
The Duct

Bringing you news on PSC



PSC PARTNERS
SEEKING A CURE

research, education, and Support

PSC Partners Seeking a Cure Foundation

Fall 2010

\$514,706 for Research Grants Awarded Since 2006

Seeking a Cure: Thanks to Your
Fundraising Activities,
We're Now Supporting
5 More Research Projects
Investigating PSC

*by David Rhodes, Chair of the Scientific/Medical
Committee*

The logo for PSC Partners Seeking a Cure evokes two images/themes. The first is support. The logo can be viewed to depict patients and/or caregivers embracing and lending support to each other.

Enabling PSC patients and caregivers to meet and connect, to share their experiences, and to support one another, are major themes of our annual conferences.

The second image/theme evoked by the logo is pieces of a puzzle. The logo depicts three interlocking pieces of a jigsaw puzzle.

The latter image encapsulates our research grants program aimed at solving the PSC puzzle. There is

The Giant Steps of a Small
Organization

A Message from Ricky Safer

When we formed PSC Partners Seeking a Cure in 2005, I could never have envisioned the progress that we would make in our first six years.

Thanks to the determination and enthusiasm of our volunteers who generously share their time, creativity and expertise with us, we are taking huge steps towards fulfilling our mission of educating and supporting PSCers and their caregivers, raising funds to research the causes and a cure for PSC, and promoting awareness of PSC and organ donation.

Here are some of our most recent advances that will benefit our entire international community.

PSC Research Progress

Please take the time to carefully read the lead article written by David Rhodes, the Chair of our Scientific/Medical Advisory Committee and Fact-O-Rama on page 19.

Thanks to Dave's leadership and dedication and the

much to do on this front. Many recent papers describe PSC as a disease of unknown etiology with no effective therapies, and it is essential that we take steps to alter this scenario.

The goals of our research grants program are on our website at <http://www.pscpartners.org/apply>.

We were delighted to be able to fund the study entitled "PROGRESS: PSC Resource Of Genetic Risk, Environment and Synergy Studies" by Dr. Lazaridis at Mayo Clinic, Rochester, MN, as our very first award in 2009:

[http://clinicaltrials.mayo.edu/clinicaltrialdetails.cfm?trial_id=100124&title=Unraveling%20the%20Genetic%20Predilection%20to%20Primary%20Sclerosing%20Cholangitis%20\(PSC\)](http://clinicaltrials.mayo.edu/clinicaltrialdetails.cfm?trial_id=100124&title=Unraveling%20the%20Genetic%20Predilection%20to%20Primary%20Sclerosing%20Cholangitis%20(PSC))

We were even more delighted to hear recently that with this "seed" funding from PSC Partners Seeking a Cure, Dr. Lazaridis has now been awarded a grant of \$3,500,000 (direct plus indirect costs) from NIH to further pursue the identification of the genetic and environmental factors involved in PSC.

The new study includes six medical centers in North America (Indiana Univ., Indianapolis, IN; Virginia Mason Clinic, WA; Johns Hopkins Univ., MD; Mt Sinai Medical Center, NY; Univ. of Pittsburgh; Virginia Commonwealth Univ., VA; Univ. of Toronto, Canada, and Mayo Clinic, MN), and collaborates with PSC investigators from Norway (NOPSC) and UK. Details of this NIH award are given at:

http://www.projectreporter.nih.gov/project_info_description.cfm

advice of the entire committee

(www.pscpartners.org/boardmembers), we have already invested over a half million dollars directly in promising PSC research.

Congratulations go out as well to Dr. Kostas Lazaridis at the Mayo Clinic, who was awarded one of our 2009 "seed" grants for "Examining the Disease Impact of Genetic Variation in Logical Candidate Genes for PSC: a PROGRESS Study."

We are thrilled to learn that recently Dr. Lazaridis received a \$3,500,000 grant from the National Institutes of Health, which was funded, in considerable part as a result of earlier "seed" grant funding from PSC Partners.

We will continue in our quest for innovative PSC research projects to fund in the future. A huge thank you to all our donors who helped fund this important research.

Special thanks to Craig and Ali Wiele who are funding the first year of Drs. Strazzabosco and Trauner's research project and to our anonymous donor who is generously funding the two year grants for Drs. Cai and Boyer and also Dr. Cho. Together, we will find a cure for PSC!

Save The Day Fundraisers

Again this year, the always-enthusiastic Sandi Pearlman organized our successful Save the Day weekend, October 1-3, and motivated members to hold their own local fundraisers. We still haven't received the final tally, but thank you to all our members who held events for us.

Our fundraiser organizers held many creative events: a Silent Art Auction (Sandi, Karen, Mike and Eileen Pearlman), three golf tournaments (Libbie Bailey, Maria Schor with Mele Ohuafi, and Kirk Franz), an opera gala event (Philip Burke), a wine tasting event (Reggie Belmont, Lia Donahue and Kristi Agli), a Dress Down Day, a Liver Walk, a Comedy Night, a Half Ironman Competition, a Half

[aid=8035823&icde=5642251](http://www.pscpartners.org/aid=8035823&icde=5642251)

Five Awards Given in 2010

PSC Partners Seeking a Cure received 13 grant proposals in August 2010, and these were reviewed and ranked by the Scientific/Medical Advisory committee. Five proposals were selected for funding in this competition:

*** Pathogenesis of PSC: Role of TGR5 in the regulation of the innate immune response in the biliary epithelium. Mario Strazzabosco, M.D., Ph.D, Department of Internal Medicine Section of Digestive Diseases, Yale University, 333 Cedar Street-1080 LMP, P.O. Box 208019, New Haven, CT 06520-8019, and Michael Trauner, M.D., Ph.D, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. Amount awarded = \$40,000 over years.**

*** Epigenetics associated with primary sclerosing cholangitis in monozygotic twins discordant for the disease. Carlo Selmi, MD, PhD, Assistant Professor of Internal Medicine, University of Milan, Physician Scientist, IRCCS Istituto Clinico Humanitas, Rozzano, Milan, Assistant Professor of Medicine, University of California, Davis, Division of Rheumatology, Allergy, and Clinical Immunology, GBSF suite 6515, 451 E Healthy Sciences Drive, Davis, CA 95616. Amount awarded = \$40,000 over 2 years.**

*** Identification of genetic profiles unique to PSC-IBD. Judy Cho, M.D., Associate Professor of Medicine and Genetics, Section of Digestive Diseases, Director, Inflammatory Bowel Disease Center, Yale**

Marathon, and letter writing campaigns.

I am particularly touched by Bek Goldsmith, a 12-year-old PSCer from Australia who is on the transplant list, and who raised over \$1,500 by selling Beanie Kids to her friends at school!

The Fredericksburg, VA, newspaper wrote a charming article about Sandi Pearlman and all her fundraising efforts. We put the article on our website and here's the URL: <http://www.pscpartners.org/donate>.

Please think about creating your own fundraiser for us for next fall's Save the Day weekend and help us fund PSC research and support our programs! We appreciate everyone's participation.

Our Google Project

After months of planning, PSCer Tom Hill and Dr. Chris Bowlus have just completed the prototype for an innovative research project to build a PSC patient registry and establish an interactive community for PSC researchers and patients, using state of the art Google Health, collaborative and applications technology.

Now, they will start testing the prototype, and be ready to launch the registry at our annual conference in April, 2011. This exciting project has been made possible by a generous grant from Google.

Deep River Snacks Awareness Project

Jim Goldberg of Deep River Snacks, in Connecticut, has approached us with a wonderful opportunity to publicize our foundation's mission. Jim's six-year-old son was diagnosed with PSC and he would like to help us build public awareness.

Deep River is about to launch a new line of Multigrain Tortilla Chips that are all natural, kosher, and gluten free. PSC Partners will be branded on the back of the bag of their Guacamole Multigrain Tortilla Chips. Thank you Jim for making people more aware of our cause!

University, Internal Medicine, 333 Cedar Street, Room LMP-1072, P.O. Box 208056, New Haven, CT 06520-8056. Amount awarded = \$40,000 over 2 years.

*** Combination treatment with ursodeoxycholic acid and all-trans retinoic acid for primary sclerosing cholangitis (PSC). Shi-Ying Cai, Ph.D., Research Scientist, Section of Digestive Diseases, Department of Internal Medicine, Yale Liver Center, Yale University School of Medicine, 1080 LMP, 333 Cedar Street, New Haven, CT 06520, and James L. Boyer, M.D., Ensign Professor of Medicine, Section of Digestive Diseases, Department of Internal Medicine, Yale Liver Center, Yale University School of Medicine, 1080 LMP, 333 Cedar Street, New Haven, CT 06520. \$37,000 over 2 years.**

*** Establishing the role and molecular mechanisms for pregnane X receptor in progressive sclerosing cholangitis. Sridhar Mani, M.D., Professor, Medicine, Oncology and Genetics, Miriam Mandel Faculty Scholar in Cancer Research, Albert Einstein College of Medicine, 1300 Morris Park Ave, Chanin 302D-1, Bronx, NY 10461. Amount awarded = \$40,000 over 2 years.**

Central themes of the research projects funded in this round, are: genetics and "epigenetics" of PSC, and the use of mouse models of sclerosing cholangitis to probe the pathogenesis mechanisms and accelerate development of novel therapies.

Details of each award

Following are the Project Summaries and Specific Aims sections of the funded proposals. Each Project Summary/Specific Aims description of the project (provided by the

2010 Holiday Cards For Sale

Again this year George Schill, a professional illustrator, has created and donated two appealing and whimsical designs for our PSC Partners holiday cards. the story is on page 20.

All proceeds from the sale of the cards will benefit the foundation's programs. Please think about ordering your holiday cards before the deadline on November 12 by going to: www.pscparatnrs.org/shop.

Looking for Co-Chair For 2012 Conference

If you are interested in being a co-chair for our 2012 conference, please go to www.pscpartners.org/conferencelocation, fill out the form and return it to us by January 15, 2011.

