



Working together to provide research,
education, and support for people
affected by Primary Sclerosing Cholangitis

www.pscpartners.org

PSC Partners Seeking a Cure Newsletter

Vol. 2, Issue 4, December, 2006

Edited by David Rhodes and Ricky Safer

PSC Partners Seeking a Cure Board Members:

Dike Ajiri, Lee Bria, Elissa Deitch, Dr. Gregory Everson,
Joanne Grieme, Chris Klug, Scott Malat, David Rhodes,
Ricky Safer, and Deb Wentz

PSC Partners Seeking a Cure Begins Funding PSC Research

The PSC Partners Seeking a Cure board is pleased to announce that PSC Partners Seeking a Cure will donate \$20,000 to support the STOPSC registry this year, with the promise of a second year of support at \$20,000, subject to adequate progress during the first year. We hope that this will be the beginning of a productive partnership between PSC Partners Seeking a Cure and the Morgan Foundation funded STOPSC registry; we certainly share a common mission.

For more details about the STOPSC registry, please see:

<https://web.emmes.com/study/psc/index.html>

PSC Partners Seeking a Cure will also fund a small prize (\$1,000 - \$3,000) to be given at the annual AASLD meeting for promising PSC research presented at this annual meeting. This prize was approved at the AASLD meeting held October 27 - 31, 2006 in Boston.

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ORDINARY MOMENTS

As I sit inside nursing the cold I've picked up, I start frantically thinking of all that I have to do - the holiday shopping, the holiday dinner party for 30.... I spend a few minutes caught up in the drama, and then I catch myself and sit back and smile. How lucky I am to have such worries.... Like all you other PSCers, my PSC diagnosis initially felt like a menacing tornado swarming around me, ending my lifestyle as I had known it. Thanks to the advice and knowledge of fellow PSCers, I am learning to live with the uncertainties of this disease. At the end of the year, as I contemplate what I am thankful for, I realize that what I appreciate most is the luxury of enjoying the ordinary moments in life that I used to take for granted. I relish my time with Don, our kids and grandkids, birthday celebrations, special outings with our grandkids Sam and Lily, walks with friends, etc. Even the rush of end of the year holiday preparations right now feels comforting....another touch of "normalcy". My New Year's wish for all of our PSC family is a year of good health plus a year of enjoying these "ordinary" moments in your lives.

FOUNDATION HIGHLIGHTS: As for a foundation update, here are a few recent highlights that point to a bright

future.

PSC Partners Supports Research Project: Thanks to the background work of the Scientific/Medical Advisory Committee, our board has voted to financially support two types of PSC research. We have sent in a \$20,000 donation to the Morgan Foundation, making us the first group to support the very important STOPSC registry. Dr. Dennis Black spoke to our group at our 2006 conference, explaining the goals of the registry. (For more information, log onto <https://web.emmes.com/study/psc/index.html>). We all hope that the STOPSC registry will be the basis for future PSC research which will eventually find the cause and cure for PSC.

We also have decided to fund a PSC research prize to be awarded next fall to the best fellow or junior faculty abstract in the area of PSC at the annual meeting of the AASLD (American Association for the Study of Liver Diseases.) This will lend support to a researcher and also increase awareness of our foundation. We are very excited to be able to start supporting PSC research as a foundation!

I'd like to welcome Joanne Grieme and Scott Malat as our two new board members. We are eager to have you work with us.

We are just firming up a few more details for Conference 2007, our third annual conference, and it is shaping up to be a fantastic weekend. Please take a look at the conference update in this edition. We hope to see you here in Denver April 13-15, 2007!

Our all-volunteer organization is expanding quickly, thanks to the help of so many individuals. A special thank you to:

- Our board members Dike Ajiri, Lee Bria, Elissa Deitch, Dr. Greg Everson, Chris Klug, David Rhodes, and Deb Wentz for their guidance and good judgment.
- Dave Rhodes for writing and publishing our newsletter, for providing us online with so much scientific information and guidance, and for chairing the Scientific/Medical Advisory Committee. Thank you to Judy and Dave for constantly updating the amazing PSC Literature site and the PSC Partners website.

- Lee Bria for continuing to head our fundraising efforts. Thank you for creating the Annual Virtual Walk, which brought in a total of \$44,500 last spring!
- Deb Wentz, our Treasurer, who prepares our monthly financial statements and keeps us in compliance with our 501(c)3 status.
- Dike Ajiri for heading our Investment Committee, and for preparing an excellent investing plan.
- Nina Russakoff, our legal advisor who advises us on all our operations.
- Dr. Gregory Everson, our Medical Advisor, whose expertise and advice is invaluable. Thank you for working so closely with us to put together such a wonderful slate of speakers for the 2007 conference.
- Chris Klug for continuing to be our hero and for speaking at our annual conferences.
- Joanne Grieme for hosting our 2006 conference. Every detail of the weekend was outstanding!
- Scott Malat and Jason Drasner for their work on the Investment Committee.
- Aubrey Goldstein, Dennis Black, Steve Deitch and Don Safer for serving on the Scientific/Medical Advisory Committee.
- Jonathan George, Tiffany Crumbliss, and Arne Myrabo for moderating the Yahoo online site.
- Sima Malat for having our tax returns prepared.
- Shelley Hussey for donating the printing costs for the new version of our brochure. Thank you to Pat McBride of Envision Printing in Marietta Georgia for offering us a special price for the second printing.
- Drs. Keith Lindor, Adam Slivka, Nora Bergasa, Thomas Shaw-Stiffel, Kapil Chopra, Kusum Tom, Leonard Baidoo, Dennis Black, and also Laura Matarese, Robert Noll, Nance Conney, Dorit Brauer, Gerald DeNucci, Glenn Sinko, Dave Rhodes, and Ivor Sweigler for their presentations

at our 2006 conference.

