTR in children with PSC.
  http://www.clinicaltrials.gov/ct/show/NCT00179439

- Morgan Foundation: The Morgan Foundation is taking the lead in forming a PSC registry among liver centers so that a database of information on adult and pediatric PSC patients can be assembled. The nearly 20 participating centers include Le Bonheur, The Mayo Clinic, Harvard University, the University of Cincinnati, Northwestern University and the Hospital for Sick Children in Toronto, Canada.
  http://www.pscfoundation.org/