2011 Annual Conference For PSC Patients and Caregivers

Save the dates (April 29-May 1, 2011), and think about joining us for our seventh conference for PSCers and caregivers to be held at the Grand Sheraton in Sacramento, California in conjunction with the University of California Davis.

If you haven't had the chance to attend one of our past conferences, I can tell you that these weekends are a rare opportunity for all of us to learn about the newest breakthroughs in PSC and also to bond with other PSCers and caregivers. You will no longer feel that sense of isolation that comes from living with a rare disease and all its life-changing aspects.

To view some comments from past participants, scroll down to read Personal Stories at www.pscpartners.org/annualconferences and www.pscpartners.org/prevannual.

Don and I were in Sacramento recently to continue our conference planning, and we are both very excited about next year's conference. It is a pleasure working closely with Dr. Chris Bowlus to

investigators) is followed by a brief Interpretation for the Layperson (prepared by David Rhodes). David Rhodes accepts full responsibility for any errors/omissions that may occur in these "layperson" interpretations.

Pathogenesis of PSC: Role of TGR5 in the regulation of the innate immune response in the biliary epithelium. Mario Strazzabosco, M.D., Ph.D, Department of Internal Medicine Section of Digestive Diseases, Yale University, 333 Cedar Street-1080 LMP, P.O. Box 208019, New Haven, CT 06520-8019, and Michael Trauner, M.D., Ph.D, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. Amount awarded = \$40,000 over 2 years.

Summary

The etiology and pathophysiology of PSC remain unclear. The strong association with IBD suggests a dysregulation of the innate immunity system and among the different hypotheses, an increased response to bacterial products released by a "leaky gut" has been suggested. This hypothesis has not been adequately tested because of the lack of adequate animal models. PSC has several features in common with Cystic Fibrosis, an autosomic recessive disease caused by mutation in CFTR, a cAMP-stimulated chloride channel that is involved in the secretory function of the biliary epithelium. We have recently found that CFTR deficiency alters the innate immunity of the biliary epithelium and generates a strong TLR4-mediated inflammatory response when the epithelium is exposed to endotoxins. Recent data suggest that TGR5, a Gprotein-coupled receptor for bile acids, that increases cellular cAMP, co-localizes with CFTR and regulates

plan the agenda for the medical presentations on Saturday, April 29.

Dr. Bowlus has put together a diverse agenda of outstanding presenters from UC Davis, UC San Francisco, and Stanford University to bring us up to date on treatments and research for PSC. Dr. Tom Karlsen (Norway), Dr. Gideon Hirschfield (Toronto, Canada), Dr. Pietro Invernizzi (Italy and Davis) and Dr. Carlo Selmi (Italy and Davis) will be our international speakers. A few of the highlights of the plenary session include:

- ❖ Dr. Eric Gershwin (UC Davis) speaking on PSC Immunology: Lessons to be learned from PBC;
- ❖ Dr. Tom Karlsen giving us an Update on PSC Genetics and the Work of the Norwegian PSC Center, and
- ❖ Drs. Hirschfield and Bowlus presenting a session on Urso: Pro and Con

On Saturday afternoon, attendees will attend two breakout sessions of their choice. Topics include supplemental therapies, cholangiocarcinoma, transplant, IBD and PSC, future therapies, coping with PSC, an overview of disability and insurance law, caregiver advice and many other practical topics.

If you can arrive in Sacramento on Thursday to attend the pre-conference activities on Friday April 28, you can join us for a casual get acquainted brunch at the California historic Capitol Building (just two blocks from the Sheraton), followed by an afternoon session on Healthy Eating.

Before or after the brunch, be sure to explore the Capitol Building with its historical museum and Assembly and Senate Chambers, and leave time to stroll through beautiful Capitol Park, forty acres which were designed as a Victorian garden. Since Sacramento is an agricultural center, our Healthy Eating presenters will be organic farmers, local restaurant chefs who specialize in eating local and

CFTR targeting and function in response to bile acids. The recent finding that the TGR5 gene is a likely disease gene in PSC let us to hypothesize that, similarly to CFTR, TGR5 may be a regulator of TLR4-mediated innate immunity and that a defective function of TGR5 may lead to an excessive inflammatory response to LPS. In this project, we plan to study the liver inflammatory response to DSS-colitis in TGR5-knockout mice, the effects of LPS on cytokine secretion in cultured TGR5-KO cholangiocytes, and the role of TGR5 on the regulation of the TLR4 pathway. These studies will eventually provide a strong rationale for the development of new therapies.

Specific Aims

Sclerosing cholangitis is a spectrum of progressive cholestatic liver diseases characterized by obliterative fibrosis and inflammation of the intrahepatic and/or extrahepatic biliary system. Primary Sclerosing Cholangitis (PSC) is associated with inflammatory Bowel Diseases (IBD), but while IBD is present in 75-80% of PSC cases, only 5-8 % of patients with IBD develop PSC. The etiology and pathophysiology of PSC, as well as the nature of the relationship with IBD remain unclear. Besides the “autoimmune” and the “toxic bile” hypothesis, the “leaky gut” hypothesis suggests that PSC is caused, in susceptible individuals, by exposure of the biliary tree to bacterial endotoxins. The lack of experimental models has hampered progresses in the study of PSC pathogenesis. Recent data generated by our lab indicate that cystic fibrosis may represent an interesting model disease. Cystic Fibrosis (CF) is a genetic disorder of secretory epithelia, caused by the defective function of a Cl⁻ channel essential for bile secretion, called CFTR.. Several patients with CF present a cholangiopathy that shares many

organic, a gluten free shop owner, etc. We will also hold a mini Farmers Market for our group.

The Sheraton Grand is located in the heart of downtown Sacramento, and it will be a great facility for us, since there are many public areas in which to chat informally with other attendees. The hotel was the original Public Market Building which was designed by Julia Morgan, the designer of the Hearst Castle, and it has been beautifully restored.

If you'd like to come early or stay late in the area, click on www.pscpartners.org/nextannual to view the document Things to Do In and Around Sacramento. If you're interested in additional sightseeing, think about visiting San Francisco, Berkeley, the Napa and Sonoma Valleys, Lake Tahoe, or the Gold Country.

In late December or early January, we will post the completed conference agenda and registration materials on our website. However, if you would like to reserve your room at the Sheraton Grand Sacramento sooner, you may do that now.

We have a wonderful group rate of \$99 per room per night at the Sheraton for the dates April 28-May 1. If you would like to add shoulder dates, the Sheraton will try to provide them. If you would like to book a reservation, check our website at: [PSC Partners reservation site](#).

Thank you to Joanne Hatchett and Jennifer Soloway, my local conference co-chairs for 2011, for all your continuing suggestions and help. California, here we come!

Ricky Safer

President

(With special thanks to our newsletter editor, Pat Bandy)

similarities with PSC. Both conditions manifest as a slowly progressive fibrosing cholangitis, affecting any tract of the biliary tree, with similar histologic and radiographic findings and a common evolution in biliary cirrhosis. Similar to PSC, that affects only a minority of IBD patients, liver disease affects a minority of CF patients. CFTR-knockout (CFTR-KO) mice do not show spontaneous liver pathology, but develop a severe cholangitis after induction of colitis with dextran sodium sulfate (DSS). DSS-treatment had no effects on wildtype animals, suggesting that development of biliary inflammation and liver disease required the interaction between genetic predisposition and acquired factors. We have shown that, independently from the secretory defect, the biliary tree of CFTR-KO mice is more susceptible to endotoxins that enter the portal circulation because of the increased intestinal permeability. In fact, CFTR-defective cholangiocytes show an altered posttranslational regulation of TLR4 activity, and exhibit a stronger Src-dependent TLR4/NF- κ B-mediated inflammatory response to an endotoxin challenge. Thus, CF-cholangiopathy, rather than being the consequence of ductal cholestasis, results from altered innate immune responses of CFTR-KO cholangiocytes. Similar mechanisms may apply to the primary form of sclerosing cholangitis. Recent genome wide association data provided circumstantial evidence that the G-protein-coupled bile acid receptor-1 (gpr1 or TGR5), is a potential disease gene in PSC. TGR5 is a bile acid receptor that generates cAMP upon binding of bile acids. TGR5 was shown to colocalize with CFTR and to be able to activate and stimulate the translocation of CFTR to the apical membrane of gallbladder cells. Moreover, TGR5 was shown to mediate bile-acid-induced suppression of LPS-induced cytokine secretion in macrophages. Thus, we hypothesize that, similar to the mechanism we

THANK YOU!!!

All PSC Partners members thank Craig and Ali Wiele, the anonymous donor, and all donors for their contributions to support our PSC research grants program.

We're together in the fight, whatever it takes!

have shown for CFTR, TGR5 modulates the innate immune response in cholangiocytes, and that defective function of TGR5 may lead to an excessive inflammatory response to LPS.

The hypothesis will be addressed through the following specific aims:

Aim 1: to study the effects of DSS-induced colitis on biliary inflammation in TGR5-KO mice.

Aim 2: to study the effects of LPS on cytokine secretion in cultured TGR5-KO and WT cholangiocytes.

Aim 3: to study the role of TGR5 on TLR4 pathway regulation in cultured TGR5-KO and WT cholangiocytes.

These studies will generate a better understanding of the innate immune response mechanisms in cholangiocytes and of the pathogenesis of PSC. Furthermore, the results of our study are likely to have a strong translational potential because several therapeutic molecules able to target these mechanisms are being developed.