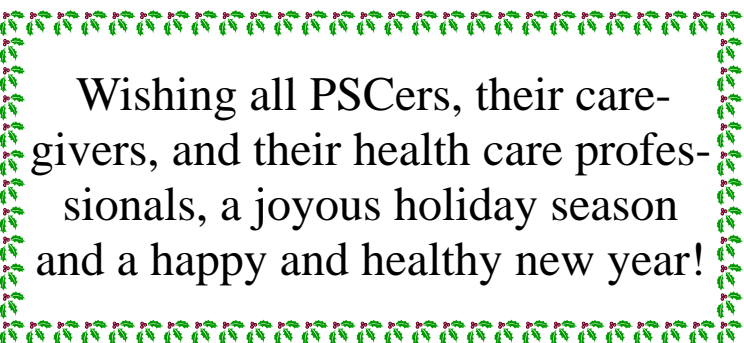
- The chairpeople of our various projects:

Barb Henshaw-Brochure project
 Lee Bria-Krogers gift cards
 Dave Rhodes-CD project
 Tim Wholey-Recycling project
 Dana Miletic-Wristband project
 Ali Lingerfelt-Tait-Notecard project

- Astellas Pharma, American Liver Foundation-Western Pennsylvania Chapter, Axcan Scandipharm, Roche Pharmaceuticals, ConAgra Foods, UPMC-Thomas Starzl Transplantation Institute, and AAA Environmental for being our corporate sponsors.
- All our individual donors who are noted in each edition of the newsletter.
- All the members of the online PSC support group who bring compassion, wisdom and encouragement to all of us.
- All the PSCers and caregivers who lend support to our organization through a variety of personal efforts.
- My husband Don, my children Elissa and Adam and their spouses Steve and Sue for always supporting me and for being able to make me laugh, no matter what!

Thank you everyone for the encouragement, love, and expertise that you provide us. Together in the fight, whatever it takes! May our shared dream come true some day that we'll find a cure for PSC, and PSC Partners Seeking a Cure will become obsolete! Until then, enjoy a healthy 2007 full of those "ordinary" moments.

Ricky Safer



HI HO HI HO...IT'S OFF TO DENVER WE GO

The countdown has begun. Our third annual conference for PSCers and caregivers will take place in Denver, Colorado the weekend of April 13-15, 2007. We are firming up plans for the weekend. Based on the phenomenal success of our first two conferences, I can promise you a weekend of very informative presentations, time to ask all your questions related to PSC, and best of all, the uplifting experience of sharing your concerns and hopes with many other PSCers and caregivers.

Very soon, we will post the final conference agenda on the online support group and on our website (<http://www.pscpartners.org>), and official registration will begin. The standard registration fee (received before March 13, 2007) will be \$170 per person or \$320 per couple. The late registration fee (received after March 13, 2007) will be \$190 per person or \$360 per couple. This registration fee covers all these costs: Friday night reception, all presentations, breakfast, lunch and snacks on Saturday and Sunday, and Saturday night's banquet.

We have been working with Dr. Gregory Everson at the University of Colorado Health Sciences Center to put together an amazing slate of speakers and interactive panel sessions. As always, after each group of speakers, we will have a question and answer session for the attendees' participation. In addition to our knowledgeable speakers from the University of Colorado Health Sciences Center, we have three out of state speakers: Dr. John Vierling, Director of Liver Health and Chief of Hepatology at the Baylor College of Medicine and Current President of AASLD (American Association for the Study of Liver Diseases), Dr. Douglas Labrecque, Director of Hepatology at the University of Iowa, and Dr. Gregory Fitz, Chairman of Department of Internal Medicine at UT Southwestern. Here is a sampling of some of the topics that will be covered: Key Issues in PSC, Immune System in PSC, Effects of PSC on the Biliary System, Medical Therapy of PSC, Endoscopic Management of PSC, Probiotics for IBD, and Transplantation for PSC. In addition, we will have these Question and Answer Panels: Social and Financial Issues Related to PSC, Pediatric PSC, and CAM Therapies.

Here is the basic time schedule. Friday evening, April 13, 2007, we will have registration and our welcome

reception from 5-7:30 p.m. This is a great time to meet fellow PSCers and caregivers. Saturday morning's breakfast will be from 7-8 a.m., and then we will have a full day of presentations, ending at 4:15 p.m.. Saturday night's banquet will start at 6:30 p.m. Sunday morning's breakfast will be from 7-8 a.m, and then we will have roundtable discussions until noon.

(In conjunction with the PSC Partners Seeking a Cure conference, Dr. Everson is putting together a CME course giving an update on PSC for medical professionals on Friday afternoon, April 14, at the University of Colorado Health Sciences Center.)

