PSC: a care-giver's perspective

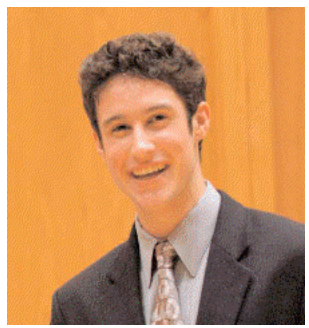
PSC Partners Seeking a Cure; Denver, CO; April 30, 2005

David and Judy Rhodes

(father and mother of Steven (19); PSC 07/03; UC 08/03)

PSC
PRIMARY SCLEROSING CHOLANGITIS

www.psc-literature.org



PSC
Partners Seeking a Cure
Working together to provide research, education, and support for people affected by Primary Sclerosing Cholangitis.

www.pscpartners.org

Advice from a care-giver:

1. Read about the disease and its many complications

2. Be aware of symptoms at different stages

3. Be aware of side-effects of medications

4. Know how the medications work

5. Encourage good nutrition, and healthy life-style

6. Keep detailed medical records

7. Join a PSC support group

PSC

PRIMARY SCLEROSING CHOLANGITIS

www.psc-literature.org

- A compilation of www resources & scientific literature on PSC and allied diseases

- Access to >24,500 abstracts on PSC, IBD & autoimmune diseases

- Scientific literature organized by keyword, authors, and dates

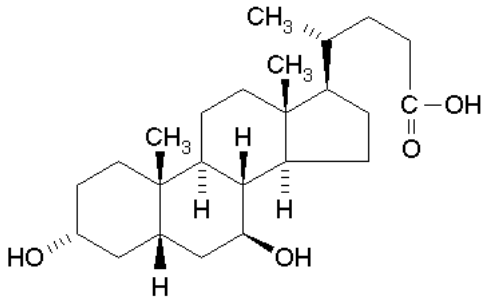
- Collected ~ 8,000 full papers since July 2003

- Web site requests = 10,000 per month (1,900 distinct hosts served per month) as of April 2005

- Updated weekly (approx. 300 new abstracts per week)

Medications/Supplements that Steven is Taking:

- Ursodiol (ursodeoxycholic acid; UDCA; URSO)
- Rifampin (rifampicin)
- Fish Oil
- Vitamins (Centrum Silver)
- Folic acid
- Spinach
- Asacol (a 5-aminosalicylic acid)



Ursodeoxycholic acid (ursodiol; URSO; UDCA)

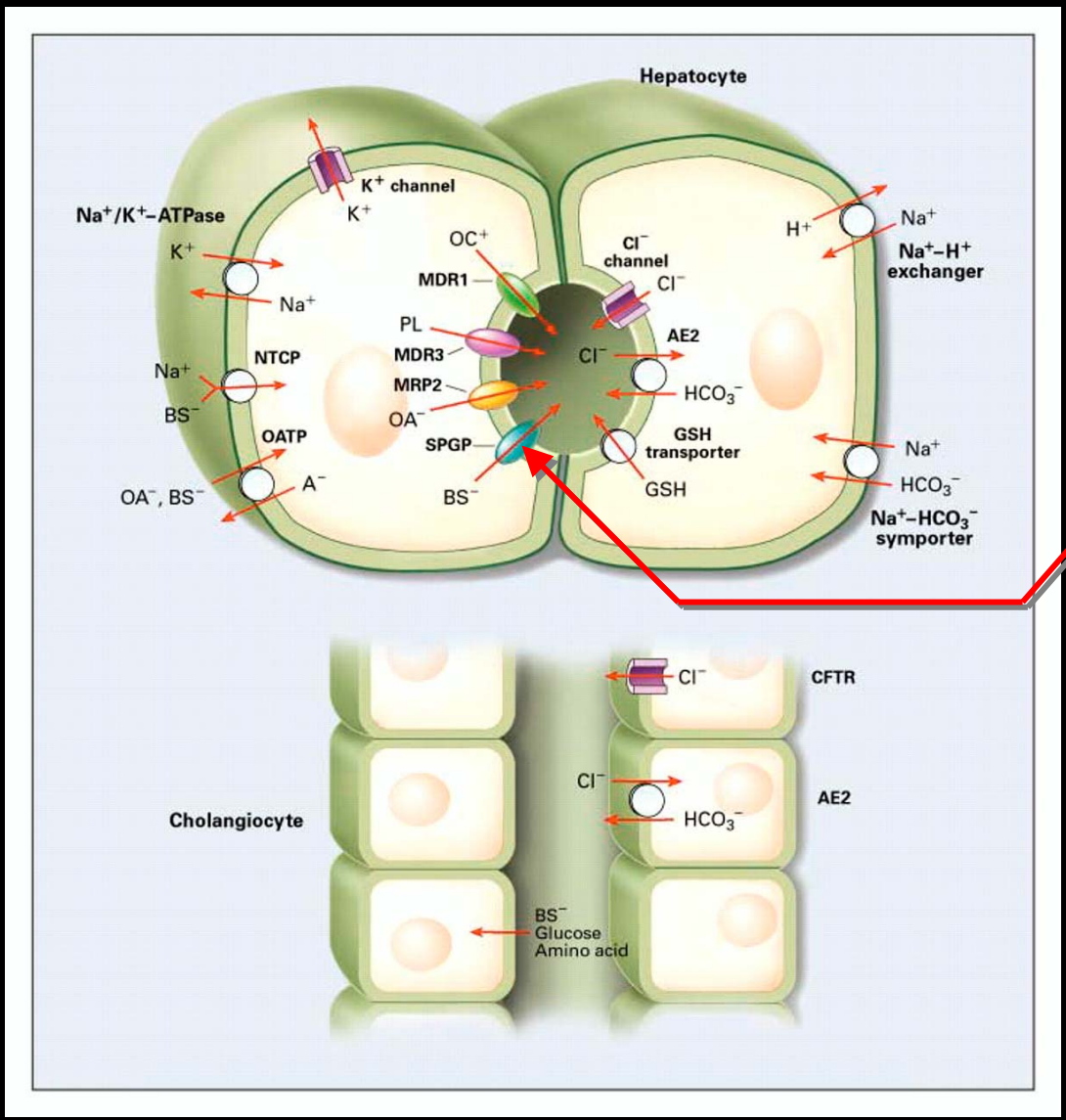
- A bile acid originally identified in bear bile (bear family = Ursidae)
- First used in Western medicine to treat/dissolve gallstones
- Improves bile flow; preserves activity of bile salt export pump