Interpretation for the Layperson

One of the explanations for the cause of PSC

(primary sclerosing cholangitis) in association with inflammatory bowel disease (IBD) is that an immune dysregulation in the gut leads to a "leaky gut" which allows toxic bacterial products to be transported to the liver, causing inflammation around the bile ducts. Both genetic and environmental factors may be involved in disease development and progression. It is essential that we understand the precise causes of PSC, so that we can ultimately learn how to slow or halt disease progression. Significant progress has been made in recent years concerning the identification of genes that may be associated with PSC. An important research approach is to take information obtained from these human PSC genetic studies to develop mouse models that mimic human PSC. Such models will be critical in understanding the pathogenic mechanisms, and accelerating the development of novel therapies. One of the existing mouse models of PSC is the cystic fibrosis mouse model. When given colitis, the cystic fibrosis transmembrane conductance regulator (CFTR) deficient mouse develops bile duct injury closely resembling human PSC. The CFTR gene encodes a protein that functions in bicarbonate

secretion into bile. This mouse model has already been used to show that docosahexaenoic acid (DHA; a component of fish oil) protects against bile duct injury, and has led to clinical trials of DHA in the treatment of PSC. The relevance of this mouse model to human PSC is that variants of the cystic fibrosis gene have been associated with PSC, and pediatric PSC patients have been shown to have a dysfunction of the cystic fibrosis protein.

The TGR5 gene has been recently identified as a strong candidate for a susceptibility gene in PSC by the Norwegian PSC research center. The TGR5 gene encodes a protein that is a "bile acid sensor" and a regulator of the cystic fibrosis protein. To learn more about what TGR5 is doing, the researchers will use mice in which TGR5 has been knocked-out, and study whether the mice develop sclerosing cholangitis.

Drs. Strazzabosco and Trauner will test whether deleting the TGR5 gene in mice will result in an abnormal inflammatory response to the bacterial product lipopolysaccharide (LPS; also known as endotoxin). A characteristic feature of inflammation caused by endotoxin is the activation

of the pro-inflammatory complex, nuclear factor kappa-B (NF-kB). Endotoxin binds to the Toll-like receptor 4 (TLR4) and activates NF-kB. Thus, the assessment of the effect of deletion of TGR5 on TLR4-NF-kB pathway regulation in biliary cells (cholangiocytes) will provide important information about the inflammatory mechanisms controlled by TGR5. Drugs that target TGR5 are already in development, and so this study will pave the way for testing whether these drugs may inhibit liver inflammation. Drs. Strazzabosco and Trauner have extensive experience working with mouse models of sclerosing cholangitis, and have been instrumental, respectively, in clarifying the disease mechanisms in biliary tract diseases, and in demonstrating that nor-ursodeoxycholic acid (nor-UDCA) is superior to ursodeoxycholic acid (UDCA) in preventing liver injury, and bringing nor-UDCA to human clinical trials.

The first year of this project will be funded by a generous donation from Craig and Ali Wiele.

Epigenetics associated with primary sclerosing cholangitis in monozygotic

twins discordant for the disease. Carlo Selmi, MD, PhD, Assistant Professor of Internal Medicine, University of Milan, Physician Scientist, IRCCS Istituto Clinico Humanitas, Rozzano, Milan, Assistant Professor of Medicine, University of California, Davis, Division of Rheumatology, Allergy, and Clinical Immunology, GBSF suite 6515, 451 E Healthy Sciences Drive, Davis, CA 95616. Amount awarded = \$40,000 over 2 years.

Summary

Primary sclerosing cholangitis (PSC) is characterized by the presence of a chronic and relapsing inflammation of the biliary tract. As illustrated by recent association studies, genomic factors cause individual susceptibility in a subgroup of patients. Monozygotic (MZ) twins are a powerful tool to estimate the role of genetic and environmental factors, yet the concordance rate for PSC in such twins is unknown. Epigenetic changes are ideal candidates to provide a link between genomic susceptibility and environmental stimuli, particularly in the unique model of MZ twins discordant for the disease. We will take advantage of MZ twins discordant for PSC to utilize cutting-edge technologies which allow a large-scale analysis of epigenomics to address two specific issues:

Issue #1. Do MZ twins discordant for PSC manifest consistent patterns in terms of DNA methylation changes within repetitive and non-repetitive elements? We will utilize custom-designed MeDIP multiplex arrays for non repetitive and the most represented repetitive elements (LINE-1, Alu).

Issue #2. Does the expression of candidate genes identified through the previous aim differ between discordant MZ twins? We will utilize RTPCR on mRNA samples and then pinpoint

methylation differences through bisulfite sequencing.

Issue #3. Is there an in silico disease model that can be summoned from the identified putative genes? The results obtained are expected to provide insights into putative epigenetic marks implicated in PSC onset that may well be integrated with the recently identified genetic loci. These results ultimately provide the bases for new epigenetic treatments in inflammatory conditions.

Specific Aims

We will take advantage of samples already available to the proponent from 6 MZ twin pairs discordant for PSC. Samples include DNA, mRNA, and mononuclear cells from peripheral blood and were previously obtained by the proponent through a worldwide effort supported by PSC Partners Seeking a Cure. We will take advantage of this unique cohort and of cutting-edge molecular methods to address two complementary and one ultimate issue.

Issue #1. Do MZ twins discordant for PSC manifest consistent patterns in terms of DNA methylation changes within repetitive and non-repetitive elements? Issue #2. Does the expression of candidate genes identified through the previous aim differ between discordant MZ twins? What is the methylation pattern of single CpG sites within differently expressed genes? Issue #3. Is there an in silico disease model that can be summoned from the identified putative genes? This analytical step will include data from the recently concluded genome-wide genetic association study as well as from the present proposal. Such findings will be utilized with the appropriate bioinformatics tools to determine what molecular pathways are involved in PSC pathogenesis or whether a genetic

signature can be extrapolated.

Interpretation for the Layperson

It is estimated that first-degree relatives of PSC patients have a 40-fold higher risk of developing PSC than the general population. Therefore there is a strong genetic component to PSC. The genetic basis of PSC is likely to be complex involving more than one gene and may well be insufficient to explain disease onset. There may also be as yet unknown environmental factors contributing to disease initiation and progression. At the interface between genetics and environment is a relatively new field of research called "epigenetics". Here, certain gene modifications can take place, such as methylation of cytosine residues of DNA, converting cytosine to 5-methylcytosine, mostly at sites called "CpG sites". When some areas of the genome are methylated more heavily than others this can alter gene expression and thus the production of the corresponding protein. A key approach to discovering whether epigenetic changes are involved in disease development/progression is to carefully examine the DNA methylation patterns of monozygotic twins (i.e. twins

that are genetically identical) but differ with respect to disease (i.e. only one twin is affected, and the pair is thus discordant for disease). This approach has been used by Dr. Selmi and colleagues to investigate the role of "epigenetics" and DNA methylation in particular, in primary biliary cirrhosis (PBC), a liver disease that mostly affects women. These pioneering studies have recently shown that monozygotic twins that are discordant for PBC have distinct methylation patterns of certain genes on the X chromosome.

Dr. Selmi and colleagues will now extend these studies to investigate DNA methylation patterns in 6 pairs of monozygotic twins discordant for PSC, recruited with the assistance of PSC Partners Seeking a Cure. The results of this project are expected to provide insights into putative epigenetic markers implicated in PSC onset, painting a more complete picture of the genetic landscape of PSC and its interface with environmental exposures. These results may ultimately provide the basis for novel epigenetic treatments.

Identification of genetic profiles unique to PSC-IBD.

Judy Cho, M.D., Associate Professor of Medicine and Genetics, Section of Digestive Diseases, Director, Inflammatory Bowel Disease Center, Yale University, Internal Medicine, 333 Cedar Street, Room LMP-1072, P.O. Box 208056, New Haven, CT 06520-8056. Amount awarded = \$40,000 over 2 years.

Project Summary

The primary goal of this proposal is to better understand the relationship between primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD). We propose to accomplish this by identifying the genetic and genomic factors which contribute to the cause of PSC-IBD, and comparing this to identified genetic and genomic factors associated with Crohn's disease (CD) and ulcerative colitis (UC). Identification of these factors will ultimately contribute to better screening for disease risk, improve predictions of disease severity, influence treatment regimens and advance therapies for treatment and quality of life care. PSC-IBD is poorly characterized, clinically and genetically. A strong association has been observed with IBD and PSC, some analyses identified IBD in

80-90% of PSC patients. Conversely, about 5% of UC patients will have associated PSC compared to 3.4% of CD patients. Genetic contributions to both have been confirmed by epidemiologic studies and by the identification of genetic associations for both IBD and PSC. A recent GWAS found the strongest PSC association for the HLA-B region at chromosome 6p21, and some evidence for associations at 2q35, 3p21 and 13q31. Interestingly, significant associations were not found for confirmed UC susceptibility loci. These observations underlie PSC and IBD as complex genetic traits, and support the hypothesis that PSC-UC is a distinct sub-phenotype of IBD. We plan to advance the genetic and genomic knowledge in PSC-IBD by expanding the collection of PSC-IBD cases and biospecimen collections (Specific Aim #1). We propose to compare and contrast both the genetic loci (Specific Aim #2) and peripheral blood serum miRNA patterns (Specific Aim #3) between PSC and IBD. The unique relationship between PSC and IBD provides an ideal opportunity to leverage these comparative studies to provide insight into disease mechanisms and course.

Specific Aims

Specific Aim #1: Development and expansion of PSC-IBD resources for collaborative genetic and genomic studies. We propose to recruit patients and collect phenotype data and biospecimens from individuals with PSC-IBD using uniform protocols to enhance collaborative studies. Identification and a better understanding of the genetic factors contributing to PSC-IBD will greatly increase the potential for identifying disease predictors/markers, novel therapies for disease management and/or the prevention of invasive treatments.

Specific Aim #2: To compare and contrast

genetic loci between PSC and IBD. The ImmunoChip Consortium has developed a genotyping platform which includes all inflammatory disease loci, many of which are shared between different diseases. We propose studies to define the genetic overlap between PSC and IBD, with a particular focus on combining PSC data with two IBD subtypes, namely, extensive colitis and fibrostenosing CD.

Specific Aim #3: To compare and contrast peripheral blood serum miRNA patterns between PSC and IBD. We propose a pilot study to explore the feasibility of using micro-RNAs as biomarkers for PSC-IBD. The analysis of miRNAs in peripheral blood may provide an important and novel source for biomarkers. At present the extent to which small RNAs can be specifically mapped to and regulate, protein-coding mRNA expression is unknown. However, given the plethora of SNP associations in 3'UTR regions, specifically for IBD, the concept that disease-associated variation may modulate mRNA expression through variable miRNA regulation of genetic variation will be explored. We propose an initial analysis of circulating miRNA from serum of CD, UC, PSC-IBD cases and healthy controls.