The conference will be held at the Hyatt Regency Tech Center in southeast Denver. (There is shuttle service from Denver International Airport to the Hyatt, so you will not need a car.) Check out the hotel at www.hyattregencytechcenter.com

We were able to secure the wonderful group rate of \$79 per room per night for our block of rooms!!! You may reserve your rooms now by calling the reservation department at 800 233-1234 or locally at 303 779-1234. In order to receive the \$79 rate, be sure to tell them that:

1. You are part of the PSC Partners Seeking a Cure conference
2. It is the Hyatt Regency Tech Center (NOT the two Hyatt hotels downtown)

If you prefer, you can book your room online by going to www.techcenter.hyatt.com. Select your check-in and check-out dates. Under Group/Corporation #, type "G-4LIV". Then click "Check Availability" and the \$79 group rate should come up and be ready to book. If you have any problems reserving your hotel room, feel free to contact me at pscpartners@yahoo.com. If you are planning to come to the conference, please reserve your room as soon as possible. We have reserved this block of rooms at the special \$79 rate, but once our block is filled, the Hyatt will try to extend the special rate to more rooms, but they can't promise this.

Thank you to our two pharmaceutical sponsors so far: Axcan Scandipharm and Cook Endoscopy. We appreciate your support.

Please read Lee's article about the Virtual Walk, our yearly fundraiser. You are welcome to participate in the walk whether or not you can attend the conference. Please join in.

If it is at all possible, I hope that you will attend the conference. You won't be disappointed! From the minute Friday's reception starts, you will feel the warmth and support from our entire PSC family in attendance. I, personally, can't wait to see my old friends and to meet our new PSCers and caregivers. I'm also excited to see that our national conference is becoming an international conference with attendees from Canada, the UK, and now the probable addition of Israel and Sweden. Please join us....

Together in the fight, whatever it takes!

Ricky Safer

Living with PSC

Remember the day the doctor came in and said "You have PSC"? It felt like the whirling house in Wizard of Oz had fallen on us, but where was our fairy god mother (Ricky)? How would we find our yellow brick road (PSC-Support)? What about those red ruby slippers (Lee) and the Wizard (David)?

Today, newly diagnosed patients can find Courage, Knowledge, and Heart-felt support in the second printing of our brochures; Living with PSC.

<http://www.pscpartners.org/PSCBrochure.pdf>

One of our goals as a foundation is to reach every new patient and, so far, 2,035 brochures have been distributed by 107 different people, however, we cannot reach over the rainbow to that pot of gold, without your help. The brochures are free and easy to order. Just send an e-mail to: pscbrochures@yahoo.com with your request. Here are a few quantity guidelines to follow:

- office of a single GI or Hepatologist - 10
- PCP/Internist/family doctor's office - 5
- liver group with several GIs/Hepatologist - 20
- transplant center - 25-30

Then, just click your heels and take them to your doctor's office the next time you visit.

When you're first diagnosed, there is no place like home and helping patients and caregivers find these brochures and our PSC-Support Group:

<http://health.groups.yahoo.com/group/psc-support/>

will lead them down the yellow brick road to our "family".

"Auntie Em" (Barb in Texas)

TREASURER'S REPORT

Following is an update of the current financial position of PSC Partners Seeking a Cure Foundation.

\$100,000 was transferred to Charles Schwab and invested in a money market fund on 8/30. Balance as of October 31, 2006 was \$100,831. Investments have been made according to the Investment Committee recommendations approved by the Board at the last meeting.

Balance in the checking account as of 10/31/06 was \$51,889. Since then, a check for \$20,000 has been distributed for the STOPSC registry.

From June 1 to Oct. 31, income increased by \$18,567. We received \$11,562 in donations and fundraising brought in \$3,394.

Net income increased by \$16,173 for a total net income of \$105,319.

Total assets are \$152,703.

As always, please direct any questions/comments to Deborah Wentz, Treasurer at debs_3@charter.net

Deb Wentz

Inflammation and Cholestasis

by David Rhodes

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease, most probably of the ductular/ductal type, involving an impairment of bile secretion and flow at the level of bile ductules or ducts. The exact mechanisms of cholestasis in PSC are not known, but because it is well established that there is a link between inflammatory bowel disease, particularly ulcerative colitis (LaRusso et al., 2006), it is useful to examine how inflammation might contribute to cholestasis.

It has long been recognized that many systemic inflammatory conditions can result in cholestasis, including intra- and extra-hepatic infections, drug-induced and alcohol-induced liver injury, total parenteral nutrition, and trauma. These diverse inflammatory conditions induce proinflammatory cytokines which then inhibit hepatocellular bile secretion (Trauner et al., 1999). The inflammation associated with inflammatory bowel disease could also contribute to this inhibition of bile transport processes in the liver. Recent research suggests that inflammation-induced cholestasis may be primarily mediated by the pro-inflammatory molecule, nuclear factor-kappa B (NF- κ B), via its interaction with key nuclear receptors that regulate bile metabolism and transport. Key targets of NF- κ B appear to be the pregnane X receptor (PXR) [also known as the steroid and xenobiotic receptor (SXR)], and its partner, the retinoid X receptor-alpha (RXR α).

The importance of the pregnane X receptor

The pregnane X receptor (PXR) controls the expression of a number of genes involved in bile acid transport and detoxification. PXR is a sensor of toxic bile acids that protects against liver toxicity (Staudinger et al., 2001). "The nuclear pregnane X receptor (PXR; NR1I2) is an integral component of the body's defense mechanism against chemical insult (chemoprotection). PXR is activated by a diverse array of lipophilic chemicals, including xenobiotics and endogenous substances, and regulates the expression of cytochromes P450, conjugating enzymes, and transporters involved in the metabolism and elimination of these potentially harmful chemicals from the body. Among the chemicals that bind and activate PXR is the toxic bile acid lithocholic acid; activation of PXR, in turn, protects against the severe liver damage caused by this bile acid. Thus, PXR serves as a physiological sensor of lithocholic acid and perhaps other bile acids and coordinately regulates genes involved in their detoxification." (Kliewer and Willson, 2002). Lithocholic acid is capable of inducing bile duct obstruction and destructive cholangitis in mice (Fickert et al., 2006).