- Competes with deoxycholic acid (DCA), a toxic bile acid
- Prevents cell death caused by DCA accumulation
- Tends to lower ALT and AST (and ALP to some extent)
- Anti-inflammatory effects (due to interaction with the glucocorticoid receptor (GR))
- Evidence growing that it protects against colon cancer & cholangiocarcinoma
- In PBC, significantly delays time to liver transplant
- In PSC, studies still in progress with high-dose ursodiol

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

BSEP activity decreased by DCA

Ursodiol preserves BSEP activity



BSEP

Bile Salt Export Pump

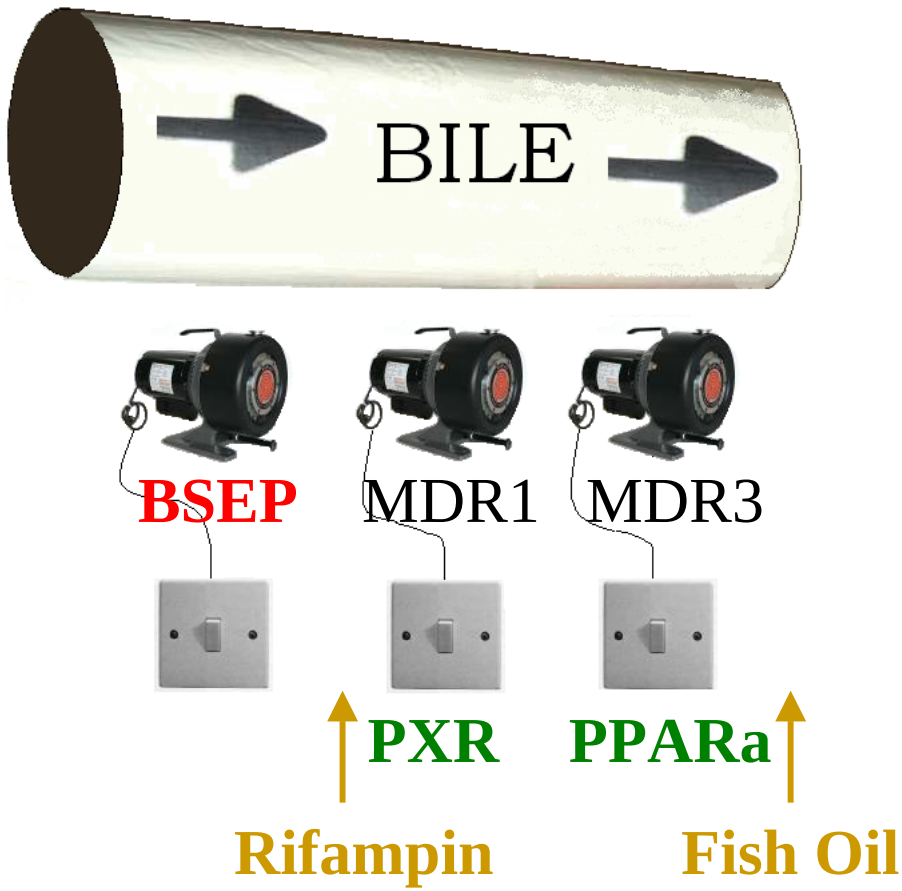
Trauner, M. et al. N Engl J Med 1998;339:1217-1227

The NEW ENGLAND JOURNAL of MEDICINE

BSEP

Ursodiol preserves bile salt export pump (BSEP) activity

Many of the pumps involved in bile transport in the liver are regulated by molecular switches