Interpretation for the Layperson

PSC (primary sclerosing cholangitis) is strongly associated with inflammatory bowel disease (IBD), particularly ulcerative colitis (UC). Both genetic and environmental (possible also dietary) factors may be involved in disease development and progression. Much work during the last decade by the NIDDK Inflammatory Bowel Disease Genetics Consortium (led by Dr. Judy Cho [<http://medicine.yale.edu/intmed/ibdgc/>]) has identified a multitude of genes associated with UC and Crohn's disease. The identification of these genes is leading to a more complete

understanding of the mechanisms of UC and Crohn's disease initiation and progression, and identification of new targets for intervention, and novel therapies for disease management. Parallel studies on the genetics of PSC are beginning to reveal that the IBD associated with PSC may have a different genetic signature from classic UC and Crohn's disease. Dr. Judy Cho will rigorously investigate this important question by recruiting patients and collecting phenotype data and biospecimens from individuals with PSC-IBD for comparison with classic UC and Crohn's disease patients, and healthy controls. Dr. Cho will use the "ImmunoChip" [which includes all known inflammatory disease genes] to investigate the precise genetic overlap between PSC and the various forms of IBD.

There is recent interest in whether microRNAs (small RNA molecules with potent gene regulatory functions) play a role in IBD and PSC [Dr. Invernizzi at UC Davis is currently funded by PSC Partners Seeking a Cure to investigate whether specific microRNAs are associated with PSC and cholangiocarcinoma]. Dr. Cho will extend this work to determine if circulating microRNAs in the serum of

Crohn's disease, UC, and PSC-IBD patients differ from one another, and from healthy controls. This work may lead to new diagnostic tools, perhaps enabling early identification of UC and Crohn's disease patients who may be at risk for developing PSC.

This project will be entirely funded by our anonymous donor who generously donated \$100,000 in our Itching for a Cure: Road to Connecticut fundraiser of 2009/2010 to help support PSC research.

Combination treatment with ursodeoxycholic acid and all-trans retinoic acid for primary sclerosing cholangitis (PSC). Shi-Ying Cai, Ph.D., Research Scientist, Section of Digestive Diseases, Department of Internal Medicine, Yale Liver Center, Yale University School of Medicine, 1080 LMP, 333 Cedar Street, New Haven, CT 06520, and James L. Boyer, M.D., Ensign Professor of Medicine, Section of Digestive Diseases, Department of Internal Medicine, Yale Liver Center, Yale University School of Medicine, 1080 LMP, 333 Cedar Street, New Haven, CT 06520. \$37,000 over 2

years.

Project Summary

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease of the liver and bile ducts that generally leads to progressive liver failure. The pathogenesis of PSC remains enigmatic, but malfunction of hepatic immunity has been proposed to play a role in the development/progression of the disease. There is no FDA approved medical treatment for PSC. Although norUDCA has shown beneficial effects in Mdr2 (Abcb4) knockout mice (an animal model for PSC), there is an urgent need to develop novel treatment strategies and to test them in animal models and in PSC patients. Very recently, we have found that combination treatment with UDCA and retinoic acid substantially improved animal growth rate and significantly reduced bile salt pool size, liver fibrosis, necrosis, inflammation, and bile duct proliferation in an animal model of cholestasis, the common bile duct ligated rat. (UDCA and retinoic acid are FDA-approved medications for treating primary biliary cirrhosis and acute promyelocytic leukemia and inflammatory disorders such as psoriasis, acne, and rheumatoid arthritis,

respectively). Parts of the molecular mechanisms of this beneficial effect of UDCA and retinoic acid have also been verified in primary human liver cells, including hepatocytes and hepatic stellate cells (manuscript submitted for publication). Therefore, we propose to test if RA alone or in combination with UDCA will improve liver pathology in Mdr2^{-/-} mice. Completion of the proposed study will provide critical information for determining whether RA alone or in combination with UDCA might be potentially beneficial for patients with PSC. If this project demonstrates beneficial effects in this animal model, we plan to test this therapy in patients with PSC.

Specific Aims

The specific aim of this study is to determine whether RA alone or in combination with UDCA has beneficial effects on liver fibrosis, necrosis and or inflammation in Mdr2^{-/-} mice, an animal model for PSC.

Interpretation for the Layperson

It is urgent that novel therapies/treatment strategies be developed for PSC, and the use of mouse models of sclerosing cholangitis will be critical in accelerating the discovery and pre-clinical testing of these new approaches. It is well recognized that vitamin A deficiencies are common in PSC patients, and that the deficiencies become more pronounced as the disease progresses. The liver is a major storage organ for vitamin A, and as cholestatic liver diseases progress, this vitamin A can be released from the vitamin A storing cells of the liver (hepatic stellate cells) as they transition away from vitamin A storage towards a state that promotes collagen biosynthesis and liver fibrosis. Vitamin A (retinol) is a precursor of all-trans retinoic acid (RA), and so loss of vitamin A

during advancing liver disease may lead to retinoic acid deficiencies, which may in turn contribute to a vicious cycle of inflammation, necrosis and fibrosis.

In this proposal, Drs. Cai and Boyer will test whether the combination of ursodeoxycholic acid (UDCA) with retinoic acid (RA) will be superior to the individual drugs alone in delaying liver fibrosis, necrosis and inflammation in a mouse model of sclerosing cholangitis, the Mdr2^(-/-) mouse model. Should positive results be obtained in these studies, this combination therapy can be immediately tested in patients with PSC.

This project will be entirely funded by our anonymous donor who generously donated \$100,000 in our Itching for a Cure: Road to Connecticut fundraiser of 2009/2010 to help support PSC research.

Establishing the role and molecular mechanisms for pregnane X receptor in progressive sclerosing cholangitis. Sridhar Mani, M.D., Professor, Medicine, Oncology and Genetics, Miriam Mandel Faculty Scholar in Cancer Research, Albert Einstein College of Medicine, 1300 Morris Park Ave, Chanin 302D-1, Bronx, NY 10461. \$40,000 over 2 years.

Project Summary

We and others have demonstrated that orphan nuclear receptors like pregnane x receptor (PXR) abrogate intestinal inflammation induced by xenobiotic compounds (e.g., DSS). These experiments serve as a proof-of-concept that PXR plays a significant role in pathogenic diseases of the gut that result from unregulated inflammatory responses (e.g., IBD). Fish oils

have beneficial effects on inflammation and are relatively non-toxic xenobiotics. Since the pathogenesis of progressive sclerosing cholangitis is parallel to that observed in arteriosclerotic inflammation (where fish oils show clear benefit), our 2-year project will focus on determining the significance of PXR activation in the pathogenesis and maintenance of PSC.

Specifically, we will use the DDC-induced mouse model of cholangiopathy in our mouse models of PXR activation [PXR wt type, PXR^{-/-} and humanized (h)PXR] to determine if PXR activation by non-hepatotoxic agonists (e.g., hyperforin or rifampicin) abrogates biliary inflammation. In our second aim, we will determine whether PXR mediates the actions of fish oils in abrogating biliary inflammation. Specifically, we hypothesize that fish oils will transactivate PXR and inhibit inflammation.

Specific Aims

1. To determine the effect of PXR activation on biliary inflammation in the DDC-induced mouse model of cholangiopathy in PXR^{+/+}, PXR^{-/-} and humanized PXR mice. DDC induces a cholangiopathy in mice at 8 weeks of treatment that

resembles early inflammatory changes seen in PSC. (a) To determine the effect of PXR on early inflammation in the bile duct tract, PXR^{+/+} will be treated with DDC (+ PCN, a potent mPXR agonist). At 4, 6 and 8 weeks, cohorts of mice from each genotype, will undergo histopathologic and immunohistochemistry assessment of the entire bile duct tract (intra- and extrahepatic) as previously described. (b) The same experiments will be repeated with PXR^{-/-} and hPXR mice (+ hyperforin or rifampicin, potent hPXR agonists), with accurate sample size estimates obtained from data from (a). These experiments will determine the clinical impact of PXR in biliary inflammation as typified in PSC.

2. To determine the therapeutic efficacy of fish oils alone or in combination with classical PXR ligands on DDC-induced mouse models of cholangiopathy. Fish oils (DHA, EPA) are commercially available and serve as weak ligands to several nuclear receptors - RXR α and PPAR α . Since PXR dimerizes with RXR α and is a direct target gene of PPAR α , we hypothesize that fish oils will transactivate PXR and inhibit inflammation. Furthermore, we surmise that

multiple ligands acting on PXR, given its promiscuous ligand-binding pocket, will synergistically activate PXR and inhibit inflammation. To test this concept, we will treat PXR^{+/+}, PXR^{-/-} and humanized PXR mice with vehicle, fish oils and/or PCN (as mPXR ligand) or rifampicin (as hPXR ligand).

Interpretation for the Layperson:

It is becoming clear that there is a complex network of nuclear receptors in the gut and liver that are "master" controllers of gene expression, regulating all aspects of metabolism, ranging from bile acid transport and detoxification, to energy metabolism, to lipid metabolism, and circadian rhythms (day-night cycles). An important "master" controller is the receptor called pregnane X receptor (PXR), also known as the steroid and xenobiotic receptor (SXR). PXR is known to be down-regulated in ulcerative colitis, and the PXR gene itself may be an ulcerative colitis susceptibility gene, and a gene that affects the rate of progression of PSC. This receptor plays an important role in detoxification of lithocholic acid, a toxic bile acid produced from ursodeoxycholic acid (UDCA)

by gut bacteria. Recent studies indicate that activation of PXR by drugs such as rifampin (rifampicin) and rifaximin results in reduction of inflammation and fibrosis.