One of the key transport proteins that PXR regulates is the MDR1 protein. The human multidrug resistance 1 P-glycoprotein, MDR1, encoded by the gene ABCB1 (localized on chromosome 7), is highly expressed in intestinal epithelial cells, where it constitutes a barrier against xenobiotics. P-glycoprotein is an ATP-dependent efflux pump that contributes to the protection of the body from environmental toxins (Schwab et al., 2003a). It transports a huge variety of structurally diverse compounds. P-glycoprotein is involved in limiting absorption of xenobiotics from the gut lumen, and in biliary and urinary excretion of its substrates. P-glycoprotein can be inhibited or induced by xenobiotics, thereby contributing to variable drug disposition and drug interactions. Recently, several polymorphisms have been identified in the MDR1 (ABCB1) gene, some of which can affect P-glycoprotein expression and function (Schwab et al., 2003a). Certain of the mutations appear to influence susceptibility to inflammatory bowel disease, including ulcerative colitis (Brant et al., 2003; Schwab et al., 2003b; Ho et al., 2005). Evidence for linkage at chromosome 7q has been reported for both Crohn's disease and ulcerative colitis, and the gene for MDR1 (ABCB1) is located within this region. Mice defective in the MDR1 gene (*mdr1a*^{-/-}) spontaneously develop colitis (Wilk et al., 2005).

Langmann et al. (2004) have reported that the expression of the MDR1 (ABCB1) gene is down-regulated in ulcerative colitis. This down-regulation of MDR1 (together with other defense genes) appears to be due to down-regulation of PXR, and may contribute to the pathophysiology of ulcerative colitis (Langmann et al., 2004). Genetic variants in the PXR gene have recently been associated with inflammatory bowel disease (especially ulcerative colitis) (Dring et al., 2006). Also genetic variants in PXR (SXR) have recently been shown to be associated with the severity of PSC (Karlsen et al., 2006).

Rifampin (rifampicin) is an activator of PXR (SXR) and is often used to control pruritus in liver diseases such as PSC (Khurana and Singh, 2006). It has been suggested that rifampin could have complementary effects to ursodeoxycholic acid (UDCA) in treating cholestatic liver diseases (Marschall et al., 2005). Ri-

fampin "enhances bile acid detoxification as well as bilirubin conjugation and export systems, whereas UDCA stimulates the expression of transporters for canalicular and basolateral bile acid export as well as the canalicular phospholipid flippase. These independent but complementary effects may justify a combination of both agents for the treatment of cholestatic liver diseases" (Marschall et al., 2005).

Certain polychlorinated biphenyls (PCBs) have been shown to inhibit human PXR (SXR) (Tabb et al., 2004). Based on the above more recent evidence, such inhibition of PXR by PCBs might be expected to predispose individuals to inflammatory bowel disease and/or bile acid toxicity?

How does ulcerative colitis result in down-regulation of PXR?

How does ulcerative colitis result in the down-regulation of PXR described by Langmann et al. (2004)? Aside from the afore-mentioned genetic mechanism [i.e. mutation in the PXR gene itself (Dring et al., 2006)], evidence suggests that persistent inflammation in inflammatory bowel diseases up-regulates both tumor necrosis factor-alpha and nuclear factor-kappa B (NF-kB) (Schreiber et al., 1998). It has recently been shown that NF-kB then down-regulates PXR (Zhou et al., 2006; Gu et al., 2006). Activation of PXR, on the other hand, down-regulates NF-kB, perhaps explaining why PXR activators, such as rifampin, also have anti-inflammatory effects (Zhou et al., 2006). This was recently reviewed by Xie and Tian (2006): "It has long been appreciated that inflammation and infection reduce drug metabolism and that exposure to drug metabolism-inducing xenobiotics can impair immune function. A new study reveals the mutual repression between the xenobiotic nuclear receptor PXR/SXR and NF-kappaB signaling pathways, providing a molecular mechanism linking xenobiotic metabolism and inflammation (Zhou et al., 2006)." Consistent with this, Shah et al. (2006) have shown that PXR activation ameliorates dextran sulfate sodium-induced colitis in mice via inhibition of NF-kB target gene expression.

The effect of NF-kB on PXR may be indirect, and may actually involve its key "partner", the retinoid X receptor-alpha (RXR α). Gu et al. (2006) have shown that NF-kB binds to RXR α , and prevents the PXR-RXR α complex from functioning, thus inhibiting expression of genes regulated by PXR. Because RXR α is a "partner" for a number of other receptors involved in lipid, bone, and bile acid metabolism (including the farnesoid X receptor (FXR), the constitutive androstane receptor (CAR), the vitamin D receptor (VDR), and the peroxisome proliferator-activated receptor-alpha (PPAR α) (Cai et al., 2002)), it will be of interest to see if the binding of NF-kB to RXR α also blocks the expression of genes regulated by these other receptors (Gu et al., 2006; Xie and Tian, 2006). Nevertheless, it is becoming clear that chronic inflammation (via persistent activation of NF-kB) could exacerbate cholestasis by blocking bile acid detoxification and transport (Xie and Tian, 2006).