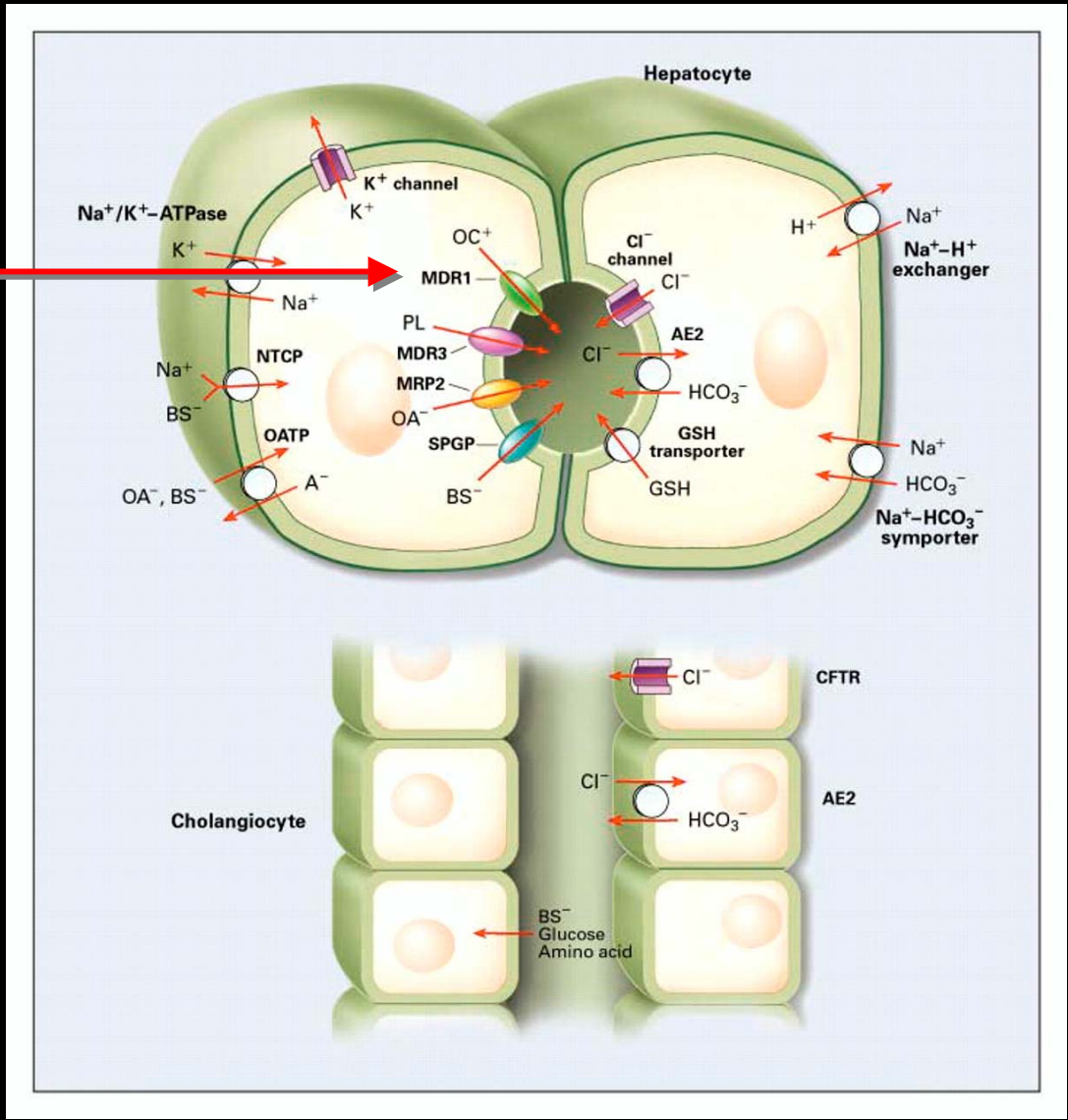
Multidrug Resistance 1

MDR1

decreased in UC due to decrease of PXR activity

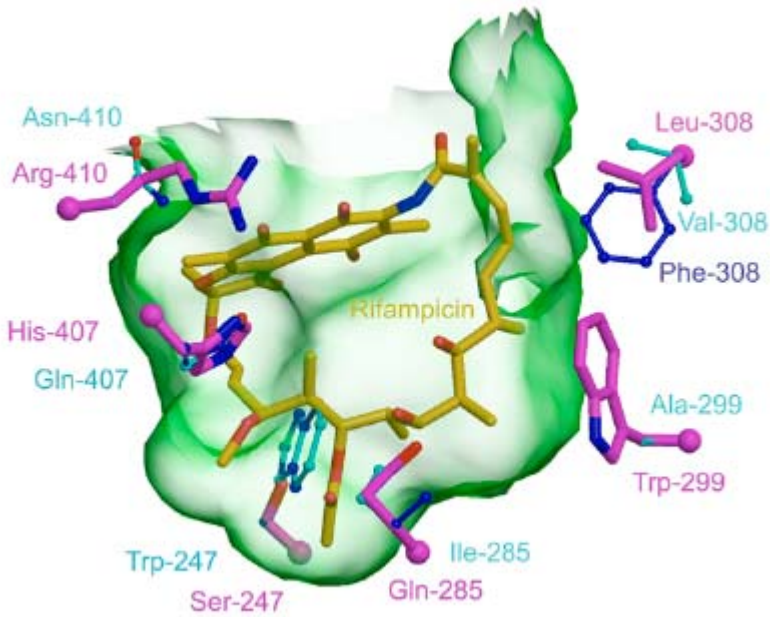
PXR activated by rifampin

(also activates enzymes of bile metabolism)



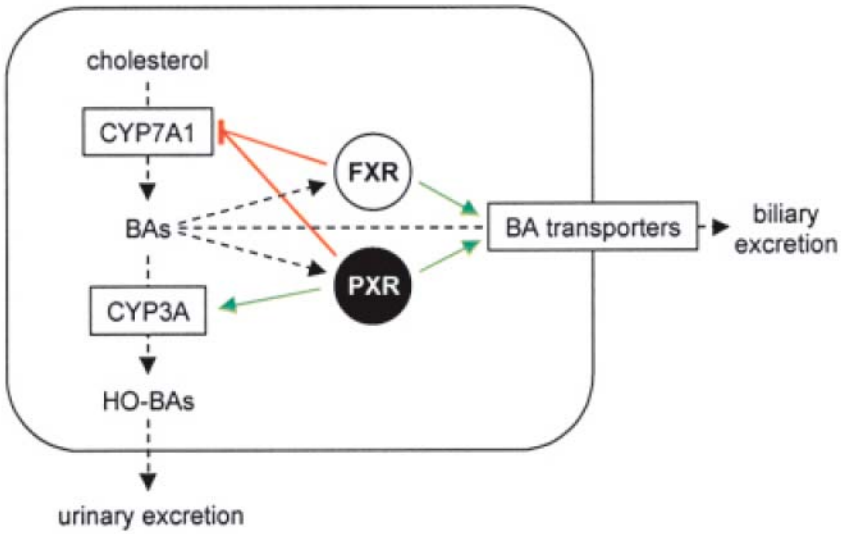
MDR1 gene mutations linked to some cases of UC

Chrencik JE, Orans J, Moore LB, Xue Y, Peng L, Collins JL, Wisely GB, Lambert MH, Kliewer SA, Redinbo MR (2005) Structural disorder in the complex of human PXR and the macrolide antibiotic rifampicin. Mol. Endocrinol. Feb 10 [Epub ahead of print]



Rifampin (rifampicin) interacts with, and activates the **PXR** (pregnane X receptor). PXR is a “switch” that regulates a number of bile transporters and enzymes of bile metabolism. Here rifampin is shown binding to PXR.