Because the adverse effects of high-dose UDCA in PSC may be associated with conversion of UDCA to lithocholic acid, there is also particular urgency in investigating whether drugs that target PXR may help prevent these adverse effects of UDCA.

In this proposal, Dr. Mani will use humanized mice in which the mouse PXR gene has been replaced with the human PXR gene so that it responds to rifampin (rifampicin), and will then test whether activation of PXR by rifampin will result in a reduction of biliary inflammation.

Another "master" controller of gene expression in the liver and gut is the receptor called retinoid X receptor (RXR), which partners with PXR (and

many other nuclear receptors) to regulate metabolism. A known activator of RXR is a component of fish oil, docosahexaenoic acid (DHA). It is plausible that the combination of DHA and rifampin, as activators of both RXR and PXR, respectively, will be superior to either drug alone in reducing inflammation. Dr. Mani will test this hypothesis. If positive results are obtained, this may lead to novel therapies in PSC, perhaps combining UDCA with rifampin and DHA. It should be noted that rifampin is already used by many PSC patients for the control of pruritus, and that DHA has shown some early positive results in reducing alkaline phosphatase levels in PSC patients. Some mouse models suggest that DHA may be protective against colitis and colorectal cancer, and there is growing evidence that human ulcerative colitis may be associated with low intake of omega-3 fatty acids such as those found in fish oils.

Just in Time for the Holidays! Watch for the Announcement!

We'll soon have something special to help spread the word and support our organization.

New PSC Partners apparel is coming to Shop PSC Partners! Hoodies, Sweatpants, and Tees—all imprinted with our logo or that cute SuperLiver guy.

These are perfect gifts for those hard-to-buy-for friends and family who say they already have everything.

Guess what? They don't have these! And Santa knows this is exactly what they want! Check it out in a few weeks at: <http://www.pscpartners.org/shop>

Save the Day: Dream a (not so little) Dream

By Sandi Pearlman, Chair, PSC Partners Save the Day Campaign

Do you all know the story of Rip Van Winkle, the dude who lay down to sleep and woke up some 20-100 years later (depending on the version you hear)? I've got to confess sometimes I envy old Rip. I don't want to be branded as lazy or be nagged and henpecked--and lord knows I'd hope somebody would be kind enough to put a waxer on retainer if I was going to sleep that long--but I do envy that extended blissful slumber that he got to take without a care in the world.

Then, we add to that the fact that he woke up years later to a world full of new possibilities and, wow, even the bluest of eyes might turn green. Can you imagine if that was our fate? If we could get some good quality sleep and wake up in a world where there was a cure for PSC? How amazing would that be? I mean, sure, there'd be a lot of drawbacks to missing the last 20 or so years, but we'll just suspend that reality for now, okay? :)

The thing is, unlike Rip, there's probably not some magic folklore wizard to wave his or her wand and make things happen; so it's up to us to be our own magical beings and help to shape and create the future we want to be a part of. The good news is we can most definitely do it. The better news is that now is that time!

Each October, PSC Partners sets its annual Save the Day international fundraiser into effect where we ask PSCers all over the world to step up and spread awareness and hold local fundraisers designed to let the world know we're here and that we're raising funds for a cure! The fantastic news is that we've got research grants just waiting to be funded and some of the most amazing scientific minds in the world ready and

willing to delve into PSC and study the heck out of it. The even more fantastic news is that every single penny helps and FUNdraising can be done by anyone of any age. And, when we all do it together, all over the world, wow, what a difference we can make! So, whether you're in Kalamazoo, Kyoto or County Clare, now's the time to stand up and be counted. And if your energy doesn't permit you to hold your own fundraiser, garage sale, bake sale, etc. and your medical bills make donating even a few dollars impossible this year, know that we've got your back and that we know when you're once again at full speed, you'll have ours. The important thing is that together, we can accomplish anything!

Wondering what fundraisers are/have been up and running this year? Here's a quick look at some of the fun and fabulous ways PSCers are spreading the word and raising funds for a cure:

Bake Sales: Because cupcakes and cookies are popular all over the world and I'm thoroughly convinced if you present somebody with delicious baked goods they'll be on your side forever.

Garage Sales: Ever look around your home and realize that there's just too much...well, everything? A garage or yard sale lets you do yourself a favor while meeting lots of neighbors and potential new allies. Put up a sign that all money goes to charity or print out our fundraising flyer from PSC Partners (www.pscpartners.org/brochures) and spread awareness like it's going out of style. Many of our garage sale holding members have told us that they set out a donation jar as well and even

when people don't purchase anything, they often donate to the cause!

Change Jar Donations: Wonder what to do with that change accumulating, well, everywhere? Leave the gumball machines to the kiddos and put your spare change to use saving lives. Collect it in a jar or get the whole family/office, etc. to drop theirs in, too and watch those pennies, quarters and dimes add up to better treatments and a cure.

Dress Down Days: It's very rare I meet anyone who doesn't love a good dress down day. I'm on disability and I still remember the reverence and awe I felt when I knew one was coming up. Dress down days are easy to set up and you'll make your coworkers eternally grateful. Like me and unable to work? Did you know that many HR departments are only too happy to help raise funds and awareness for a good cause? Ask your local companies and you may find that quite a few are willing to "jeans it up" in the name of awareness and education and to help a local community member.

Silent Auctions: Big or small in scale and with any combination of items under the sun, silent auctions are a fun way to shop for a cause. So, ask everyone to bring a white elephant item to your next dinner party and then bid on all your pals' great stuff while they bid on yours. It really is true what they say about one man's trash being another man's treasure. The last small scale silent auction I attended had only 30 people and we raised over \$1,000 for PSC Partners! Want to go grander? Get your religious organizations involved, hit up your neighbors, community hangouts, local artists and friends. Let everyone know 100 percent of profits go to PSC Partners and get ready to score some great new finds.

Benefit Concerts: Have a talent that you'd like to share with the world? Whether you're a talented operatic singer like this year's concert holder or an actor who's always looking for a role or you can play a mean guitar, you can use your abilities to rock out and raise awareness and funds. Gather talented friends and colleagues and put on a performance that'll not only raise the roof but also let everyone know that PSC exists and that they can help us to find a cure all while enjoying a bit of culture!

Wine Tastings: Yes, you'd think that wine tastings and liver disease wouldn't go together; but let me tell you, they're a match made in spades, like champagne and caviar. Whether you want to go low key and host an at-home version or pair up with a local winery, wine tastings are popular ways to reach a broad audience and have mega appeal! (Caveat: I'm not advocating that wine consumption is okay for PSCers, that's between you and your docs, or at the very least you and your liver!)

Marathon Runs: Do you know how many people attend a marathon? Ask friends and family to sponsor you for miles, put SuperLiver right on your jersey—do marathoners wear jerseys? In any case, while doing your thing, you can advertise to runners, bystanders and, maybe if you're lucky, local TV and/or radio. No matter where you place, you'll definitely be the winner in our eyes!

Firstgiving Pages: Firstgiving makes it incredibly easy to raise funds for whatever cause you choose. You can use it for birthday donations, walk/run events, in lieu of wedding gifts; the sky's the limit. Another great thing about Firstgiving fundraising, not only can you e-mail it and share it with your entire address book, your friends and family can pass on your fundraising info to all their friends and

family and it only takes moments to set up. For me and for many of the other Firstgiving fundraisers I know, the last thing we needed was another coffee mug, tie, pair of fuzzy socks. Through Firstgiving pages, we felt all the love and the funds donated do so much more good than even the best box of chocolates or the most gorgeous blooms!

Advertisements/Publicity:

Talk to your local papers, newsletters, community events coordinators, you name it. You never know who would be willing to run a story on you and PSC or PSC Partners. Tell them the truth about what life is like living with a too little known chronic, incurable illness and give every reader the information they need to be a part of PSC Partners' grant funding from the comfort of their own homes. Wouldn't it be amazing to inform and empower all those people in your own neighborhoods while they're browsing their morning papers or checking out their favorite news site online? Just one or two clicks and they can "Donate Now" right on our homepage at:

www.pscpartners.org.

These are just a few of this year's fundraisers. There are so many more and the best part is it's not only easy and fun, it

makes a real difference. So many of us feel at a loss with our diagnosis, we feel we're living a nightmare and that the power has been taken from us, our lives and our loved ones. It's time to take that power back. We can't let the days pass us like they did old Rip Van Winkle, as much as we might crave a nap that would make cats around the world jealous. Finding and funding a cure doesn't have to be just a dream! Can you imagine if we all just took one weekend, one week or one month to work together to broadcast our plight and raise funds? It's not just a dream, it's happening and it's never too late to join in.

Save the Day runs through the end of November, so check back next issue to learn how this year's fundraisers went and some of the lowdown on what we loved doing, what we think everyone should do and what we now realize we were just plain old crazy to attempt. All that and early returns that'll give us an idea of just how many research grants we can fund! Sounds pretty dreamy, right?

Don't forget to check out Shop PSC Partners Seeking a Cure to purchase great gifts, mementos and more! Shopping while helping to fund a cure

How Much Did We All Raise During the Save the Day Campaign?

We'll have all the results in the Winter issue of The Duct!

Thanks to everyone who is helping us Seek a Cure for PSC. Every penny, every dime, every dollar can make a difference!

for PSC, how can you possibly beat that? :)

To all of this year's fundraisers, thank you for making 2010's PSC Partners Save the Day absolutely rock. We're inspired by your creativity and determination and awed by your dedication. In fact, we just couldn't dream up better folks to be in the trenches with. Thank you for reminding us we're not all alone out there and for making sure that researchers the world over find discoveries that keep them up at night pondering the fantastic possibilities.

To talk fundraisers and how to get started, contact Sandi at sandi@pscpartners.org.

Fact-O-Rama

PSC Partners-Supported Medical Research: Thanks to You!