If NF-kB directly binds to RXR α and prevents it from functioning (Gu et al., 2006), could this help explain why males are more prone to PSC than females. It has been shown that the "expression of CYP450 genes is differentially expressed in male and female hepatocyte RXR α -deficient mice; male mice have reduced expression of cytochrome P450 (CYP) CYP4A,

CYP3A, and CYP2B mRNAs, but females do not exhibit such phenotypes" (Cai et al., 2003). It has been proposed that testosterone has a negative impact on retinoid signaling when the level of RXR α is low, which may in turn reduce the expression of the CYP450 genes (Cai et al., 2003).

It has been assumed that the main ligand (activator) of RXR α is 9-cis retinoic acid, derived from vitamin A. Could vitamin A deficiency lead to a susceptibility to RXR α inhibition by NF-kB during inflammation? Vitamin A deficiency certainly causes increased inflammation during colitis in experimental animal models (Reifen et al., 2002). Vitamin A deficiency is commonly associated with inflammatory bowel disease (Bousvaros et al., 1998) and PSC (Jorgensen et al., 1995).

Is docosahexaenoic acid (DHA) an alternative ligand/activator of RXR α ?

Recent studies suggest that the omega-3 fatty acid, docosahexaenoic acid (DHA), can also serve as a ligand/activator for RXR α (de Urquiza et al., 2000; Egea et al., 2002; Lengqvist et al., 2004; Fan et al., 2003). Indeed, Egea et al. (2002) have suggested that docosahexaenoic acid and related fatty acids could be natural agonists of RXRs and question the real nature of the endogenous ligand(s) in mammalian cells.

Could this explain why DHA has been shown to protect against bile duct injury (resembling sclerosing cholangitis) in mice that are deficient in the cystic fibrosis transmembrane conductance regulator (cfr) when given colitis (Blanco et al., 2004)? It has been proposed that DHA protects against bile-duct injury in these mice because it up-regulates PPAR α (Pall et al., 2006), but this effect might also be attributed to activation of RXR α by DHA. The up-regulation of PPAR α (or the PPAR α -RXR α complex) by DHA is thought to be involved in down-regulating NF-kB, contributing to the anti-inflammatory effects of omega-3 fatty acids (Calder, 2002; Calder, 2006). This may explain the beneficial effects of omega-3 fatty acids in trauma, burn injury, and sepsis (Calder, 2006). Interestingly all of these conditions can lead to sclerosing cholangitis (Schmitt et al., 1997; Engler et al., 2003; Benninger et al., 2005). Parenteral nutrition-associated liver disease in infants with short bowel syndrome has been shown to be reversed by fish oils supplementation (Gura et al., 2006). Deficiency of omega-3 fatty acids (DHA and eicosapentaenoic acid (EPA)) has been linked to susceptibility to inflammatory and autoimmune diseases (Simopoulos, 2002). Perhaps DHA deficiency (like vitamin A deficiency) also leads to susceptibility to inflammation mediated (i.e. NF-kB mediated) inhibition of RXR α -PXR, and hence susceptibility to cholestasis? Results from the ongoing trial of DHA in PSC are eagerly awaited:

Evaluation of DHA for the Treatment of PSC

<http://www.clinicaltrials.gov/ct/show/NCT00325013?order=1>

References

- Benninger J, Grobholz R, Oeztuerk Y, Antoni CH, Hahn EG, Singer MV, Strauss R 2005 Sclerosing cholangitis following severe trauma: description of a remarkable disease entity with emphasis on possible pathophysiologic mechanisms. *World J. Gastroenterol.* 11: 4199-4205.
- Blanco PG, Zaman MM, Junaidi O, Sheth S, Yantiss RK, Nasser IA, Freedman SD 2004 Induction of colitis in cfr-/-

mice results in bile duct injury. *Am. J. Physiol. Gastrointest. Liver Physiol.* 287: G491-G496.

Brant SR, Panhuysen CI, Nicolae D, Reddy DM, Bonen DK, Karaliukas R, Zhang L, Swanson E, Datta LW, Moran T, Ravenhill G, Duerr RH, Achkar JP, Karban AS, Cho JH 2003 MDR1 Ala893 polymorphism is associated with inflammatory bowel disease. *Am. J. Hum. Genet.* 73: 1282-1292.

Bousvaros A, Zurakowski D, Duggan C, Law T, Rifai N, Goldberg NE, Leichtner AM 1998 Vitamins A and E serum levels in children and young adults with inflammatory bowel disease: effect of disease activity. *J. Pediatr. Gastroenterol. Nutr.* 26: 129-135.

Cai Y, Dai T, Ao Y, Konishi T, Chuang KH, Lue Y, Chang C, Wan YJ 2003 Cytochrome P450 genes are differentially expressed in female and male hepatocyte retinoid X receptor alpha-deficient mice. *Endocrinology* 144: 2311-2318.

Cai Y, Konishi T, Han G, Campwala KH, French SW, Wan YJ 2002 The role of hepatocyte RXR alpha in xenobiotic-sensing nuclear receptor-mediated pathways. *Eur. J. Pharm. Sci.* 15: 89-96.

Calder PC 2002 Dietary modification of inflammation with lipids. *Proc. Nutr. Soc.* 61: 345-358.

Calder PC 2006 Use of fish oil in parenteral nutrition: rationale and reality. *Proc. Nutr. Soc.* 65: 264-277.

de Urquiza AM, Liu S, Sjoberg M, Zetterstrom RH, Griffiths W, Sjoval J, Perlmann T 2000 Docosahexaenoic acid, a ligand for the retinoid X receptor in mouse brain. *Science* 290: 2140-2144.

Dring MM, Goulding CA, Trimble VI, Keegan D, Ryan AW, Brophy KM, Smyth CM, Keeling PW, 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.