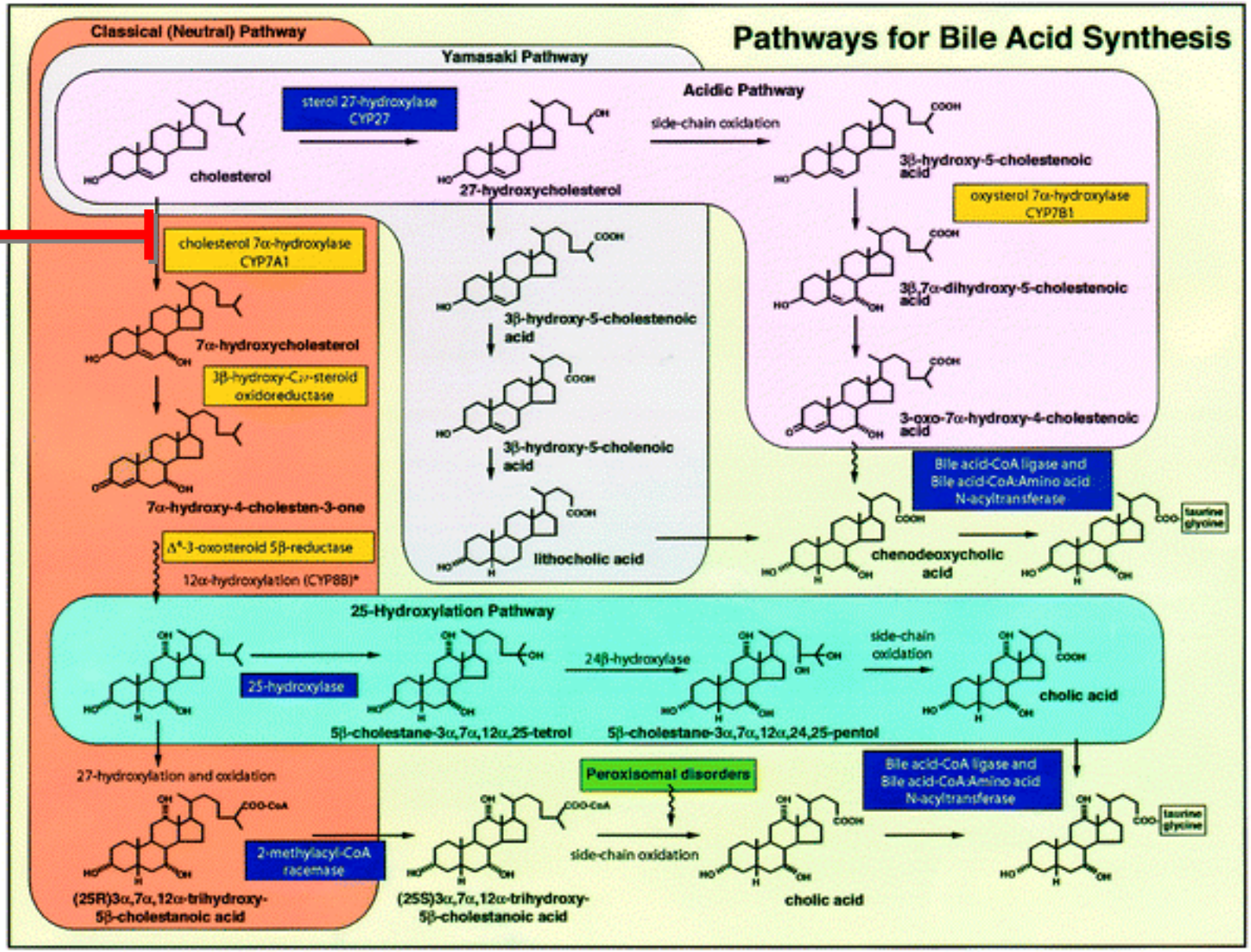
Kliewer SA, Willson TM (2002) Regulation of xenobiotic and bile acid metabolism by the nuclear pregnane X receptor. J. Lipid Res. 43: 359-364.



The pregnane X receptor (PXR) **activates** bile transporters, **increases** bile acid hydroxylation (promoting urinary excretion) and **inhibits** one pathway of cholesterol metabolism to bile acids

PXR

Rifampin



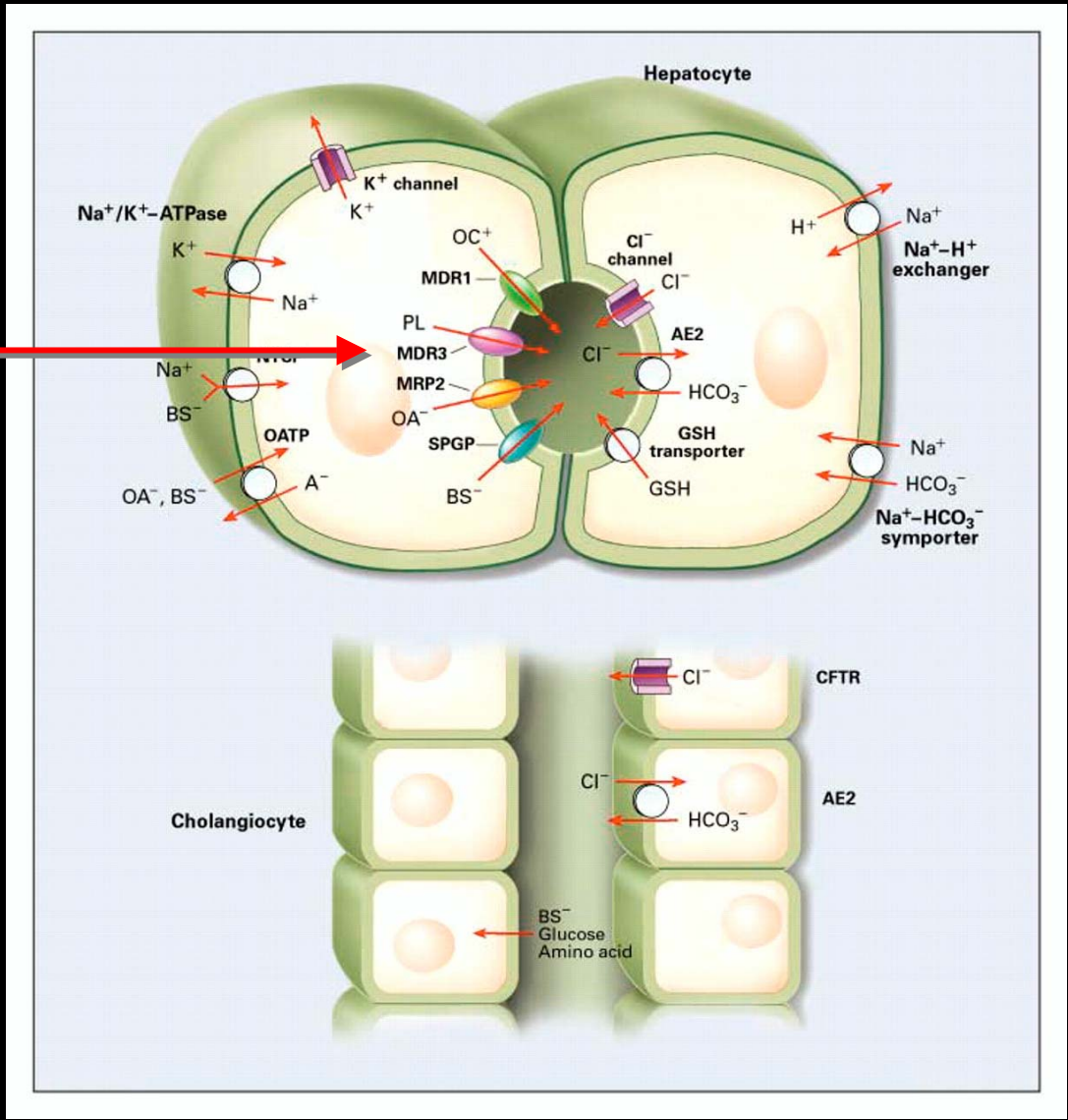
Rifampin interacts with, and activates the **PXR** (pregnane X receptor), inhibiting the "Neutral" pathway of bile acid synthesis