- ◆ Amount of money we've raised and awarded to researchers since 2006: \$514,706
- ◆ Number of research proposals considered in two rounds in 2009: 24
- ◆ Number of research proposals considered in 2010: 13
- ◆ Number of grant awards made since 2009: 13
- ◆ Medical Centers where our lead investigators work on the two-year projects:

US Centers:

Mayo Clinic/Rochester
UC-Davis
U of Colorado
Northwestern University
Yale University
Albert Einstein College of Medicine

International Centers:

Academic Medical Center, Amsterdam,
University of Toronto, Liver Centre, Toronto Western Hospital
University of Milan
Medical University of Vienna

- ◆ Our “seed” grant funding recently led the National Institutes of Health to expand on work by Dr. Lazaridis (Mayo Clinic) to leverage research on the topic with a \$3.5M five-year grant, the first large study to look at PSC and its relationship with IBD
- ◆ AASLD research prizes awarded since 2007 at \$3000 each: 2007, Dr. Tom Karlsen, Norwegian PSC Center; 2008, Dr. I. Tornai, University of Debrecen, Hungary and Dr. P.G. Blanco, Beth Israel Deaconess Medical Center; 2009, Dr. V.S. Teaberry, Duke University. The 2010 award will be announced in late October.
- ◆ STOPSC received \$40,000 for research at multiple centers
- ◆ Next deadline for research grant proposals: August 1, 2011

2010 Holiday Cards are Now Available: Two Great Choices

Once again, PSC Partners thanks professional graphic designer, George Schill, for designing holiday cards you can't get anywhere else. That's right, these are beautiful custom designs created just for us.



All proceeds from the sale of these cards will benefit our research, educational, and support programs. Please send in your order now!

The holiday cards are available in packs of 25 at a cost of \$35 per pack plus shipping and handling. For domestic orders (USA), shipping and handling is \$5 for an order of 1-2 packs and \$10 for 3 packs or more. For international orders, please email contactus@pscpartners.org and a shipping quote will be provided.

Designate the design you'd like: Snowmen or Holiday Deer.

Inside verse for Snowmen is: Wishing you every happiness this Holiday Season and throughout the New Year.

Inside verse of Holiday Deer is: May the peace and joy of the Holiday Season be with you always.



Message on the back of each card is also the same: Proceeds from the sale of these cards benefit the research, education, and support programs of PSC Partners Seeking a Cure.

To learn more about Primary Sclerosing Cholangitis, please go to www.pscpartners.org.

To order cards, please fill in the order form provided at: http://www.pscpartners.org/Holiday_card_order_form.pdf

Order deadline is November 12! You'll receive the cards around Thanksgiving.

Get Moving

Cirrhotic Cardiomyopathy: A Plausible Exercise Inhibitor

By Julianne Vasichek, PSCer and Professional Strength and Conditioning Coach

It is important to note that the condition described below requires diagnosis by a physician and may not be present in all severe liver disease patients. There is peer-reviewed research easily accessible on cirrhotic cardiomyopathy to complement this article.

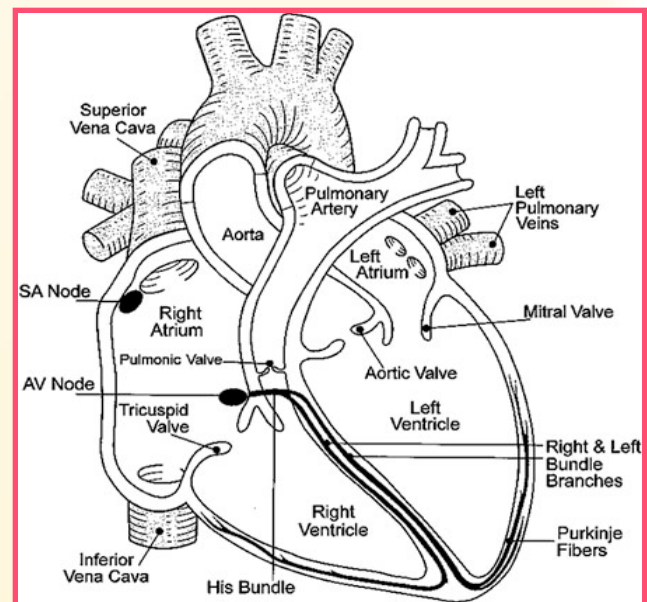
As we continue to further understand how our ability to exercise is affected by impaired liver function, it is important to consider how our cardiovascular system handles the added stress on the body.

Before jumping into this somewhat complex but interesting myriad of circulatory system responses, it is necessary to review a little background anatomy to keep the explanation clear (see heart diagram at right). In the interest of space, we will look at the most relevant chambers to this issue, the left atrium and left ventricle. Oxygenated blood returns to the left atrium from the lungs through pulmonary veins, then continues through the mitral valve and into the left ventricle. The left ventricle, much thicker and larger than the right ventricle, is responsible for generating enough pressure to pump the blood through the aorta and out into the systemic circulation, which carries the blood throughout the body. The left ventricle must overcome vascular resistance to get the blood out to the body.

The amount of blood pumped from the left ventricle is known as the stroke volume and the pace at which it is pumped is referred to as heart rate. The multiplication of the stroke volume (liters) and heart rate (beats per min) gives you the cardiac output (L/min), which represents the amount of blood pumped through the circulation in one minute. The heart rate is controlled by

electrical conduction throughout the heart led by the SA node. When the body is placed under stress such as exercise, the muscles are calling for the heart rate to speed up and deliver more oxygen in the blood to the muscles.

Cirrhotic cardiomyopathy is best defined through its characteristics: hypertrophy of the myocardium leading to a stiffer ventricle and abnormal systolic (contraction) function under



stress. At rest, studies have shown that cirrhotic patients experience a higher heart rate and a lower systemic resistance, resulting in a higher cardiac output than normal, termed hyperdynamic circulation. However, when, stress is placed on these patients, the ventricle is not responding as predicted.

To further describe these changes I have chosen a study devised in 2001 by Wong et al. involving 39 cirrhotic patients. Their hypothesis was that an abnormal cardiac response was leading to decreased oxygen delivery in the body and therefore a lower capacity for exercise. Eighteen of the patients were termed pre-ascitic to indicate no presence of ascites, and the remaining 21 patients clearly had ascites.

The patients first were measured at rest. Cirrhotic patients had a higher heart rate and a lower blood pressure as a result of the lower vascular resistance as previously indicated. Furthermore, total blood volumes in the ventricle before and after contraction were lower, but a higher percentage of blood volume was left in the ventricle after contraction, likely the result of smaller left ventricle dimensions and thickening of the walls. Despite this, the cardiac output was higher than controls due to a higher resting heart rate.

In effect their heart was working faster at rest to pump a smaller total volume of blood to meet the same demands as control subjects with normal function. To measure physiological parameters under stress, an upright cycle test was administered. The main results demonstrated that cirrhotic patients had a significantly reduced cardiac response to exercise. They were not able to last as long in the test, peaked at a lower heart rate, and performed at lower total intensities. The increase in cardiac output was also much less

then the control subjects, the lowest coming from ascitic patients.

Explanations for the reduced cardiac response to exercise refer back to the stiffer left ventricle, smaller chamber size and also further explanation in the article regarding diminished responses of the left ventricle, including a slower deceleration time for left ventricle filling, a longer total filling time, and longer relaxation time between left ventricle filling and contraction.

In addition, the plausibility exists that diminished exercise capacity in cirrhotic patients could come from greater inactivity, increased weight, anemia, or fatigue.

It seems pertinent to continue exploring how liver dysfunction is affecting our heart. It is appropriate to adjust expectations for exercise programming in relation to type of activity, amount of rest, intensity of exercise, and length of exercise. It does not mean that exercise is impossible. It should be manipulated individually and especially in the face of additional cardiac dysfunction. Further reading is available in the reference section of the citation below. My winter article will continue exploration on this topic. Be well!

Wong, F et al. (2001). "The cardiac response to exercise in cirrhosis." *Gut*, 49, 268-275.
Heart Diagram: *Beyond Biology*. Web. 8 Oct 2010. www.beyondbiology.org.

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We love our sponsors and recognize their gift to help support the conference. Several levels of donation are available: Premier Platinum Level Sponsorship (\$10,000), Gold Level (\$5,000) Silver Level (\$2500), and Bronze Level (\$1,000) are available.

Think about pooling donations with friends to have a greater impact. It's all tax deductible.

My Words, My Story

A Sudden, Tragic Loss And Our Project to Help Fund the Search for a Cure

By Mele Ohuafi, who attended the golf outing.

In the summer of 2003, when he was only 25, Jess Patterson, my brother-in-law, was diagnosed with PSC and ulcerative colitis after experiencing incredibly itchy skin and extreme weight loss. He was seen and diagnosed at a top hospital in Southern California. Although he was exhausted and sick, Jess's symptoms never kept him from doing the things he enjoyed. He loved photography, golfing, playing video games, working on his cars, figuring out computers and visiting his family. He continued to work and live his life optimistically, patiently waiting to be normal again.

They estimated that he would need a liver transplant some day, but reassured us that many people live long normal lives with PSC. We were told that Jess was not a candidate for a live donor transplant, so he was put on the UNOS list to wait for a donor.

Due to insurance battles Jess had to switch hospitals. Jess started with the second hospital in early 2010 where we were told he was an ideal candidate for a live donor transplant. Since we were told years earlier that he was not a live donor candidate this news was confusing to us, but we thought there might be something this

hospital knew that the first one did not. One difficulty with seeing multiple doctors is that they all have different opinions.

Jess was very excited and emotional when he learned that several of his family members and friends were willing to donate part of their liver to him. After several tests his younger brother was chosen as the best match, and live donor surgery was scheduled for July 8th.

In early June, Jess had a colitis flare up and lost a lot of weight so he was admitted to the hospital on June 19th. There we were told he was no longer a candidate for a live donor transplant due to a clot in his portal vein. This was a total set back for us since we thought the live donor surgery was just a few weeks away. Jess was put on and taken off the UNOS list many times as he continued to fight through several complications. He continued to stay positive and strong, and he never stopped fighting for his life.

Left to right: Tim Wholey, Scott Clouser, Todd Clouser, Collin Bookleiner.