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

Engler S, Elsing C, Flechtenmacher C, Theilmann L, Stremmel W, Stiehl A 2003 Progressive sclerosing cholangitis after septic shock: a new variant of vanishing bile duct disorders. *Gut* 52: 688-693.

Fan YY, Spencer TE, Wang N, Moyer MP, Chapkin RS 2003 Chemopreventive n-3 fatty acids activate RXRalpha in colonocytes. *Carcinogenesis* 24: 1541-1548.

Fickert P, Fuchsbichler A, Marschall HU, Wagner M, Zollner G, Krause R, Zatloukal K, Jaeschke H, Denk H, Trauner M 2006 Lithocholic acid feeding induces segmental bile duct obstruction and destructive cholangitis in mice. *Am. J. Pathol.* 168: 410-422.

Gu X, Ke S, Liu D, Sheng T, Thomas PE, Rabson AB, Gallo MA, Xie W, Tian Y 2006 Role of NF-kappaB in regulation of PXR-mediated gene expression: a mechanism for the suppression of cytochrome P-450 3A4 by proinflammatory agents. *J. Biol. Chem.* 281: 17882-17889.

Gura KM, Duggan CP, Collier SB, Jennings RW, Folkman J, Bistrrian BR, Puder M 2006 Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. *Pe-*

diatrics 118: e197-e201.

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.

Jorgensen RA, Lindor KD, Sartin JS, LaRusso NF, Wiesner RH 1995 Serum lipid and fat-soluble vitamin levels in primary sclerosing cholangitis. *J. Clin. Gastroenterol.* 20: 215-219.

Karlsen TH, Lie BA, Frey Frosli K, Thorsby E, Broome U, Schrupf E, Boberg KM 2006 Polymorphisms in the steroid and xenobiotic receptor gene influence survival in primary sclerosing cholangitis. *Gastroenterology* 131: 781-787.

Khurana S, Singh P 2006 Rifampin is safe for treatment of pruritus due to chronic cholestasis: a meta-analysis of prospective randomized-controlled trials. *Liver Int.* 26: 943-948.

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

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.

LaRusso NF, Shneider BL, Black D, Gores GJ, James SP, Doo E, Hoofnagle JH 2006 Primary sclerosing cholangitis: summary of a workshop. *Hepatology* 44: 746-764.

Lengqvist J, Mata De Urquiza A, Bergman AC, Willson TM, Sjoval J, Perlmann T, Griffiths WJ 2004 Polyunsaturated fatty acids including docosahexaenoic and arachidonic acid bind to the retinoid X receptor alpha ligand-binding domain. *Mol. Cell. Proteomics* 3: 692-703.

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

Reifen R, Nur T, Ghebermeskel K, Zaiger G, Urizky R, Pines M 2002 Vitamin A deficiency exacerbates inflammation in a rat model of colitis through activation of nuclear factor-kappaB and collagen formation. *J. Nutr.* 132: 2743-2747.

Schmitt M, Kolbel CB, Muller MK, Verbeke CS, Singer MV 1997 Sclerosing cholangitis after burn injury. *Z. Gastroenterol.* 35: 929-934.

Schreiber S, Nikolaus S, Hampe J 1998 Activation of nuclear factor kappa B inflammatory bowel disease. *Gut* 42: 477-484.

Schwab M, Eichelbaum M, Fromm MF 2003a Genetic polymorphisms of the human MDR1 drug transporter. *Annu. Rev. Pharmacol. Toxicol.* 43: 285-307.

Schwab M, Schaeffeler E, Marx C, Fromm MF, Kaskas B, Metzler J, Stange E, Herfarth H, Schoelmerich J, Gregor M, Walker S, Cascorbi I, Roots I, Brinkmann U, Zanger UM, Eichelbaum M 2003b Association between the C3435T MDR1 gene polymorphism and susceptibility for ulcerative colitis. *Gastroenterology* 124: 26-33.

(continued from p. 7)

Shah Y, Ma X, Morimura K, Kim I, Gonzalez FJ 2006 Pregnane X receptor activation ameliorates DSS-induced IBD via inhibition of NF- κ B target gene expression. *Am. J. Physiol. Gastrointest. Liver Physiol.* Dec 14 [Epub ahead of print].

Simopoulos AP 2002 Omega-3 fatty acids in inflammation and autoimmune diseases. *J. Am. Coll. Nutr.* 21: 495-505.

Staudinger JL, Goodwin B, Jones SA, Hawkins-Brown D, MacKenzie KI, LaTour A, Liu Y, Klaassen CD, Brown KK, Reinhard J, Willson TM, Koller BH, Kliewer SA 2001 The nuclear receptor PXR is a lithocholic acid sensor that protects against liver toxicity. *Proc. Natl. Acad. Sci. U.S.A.* 98: 3369-3374.

Tabb MM, Kholodovych V, Grun F, Zhou C, Welsh WJ, Blumberg B 2004 Highly chlorinated PCBs inhibit the human xenobiotic response mediated by the steroid and xenobiotic receptor (SXR). *Environ. Health Perspect.* 112: 163-169.