Multidrug Resistance 3

MDR3

Mice deficient in MDR3 develop SC

MDR3 regulated by PPARa; activated by fibrates



Fibrates lower ALP and GGT in PBC and PSC

Other activators of PPARa include DHA; a component of fish oil

Essential Fats: Metabolism and Dietary Sources

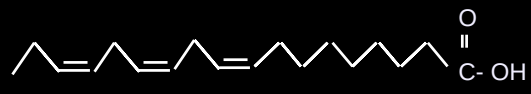
http://efaeducation.nih.gov/sig/food.html

Omega-6

18:2n6 linoleic acid, LA

Safflower oil
Corn oil
Soy bean oil

Omega-3



18:3n3 linolenic acid, LNA

Canola oil
Walnuts
Flax seed
Leaf plants

competition for Δ6 and Δ5 desaturase and elongation enzymes

20:4n-6, arachidonic acid AA

Meat, Organs

20:5n-3,eicosapentaenoic acid, EPA

Fish
Seafood
Seaweed

Series 2
Prostaglandins
Thromboxanes
Series 4
Leukotrienes

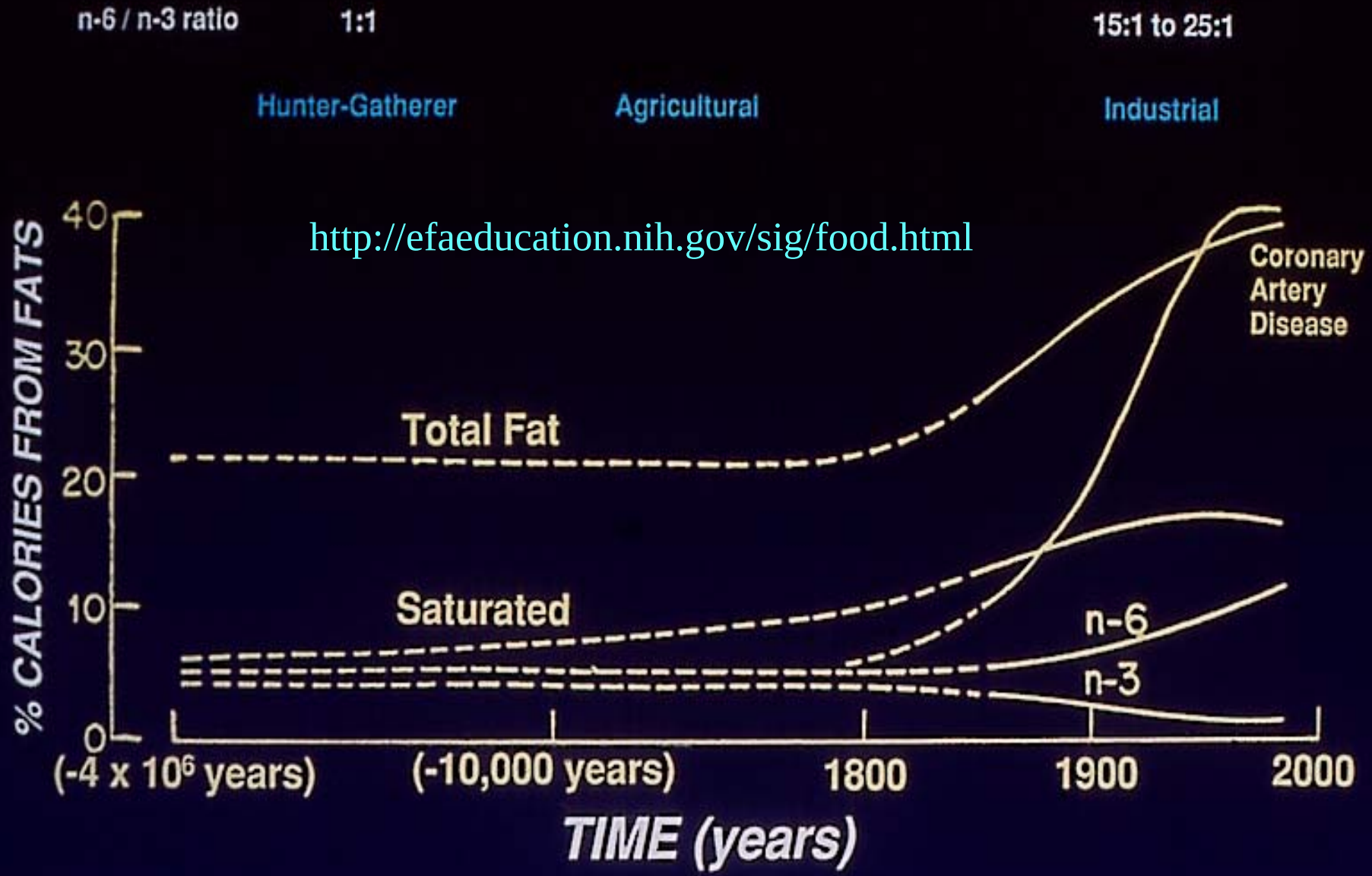
Series 3
Prostaglandins
Thromboxanes
Series 5
Leukotrienes