Often a doctor would say “You look great. Why are you in here?” or “You are not quite ready for a liver.” Those words were frustrating and shocking to all of us, as we knew that he was ready and needed a transplant immediately. He was extremely tired of feeling sick all the time, but he continued to have a positive outlook. All of his loved ones were cheering him on, and we always thought Jess would conquer this disease.

On July 21, 2010, our worst nightmare happened. We lost Jess. To this day we cannot believe this could happen to such an incredible man. Jess lost his battle with PSC at the young age of 32, just seven years after his diagnosis. We hope that other families do not have to go through this tragedy that we have experienced. We wish we could have been more educated on this disease to enable us to help and protect Jess.

My co-worker had found the PSC Partners website and thought that instead of sending flowers, we could do a fundraiser and donate the proceeds to PSC Partners in Jess' memory. So all the money we raised is going to PSC Partners.

Golfing was one of Jess' favorite things to do, so what better way to honor him? We held a golf



Bottom left, clockwise: Jay Patterson, Brad Patterson, Rick Patterson, Sr., and Rick Patterson, Jr.

outing to celebrate Jess' life and raise awareness of PSC. The event took place at Quicksilver Golf Club in Midway, PA. We had 38 in attendance, which was a great turnout for our first outing.

Jess would've been humbled by the generosity of everyone that showed up and donated to a cause that is very important to him and his family. We are happy to donate to PSC Partners, knowing that it will help other PSCers, their families, and fund research to find a cure!

The 2011 Annual Conference is Just Six Months Away!

See you in Sacramento! We're joining with the University of California Davis next year to put on another memorable event. You won't want to miss the jam-packed weekend, April 29-May 1, where you'll learn, network, chill, and laugh.

Details will be announced in January. But you can reserve your room now at: www.pscpartners.org/nextannual.

The 20-30 Somethings

Meme x 2

By: Sandi and Karen Pearlman

There's this thing that happens every September. It's not a big event in the grand scheme of things. It's not going to fall on many calendars with bright, red circles around it and, chances are, you've never even heard of its existence. It's called Invisible Illness Week., or more technically, National Invisible Chronic Illness Awareness Week, but that's a mouthful, so let's go with the shorthand version, shall we?

IIW (nice, right, I even shortened the shorthand!) was started in 2002 by a woman named Lisa Copen and I'm sure there are lots of other interesting factoids, but they're not pertinent and I'm a PSCer and realize that life and time are precious, as are our attention spans, so let's not dwell on any of the mysteries of its origin right now.

What is relevant is that every year IIW asks people with chronic illnesses to do a "meme," which is essentially their interpretation of a memo all about me (or you as the case may be). In these 30 questions, they ask those with chronic illnesses to open up and bare their souls and share with the world what it's like to be invisible and ailing.

I've done it and it's cathartic and nerve-wracking and freeing and depressing and about 100 other adjectives. But something's always bothered me: Why is it only for those diagnosed with a chronic illness? Who knows better than a PSCer that while the disease may lie in our particular bodies, it's a community diagnosis? PSC affects our friends and families and spouses and siblings and it just doesn't seem fair that there's no meme for them.

So, this year, I'm changing that and I'm challenging you to change it, too. Below, you'll find my answers to the wordy 30 and those of my little sis's (with the questions modified a bit for non-PSCers or PSCEers* as my sis and I call 'em). Once you're done reading (the WHOLE newsletter, of course), head over to <http://tinyurl.com/pscpartnersfacebook> (there's a Discussion Board heading all ready and waiting for you!) to find the questions and fill out your 30 and urge your friends or family members to do the same.

Then, share them on PSC Partners FB or on your own Facebook pages. Send them out to your e-mail list. Revel in the fact that you're accomplishing the impossible: you're making the invisible visible and you don't need a certain day, month, or time to make that more than okay. Talk about Power, Strength and Courage.

From Sandi: 30 Things About My Invisible Illness You May Not Know: Some Time in The Life of a PSCer

1. The illness I live with is: Primary Sclerosing Cholangitis (PSC) as well as Ulcerative Colitis, Gastroparesis and more.

2. I was diagnosed with it in the year: Honestly, I don't even know anymore. I was so sick the whole thing is a blur. I'm guessing it was 2006 or 2007.

3. But I had symptoms since: I'd been sick off and on for years and one doctor after another told me it was just "stress." I eventually became so ill that I lost the ability to walk, went into renal failure and was, quite literally according to the docs, three days from dead before I got an actual diagnosis. Guess I proved them wrong about that three days from dead thing though, huh? :)

4. The biggest adjustment I've had to make is: Every single day with PSC is a million little battles fought in a (currently) unwinnable war. I miss my privacy and independence. I miss my savings (being ill costs an awful lot). I miss my energy. I miss my cellphone being filled up with friends' names instead of doctors' names and nurse coordinators and transplant secretaries and pharmacies and the like. I miss being able to count on my body and my brain to work the ways they always had in the past. Depending on the day or the moment, any or all of these things are my biggest adjustment.

5. Most people assume: I'm healthy (unless they know me). Even those who know I'm ill generally think things are far better or more stable than they truly are. I think that's one part because they're not capable of understanding (thank goodness, because it means they've never experienced something like PSC themselves) and one part my being unwilling to always show the world exactly how tough things can be.

At the Click of a Mouse: Online PSC Support Groups to Check Out!

An online PSC support group, established in 1998, is a message board (forum) on Yahoo/Health, where PSC patients and caregivers can exchange information and lend support/advice to one another:

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

In the United Kingdom, there is a similar PSC support group that publishes a newsletter and holds an annual meeting in Oxford with Dr. Roger Chapman, a leading PSC expert:

<http://www.psc-support.demon.co.uk/>

There is also a parent's support group, especially helpful for parents of young children, as PSC presents itself differently in pediatric patients, and

is treated accordingly. This group is found at:

<http://health.groups.yahoo.com/group/pscmoms/>

Pre-teen kids and teens with PSC can get acquainted with others through a new online board:

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

For post-transplant PSC patients, there is a support group with discussions based on the special needs of being post-surgical, immunosuppressed, and having an "at-risk" status. You may join this group at:

<http://health.groups.yahoo.com/group/Livertx-PSC/>

To join a global group of PSCers and caregivers for social connection, education and sharing, check out Facebook at:

<http://tinyurl.com/pscpartnersfacebook>

To join the group, go to facebook.com and type in (or click on) the link above. To find other PSC Facebook groups, click on the info tab at the above address.

6. The hardest part about mornings are: Um, waking up? How are we defining “morning?” :) Again, depends on the day for me. Sometimes, it’s getting up to feed the cat and finding that by the time I’ve walked to the kitchen my energy for the day is already gone. Sometimes it’s the fact that I’m okay with “morning” being whenever I decide to wake up, even if it’s 5:00 p.m., and others in my household are not. (Which I still can’t quite figure out. Why do they wake me? If it’s to check and see if I’m breathing, I clearly am or I wouldn’t be sleeping and if I wasn’t, they couldn’t wake me anyhow, and if I’m sleeping, clearly I need sleep more than anything else! Don’t they watch CSI? Don’t they know if I was dead my eyes would be opened, not closed?)

My favorite medical TV show is: General Hospital, although these days that’s more of a Mobster show, so I’ll go with Grey’s Anatomy in that case :)

8. A gadget I couldn’t live without is: my laptop. I love you, my beautiful Mac! :)

9. The hardest part about nights are: Insomnia. I’m beyond exhausted so much of the time and I’m completely befuddled by the fact that my body won’t let me sleep. I’m too exhausted to watch tv or talk or anything other than to stare into space and still sometimes sleep won’t come! What’s up with that? I don’t need Mr. Sandman to bring me a dream, just a little restorative shut-eye would be nice every once in a while.

10. Each day I take 20+ pills & vitamins. And that’s on a good day. If it’s a rough day or I’m having a cholangitis attack, that number shoots up closer to the 30+ mark and some of those pills I take more than once a day.

11. Regarding alternative treatments: I have tried so many of them. I’d say the one that works the best for me is mindfulness, trying to stay present and enjoying what life has to offer whether that’s a great TV show, a conversation with a friend or even just laughing at my rascal of a cat. Part of mindfulness is also forgiving myself for things I didn’t choose. So, I’m upset when my body won’t let me do what I want, but I work on not dwelling there and instead I search for the good points to whatever the case may be. Oh, and chocolate sometimes helps a lot. :)

12. If I had to choose between an invisible illness or visible I would choose: They both have their drawbacks, right? Nobody wants to look horrible, but I will say that the days when I’m in my wheelchair or exceptionally pale or thin, people do seem to be kinder, more willing to cut me some slack and accept that I’m sick rather than when I’m walking around and feeling horrid but they can’t tell. The “healthy looking days” people tell me I must be feeling well or they think I’m exaggerating how bad things are or even faking the whole thing. It puts me in the position of feeling defensive, which I hate, so I try hard to remember that most people don’t mean anything other than kindness and support. Hopefully that counts as an answer! :)

13. Regarding working and career: I was devastated to lose my job when I became ill. Being in your 30s and unable to work is humiliating, difficult and hard to explain to people whose first question is generally, “What do you do?” I know my body isn’t capable of what it once was and that regular “work” is not an option for me. But I still miss it (or aspects of it) almost every day! But as my friends and family tell me, I do still work. I might not get a paycheck, but the dividends are far greater. Fighting to eradicate PSC and being a part of

PSC Partners fulfills my heart and soul in ways I consider myself truly blessed to experience!

14. People would be surprised to know: I'm pretty much an open book. Hmm, should I worry that I have no mystery left? Um....