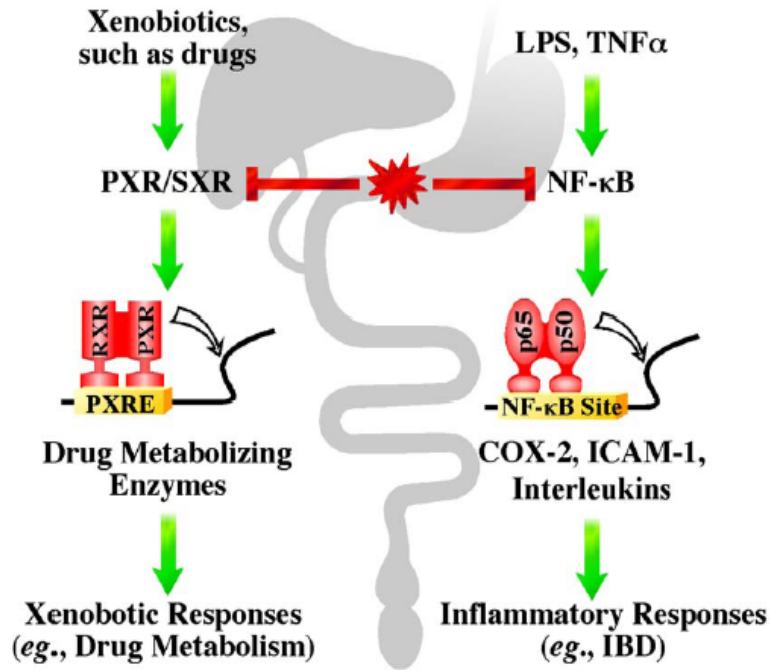
Trauner M, Fickert P, Stauber RE 1999 Inflammation-induced cholestasis. *J. Gastroenterol. Hepatol.* 14: 946-959.

Marschall HU, Wagner M, Zollner G, Fickert P, Diczfalusy U, Gumhold J, Silbert D, Fuchsichler 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.

Wilk JN, Bilsborough J, Viney JL 2005 The *mdr1a*^{-/-} mouse model of spontaneous colitis: a relevant and appropriate animal model to study inflammatory bowel disease. *Immunol. Res.* 31: 151-159.

Xie W, Tian Y 2006 Xenobiotic receptor meets NF- κ B, a collision in the small bowel. *Cell. Metab.* 4: 177-178.

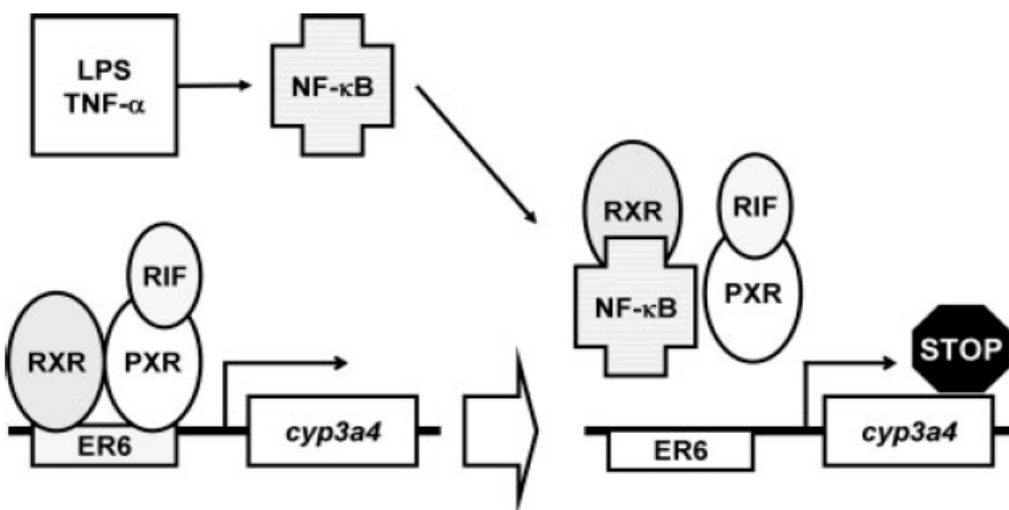
Zhou C, Tabb MM, Nelson EL, Grun F, Verma S, Sadatrafiei A, Lin M, Mallick S, Forman BM, Thummel KE, Blumberg B 2006 Mutual repression between steroid and xenobiotic receptor and NF- κ B signaling pathways links xenobiotic metabolism and inflammation. *J. Clin. Invest.* 116: 2280-2289.



Mutual repression between PXR/SXR and NF- κ B signaling pathways (From: Xie W, Tian Y 2006 Xenobiotic receptor meets NF- κ B, a collision in the small bowel. *Cell. Metab.* 4: 177-178).

The PXR/SXR and NF- κ B mutual suppression may link xenobiotic metabolism and inflammation in the hepatointestinal axis. IBD, inflammatory bowel disease; ICAM, intercellular adhesion molecule; LPS, lipopolysaccharide; NF- κ B, nuclear factor kappa B; PXR, pregnane X receptor; PXRE, PXR response element; SXR, steroid and xenobiotic receptor; TNF, tumor necrosis factor.

Explanatory Figures



Schematic illustration of the suppression of CYP3A4 gene expression by NF- κ B. (From: Gu X, Ke S, Liu D, Sheng T, Thomas PE, Rabson AB, Gallo MA, Xie W, Tian Y 2006 Role of NF- κ B in regulation of PXR-mediated gene expression: a mechanism for the suppression of cytochrome P-450 3A4 by proinflammatory agents. *J. Biol. Chem.* 281: 17882-17889.)

Upon activation of NF- κ B by TNF- α or LPS, NF- κ B p65 translocates into the nucleus and disrupts the binding of the PXR-RXR α heterodimer to its regulatory sites by interacting with RXR α , which is the obligate partner of PXR, thereby suppressing *cyp3a4* expression. RIF = rifampin.

Help us keep up the fight to beat PSC!