22:6n-3, docosahexaenoic acid, DHA
(brain, retina, testis)

platelet activity
immune responses
smooth muscle
many other functions

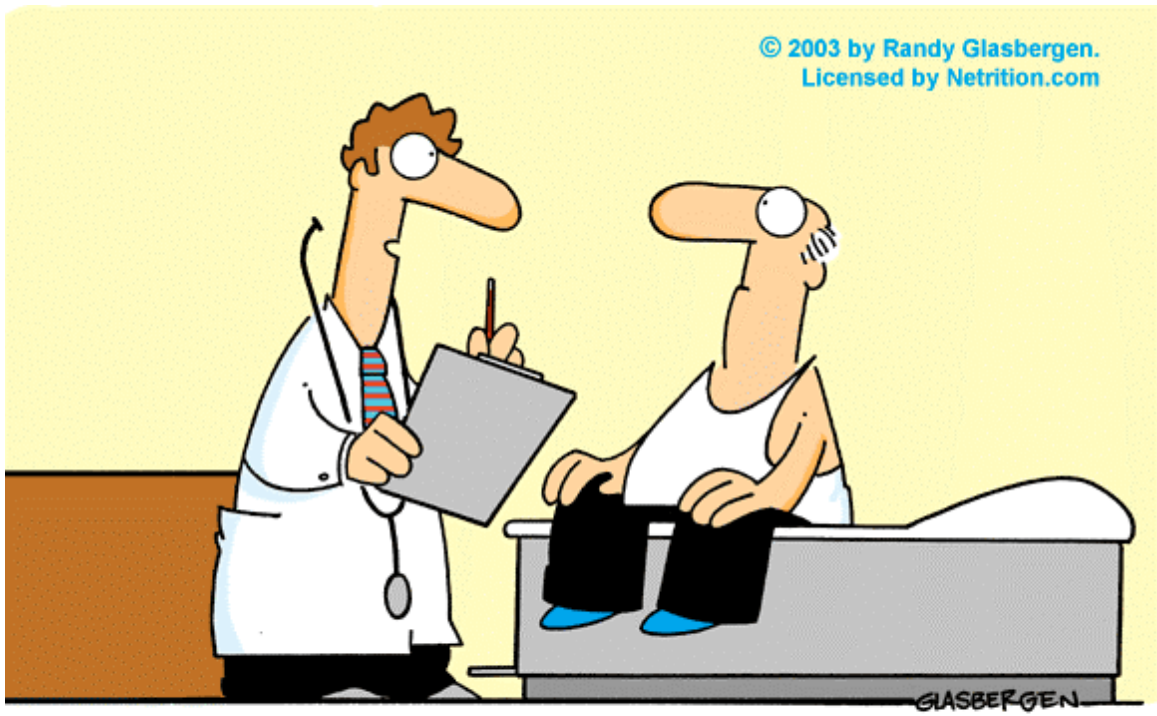
pro-inflammatory

anti-inflammatory

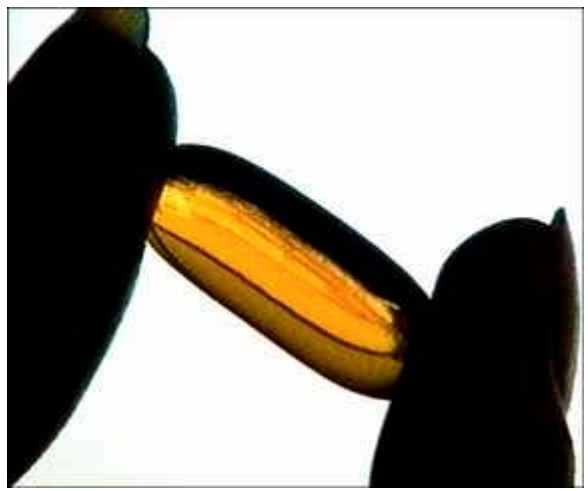


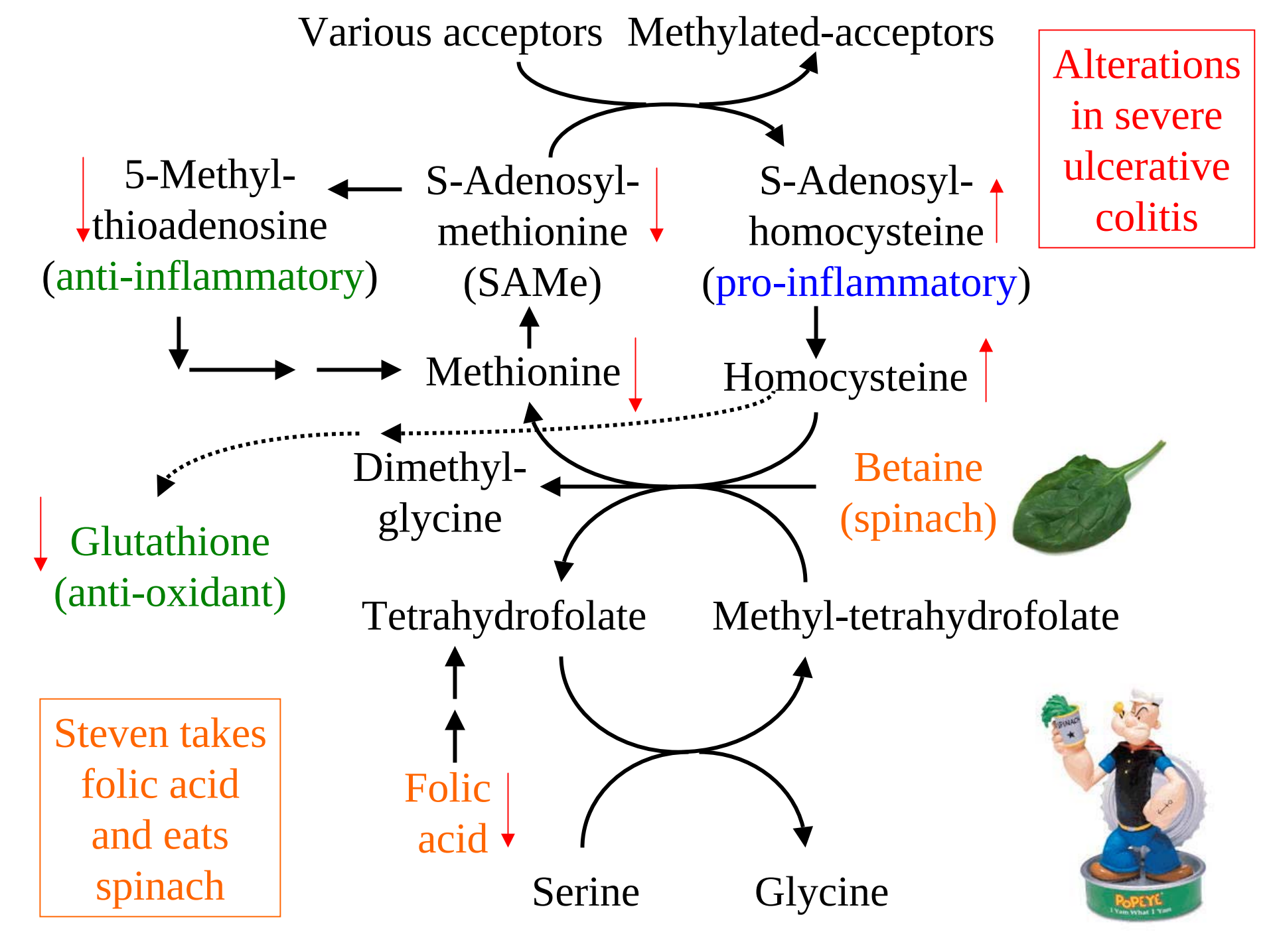
Leaf and Weber Am J Clin Nutr 1987; 45: 1048-1053

Take Home Message:
Fish Oils are Anti-Inflammatory

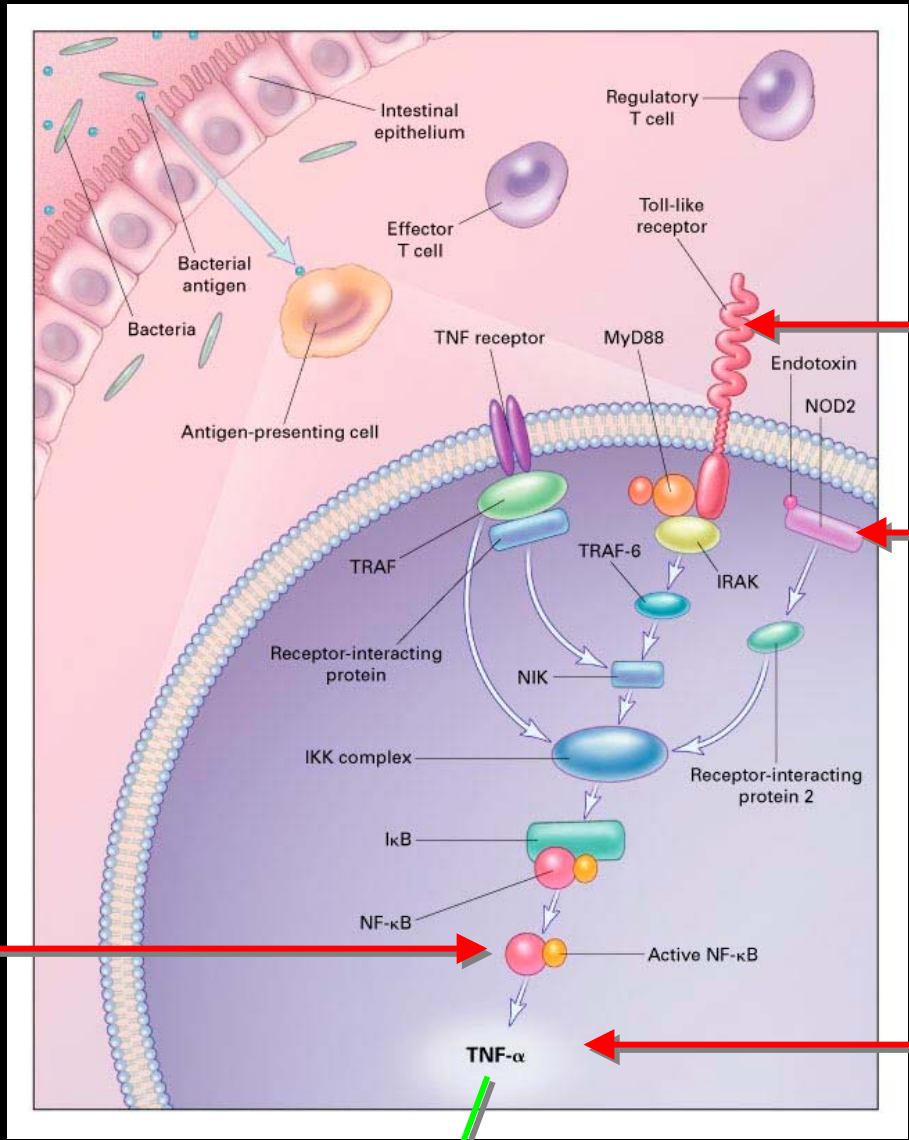


"Large doses of fish oil are very good for your heart. Especially when you get the urge to swim upstream."




Various acceptors
Methylated-acceptors
Alterations in severe ulcerative colitis
5-Methyl-thioadenosine (anti-inflammatory)
S-Adenosyl-methionine (SAMe)
S-Adenosyl-homocysteine (pro-inflammatory)
Methionine
Homocysteine
Dimethyl-glycine
Betaine (spinach)
Glutathione (anti-oxidant)
Tetrahydrofolate
Methyl-tetrahydrofolate
Steven takes folic acid and eats spinach
Folic acid
Serine
Glycine
POPEYE