We are really excited by the variety of ways that people are helping PSC Partners Seeking a Cure. Generous donations continue to come in through checks and online PayPal. We have many **In Kind** donations and we thank those who have held private fundraisers to help us. I want to take this opportunity to remind you of a few other easy ways to help.

This is the time of year to consider the option of donating stock to take advantage of end of the year portfolio adjustments. For more information please contact us at pscpartners@yahoo.com.

The fall is also the time to sign up to give through United Way. If you have already made your United Way pledge, you may be able to still redirect your donation to PSC Partners Seeking a Cure. You can also check to see if your company has a matching gifts program. Please contact us if you want more information on this.

Notecards designed by our own Ali Lingerfielt-Tait can be ordered through our web-site www.pscpartners.org. The cost is \$10.00 plus \$1.00 for shipping for a bundle of six cards. They are wonderful cards that make great thank you notes for our families and friends who are helping us. They are blank cards and can be used for many other occasions.

We also have two excellent programs that are free to use and help to bring in steady money to fight PSC:

- Krogers grocery stores are extremely generous in donating 5% of grocery money spent to PSC Partners Seeking a Cure. All you need is one of their grocery rechargeable cards registered to PSC Partners Seeking a Cure. They are so easy to use. Once you get one of our cards, you can fill it right at the cash register for any amount, each time you do, the foundation receives a donation from Krogers. It is free to you. Krogers has many different stores, please check our website (www.pscpartners.org) to see the names of their other stores that qualify.
- AAA Environmental Recycling is another free program that brings in steady donations. Just order their free plastic mailers, place old ink cartridges or cell phones into the mailer, seal and place in your mailbox. All postage is pre-paid. Please hand out as many of these mailers as you can to friends and family. You can order these mailers from: www.aaaenvironmentalinc.com or call 1-866-332-2234 and leave a message with your address. Our code is PSCPARTNE001 which registers the envelopes to us. Note: no Epson cartridges can be used.

Thanks to each and everyone of you who are already helping us fund the fight! Together we will change the future treatment of PSC.

Lee Bria

Update on PSC Literature

The PSC Literature database (www.psc-literature.org) now includes about 50,500 abstracts. The site continues to be heavily used. For example, data transfer exceeded 4.8 gigabytes in September, 2006. Since we are charged a fee for “excess” traffic above 50 megabytes per month, we have duplicated the web site at:

<http://home.insightbb.com/~rhodesdavid/index.htm>

It is hoped that this will draw some of the traffic away from www.psc-literature.org and thus reduce the costs of maintaining this site. We apologize for any inconvenience that this may cause.

David and Judy Rhodes

UPDATE ON DONATIONS TO PSC PARTNERS SEEKING A CURE

IN HONOR OF:

Josh Miletic
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Vreni Mc Master
Lee Bria
Billy Bria

For research
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Mike Zaloudek
Mike and Rebecca's birthdays
Jecy Belmont's birthday and the PSC
Support Group
Dave Rhodes' family
James Traficant
Doug Procarione
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Todd Clouser's third anniversary
Don Safer's 65th birthday
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We'd like to thank ALL our donors who have supported us in 2006. In addition, here's a special thank you to these donors:

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Virtual Walk 2 is Coming!!

We invite everyone to join us for this exciting event. Last year's Virtual Walk was a resounding success that helped to raise \$44,493.29 to help us fight PSC. It is easy and fun!

Our Virtual Walk 2 registration forms will be available in February and we will virtually walk across the country together for the month of March. Registration will be \$25 and you will receive our Virtual Walk kit with a tee-shirt, a permanent marker, directions, a signature sheet, and return envelope.

The signatures of support and donations we collect, give us both a morale boost and help us to support PSC research. Once a year this walk helps us to reach out to family, friends and co-workers for the support we need. People love signing the shirt and can give any amount they choose, from pocket change to generous checks. All donations are tax deductible. We encourage everyone to get creative and to have fun collecting signatures on their shirts. Have a "signing" dinner, party, recipe exchange or poker night. Lend out your shirt to friends, family and neighbors to help you gather signatures. Use email to let people know that you can add their signatures too. Last year Mike Zaloudek was our top fundraiser by using a bike ride to gather support. Need ideas? We can help.

Shirts that "walk" their way to the Denver conference will be proudly displayed. We will acknowledge our most creative shirt, most signatures and donations at our awards banquet on Saturday night. It is an uplifting time that brings the hope we all need for a future with better treatment for PSC. Everyone can be a part of this effort, join us in the fight against PSC.

Lee Bria

Additional Contact Information

Ricky Safer is the principal contact person for our PSC Partners Seeking a Cure Foundation. She can be reached at:

pscpartners@yahoo.com

Submitting Newsletter Articles

If you would like to contribute an article to a future issue of this Newsletter, please e-mail it to David Rhodes:

rhodesdavid@insightbb.com

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Please include a note to indicate whom the donation is in honor and/or in memory of, and your return address.

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- Platinum level: \$10,000
- Gold level: \$5,000
- Silver level: \$2,500
- Bronze level: \$1,000
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Thank you for your generosity!

One of our foundation goals is to increase organ donor awareness. We encourage U.S.A. readers to visit www.donatelife.net and click on their state. This site gives a state by state guide to the organ donation process. This would be a good place for our members to start thinking about how to help locally, if they are interested....“While donated organs and tissue are shared at the national level, the laws that govern donation vary from state to state. Therefore, it is important for you to know what you can do to ensure your decision to be a donor is carried out.”



GiveLife

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