Components of the inflammation signaling pathway in IBD



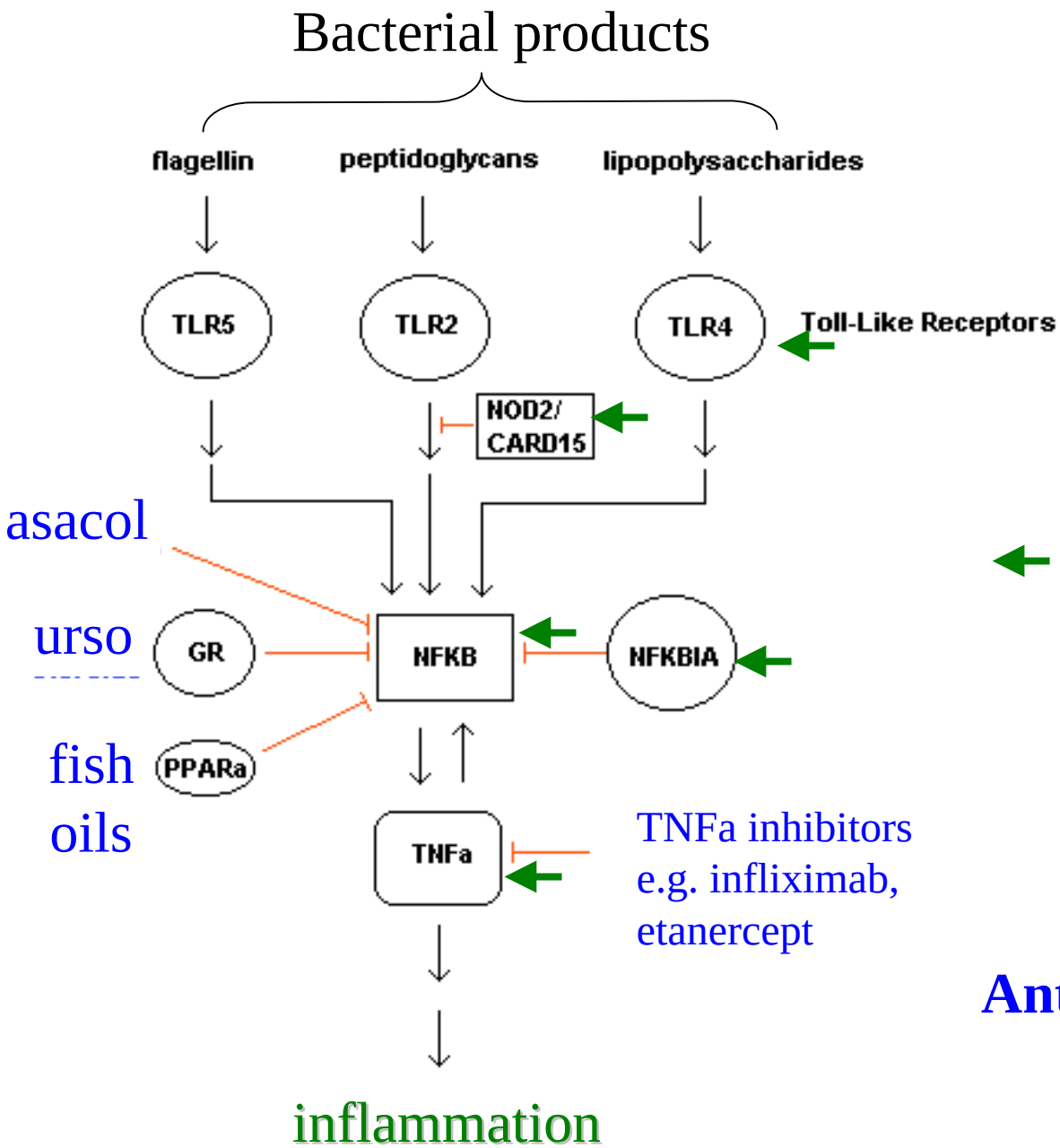
Toll-like Receptor

NOD2/ CARD15

Nuclear Factor-kappa B

Tumor Necrosis Factor Alpha

inflammation



Mutations in these genes linked to IBD; mostly Crohn's

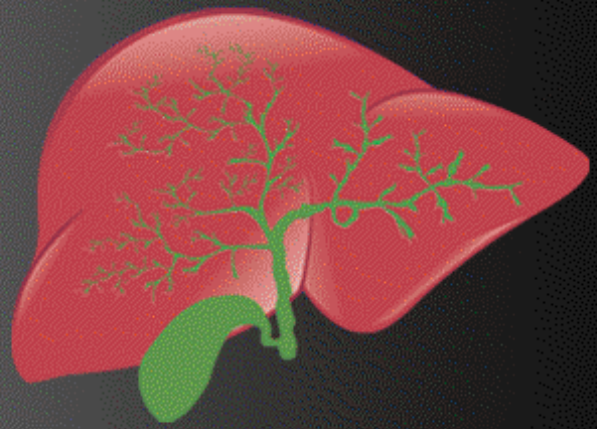
Anti-inflammatory medications

Matrix of Research Goals in Autoimmune Liver Disease

	Short Term (0-3 years)	Intermediate Term (4-6 years)	Long Term (7-10 years)
High Risk	**A3.** Define the roles of CD4+ and CD8+ T cells, other effector immunocytes, dendritic cells, and the innate immune system in liver injury in humans (and animal models) with autoimmune liver disease.	**B3.** Identify genetic linkages in PBC and refine the HLA-associations in autoimmune hepatitis and PSC. Develop animal models for each of the autoimmune liver diseases.	**C3.** Identify modifiable environmental (with or without genetic) triggers for induction of autoimmune hepatitis (from human studies or murine models).
Intermediate Risk	**A2.** Develop multicenter networks of investigators to study natural history, pathogenesis, etiology, and therapy of autoimmune liver diseases.	**B2.** Develop sensitive and specific biomarkers for disease activity and stage in PBC and PSC. Develop diagnostic criteria and standard definitions for endpoints of therapy.	**C2.** Develop sensitive serum markers for early detection of cholangiocarcinoma in PSC.
Low Risk	**A1.** Organize and convene an international, interdisciplinary research workshop on development of animal models of autoimmune liver diseases.	**B1.** Demonstrate whether high-dose ursodiol therapy is effective in retarding the progression of PSC and identify risk factors for progression and for response to treatment.	**C1.** Develop alternatives to prednisone/azathioprine as maintenance therapy of autoimmune hepatitis and define markers for when and how therapy can be safely stopped.

NIDDK Action Plan for Liver Disease Research: Autoimmune Liver Disease

Primary Sclerosing Cholangitis Conference



September 19-20, 2005

Lister Hill Conference Center
National Institutes of Health
Bethesda, MD

- HOME
- REGISTRATION
- AGENDA
- HOTEL INFORMATION
- LOCAL AREA INFORMATION
- CONFERENCE LOCATION
- CONTACT

To assess current knowledge about primary sclerosing cholangitis (PSC) focusing on its prevalence and incidence, diagnosis and staging, pathogenesis, disease associations, management, and treatment, including use of surgery and liver transplantation. The meeting will be sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, the Office of Rare Diseases, and the Morgan Foundation. The aims of the meeting are to stimulate clinical and basic research interest in PSC and identify gaps in knowledge and challenges for medical research in this disease. The meeting will include poster sessions with noon and evening attendance of speakers, presenters, and participants. The meeting summary will be prepared for publication by members of the organizing committee.

Sponsored By:

- National Institute of Diabetes and Digestive and Kidney Diseases
- The Morgan Foundation
- Office of Rare Diseases

Organizers:

- Dennis Black
- Benjamin Shneider
- Nicholas LaRusso
- Edward Doo
- Jay Hoofnagle

In Memory of Shauna Saunders

Shauna Saunders, a sixth-year doctoral student in the Department of Economics, died Dec. 3, 2004 at Duke University Hospital. A burgeoning force in her field, a devoted teacher and a wit with a shoe obsession, Shauna struggled with a chronic liver disease she carried since childhood even as her body broke down and multiple liver transplants at Duke fell through. She was 29.