15. The hardest thing to accept about my new reality has been: that there's no normality. When most people wake up in the morning, they can expect their day to go a certain way to a certain degree. They expect to have the energy to get out of bed. They expect to be able to keep down their breakfast and remember the word for "car" or "phone." They expect that if they've made plans, even little ones like throwing the wash in the dryer, that they'll be able to accomplish those goals. For a PSCer, we can't count on any of those things. Despite our wants, our bodies sometimes just say no to things we need and want to do. In terms of doing the wash though, my best advice is to screw the laundry and just buy a lot of underwear. I'm a fan of Victoria's Secret myself, but your underwear is your choice. :)

16. Something I never thought I could do with my illness that I did was: Turn it into a

positive. Don't get me wrong, there's PLENTY of suckage with PSC (hmm, I all of a sudden went Pauly Shore mid-90s on that one, huh?). Anyhow, PSC isn't fun and it isn't something I'd wish on even my worst enemy, well . . . :) PSC brings so many negatives it practically requires its own ZIP code, but it can also bring good. In my case, it brought closer, real friendships and focus on the people, issues and things that really matter to me. It brought a realization that my life is mine to choose and I can wallow or laugh or sleep or play or see each day as a new possibility instead of one day closer to not having any more days, which, if you think about it, is a boat we're all in anyhow, might as well enjoy the ride and not drive yourself crazy scrambling for a paddle.

The commercials about my illness: are nonexistent. Hopefully, one day that will change.

18. Something I really miss doing since I was diagnosed is: Hmm, I miss being ridiculously reliable. I miss knowing that if I say I'll be somewhere that I know my body will let me be there and my brain will be on board. As to what do I miss doing, I miss just sitting down to write and

not having to really think and knowing my words would be there for me without my even acknowledging them. Oh, and I miss white water rafting, too. :)

19. It was really hard to have to give up: this idea that I am/was what I do. I had to learn to separate myself from a traditional job-titled society where you're measured by your paygrade and office size or the alphabet soup of letters behind your name. I'm actually still working on this one and I lost my ability to work and my job around 4 years ago now. (By the way, I don't mean to imply anything bad about people who are their work. Let's face it, whatever part of me isn't water and liver disease is entirely PSC Partners, it's just that I had to learn to separate and realize I can be more than just whatever my job title may be. And if you think that's easy or an odd thing to miss, try introducing yourself to somebody new and don't talk at all about what you do for a full 5 minutes. Bet it'll feel like 40!)

20. A new hobby I have taken up since my diagnosis is: Facebook. Oh, Heaven bless Facebook! :)

If I could have one day of feeling normal again I would:

Is it sad that I don't even know? I think the word "normal" should be in quotes in the question above. Who defines normal anyhow?

22. My illness has taught me: Appreciation for what life has to offer. It's taught me to love with a bigger heart and listen on a grander scale. It's taught me that sometimes some of the most wonderful things in the world are born out of some of the most devastating.

23. Want to know a secret? One thing people say that gets under my skin is: Do I have to pick just one? I hate people telling me if I had accepted religion or religious figures properly I wouldn't be sick. I can't stand when somebody tells me they know a "surefire" cure (like rubbing sesame oil on my feet is really going to fix my PSC. Grrr)! I'm annoyed when people offer advice and I thank them and then they still keep pressuring me every single time they see me. Okay, I'm really hung up on the sesame oil lady, but she drives me crazy! I'm horrified when people tell me I must have invited illness in. Why would anyone say such a thing? Oh, I also don't like it when people say the words "moist" or "ooze," but that's just because they sound nasty. :)

24. But I love it when people: remember I'm a person and not just a "sick chick." I love when people laugh with me and show me they care and ask questions because they want answers and not because they're trying to be polite. I love it when people surprise me with their generosity and understanding and I love it when people remember I'm not an only child and that my sister still exists and matters and that my parents are more than just the parents of a chronically ill daughter. I love it when people see me as a person first rather than a sick person and then, if at all, a person.

25. My favorite motto, scripture, quote that gets

me through tough times is: Laugh, don't cry. Is that really narcissistic, to quote myself? It's what I live by though!

26. When someone is diagnosed I'd like to tell them: that they're not alone, they have a hand to hold and a shoulder to cry on and a partner in the millions of battles and wars PSC puts us through on a daily basis.

27. Something that has surprised me about living with an illness is: The irregularity of it all and the expense of it all. Also, the guilt can be a lot to take. All of the sudden, I went from independent to a burden (or potential burden, anyway). It's tough to reconcile all of that guilt.

28. The nicest thing someone did for me when I wasn't feeling well was: There have been so many things, my little sister staying with me in my hospital bed when I couldn't walk or move and literally, physically and emotionally, getting me through the day, my parents spending hours and days in ugly, uncomfortable hospital chairs eating nasty vending machine food, my friends who constantly check in and never make me feel bad when I'm too ill to do something we've planned. There are a million and one reasons to be grateful every single day for all the love headed my way from family and friends, even if sometimes I'm too ill, exhausted or scared to remember that.

29. I'm involved with Invisible Illness Week because: everybody needs to know they're not invisible and that they matter. Because it's horrible to walk into a doctor's office and have them stare at you blankly and say they've never heard of your disease or give you unforgivably wrong information. Because it's our chance as PSCers to tell the real truth about what our lives are like and show others they're not alone and still others that we may be down occasionally,

but we're definitely not out!

The fact that you read this list makes me feel: honored, grateful, and nervous! There's a lot of personal stuff here! :)

From Karen: 30 Things About My Invisible Illness You May Not Know: Some Time in The Life of A PSCer

The illness I live with is: PSC

My sister was diagnosed with it in the year: How long has it been now?

Upon hearing the diagnosis I felt: Scared, confused, but mostly ready to find out what PSC was and what could be done to fight it.

The biggest adjustment I've had to make is: Allowing for more understanding regarding how tired, sick, full of pain, etc., my sister is. I went from the bratty little sister to trying to be more of a support system.

Most people assume: That I grieve daily and I may. However, I do not think about PSC all day every day. In so many ways this disease has allowed a closer bond to form between my sister and me. It has allowed me to see her for the strong and inspiring person that she truly is.

Here's what I usually tell people: PSC is an autoimmune disease that affects the liver and bile ducts and, if you really want to know all the details, go to www.pscpartners.org. Or if somebody asks me the "How is Sandi doing?" question, I usually respond that she is still alive. After being so close to death early on and fighting her way back, I consider the fact that she's still alive a pretty miraculous thing. Maybe it's not the best answer; but it does get frustrating to be asked that question so often, especially since there are good-ish days and bad days, but no real "relief" days.

My favorite medical TV show is: I guess Grey's only b/c Sandi watches it and, therefore, I end up watching it. Otherwise, it probably would've been House. I love me a sarcastic man :)

A gadget I couldn't live without is: my camera. It allows me the outlet I need in life.

The hardest part about living with PSC is: Watching the toll it takes on my family. While there are positives I can see, it is hard to see the years it has added to my parents and the pain and suffering that my sister deals with on a daily basis.

I hope my PSCer knows: How inspired I am by her, all that she deals with and with such a positive attitude and, also, how she has become such a driving force among other PSCers to keep their spirits up and give them a place to vent and let them know they are not alone.

Regarding alternative treatments: I think, why not, what do you have to lose? Of course, it's not my body in this particular case. :)

One thing that surprised me about life with a PSCer is: How much more valuable a laughing fit can be or simply time spent together, although not necessarily the Victoria's Secret runs :)

PSC makes me feel: Angry, upset, bitter. However, PSCers make me feel inspired and amazed.

People would be surprised to know: That while I would never wish PSC on anyone, I can see quite a bit of beauty that this diagnosis has brought into our lives.

I'm embarrassed to admit: That at times I forget how sick my sister is and get annoyed by the fact that she cannot accomplish simple things.

I feel most reassured when: I see that Sandi has been active on Facebook, then I know she's having a good day. :)

The commercials about my illness: What commercials? This is a problem. We need to get the word out there!

Something I really miss doing with my PSCer: Simple things like apple picking, walking around the neighborhood, going to events, seeing her in action in the library, etc. While we can still do these things, it is with much more difficulty for Sandi.

It was really hard to have to give up: That feeling that my sister was always going to be around, that sense of security.

To deal with the bad days I: Usually go to the gym, hike, or kayak, to rid myself of any sadness and/or stress.

If my PSCer could have one day of feeling normal again I'd want them to: Relax, do

anything she wants, even if it was just sitting around watching television enjoying a pain free day. However, I seriously doubt, that sitting around would be her choice activity if that wonderful "normal" day were to come.

This illness has taught me: To appreciate everyone, namely my sister/family and just how strong people can be.

Want to know a secret? One thing people say that gets under my skin is: "How is Sandi doing?" I know this sounds terrible, but I get asked that question 20 times a day by the general public. While I love that so many people care, how lovely would it be if they followed that question up with, "What can I do to help?"

But I love it when people: Take the time to learn what PSC is, ask questions and care enough to get involved.

My favorite motto, scripture, quote that gets me through tough times is: Hmm, not sure I have one. As a general rule, I am not a worrier and that gets me through everything. Why should I worry and cause myself all that stress?

When someone is diagnosed I'd like to tell them: You are not alone. And then I'd direct them to the FB site as well as strongly encourage them to come to the next conference. I look forward to the conference every year. Every PSCer and caregiver should have the experience of being in a room with so many others in a similar situation.

Something that has surprised me about living with an illness is: The positives that come with it. Granted, I'm not the one with the actual disease; but, as mentioned earlier, PSC has made me appreciate my sister and own healthy life even more and it's definitely brought my family even closer.

I know I'm appreciated when: I can make my family laugh. Laughter is one thing that this disease tries to diminish, but as Sandi always says, "You can laugh or cry. So, choose laugh."

I'm involved with Invisible Illness Week because: I love my sister and the many other PSCers I have met.

The fact that you read this list makes me feel: It doesn't make me feel any certain way, but hopefully it makes other caregivers feel less alone.

For those that are interested, these lists were made without any input from the other and only combined together once we'd each individually completed them...oh, and I think I've officially been outed for my obsession with Victoria's Secret. :)

**PSCEer: the loved one of a PSCer. The E in PSCEer stands for either empathy or envy depending on the situation.*

FEATURING: SANDI!

Your favorite PSC columnist, Sandi Pearlman, was featured in the Fredericksburg (VA) *Freelance-Star* in early October. The article focused on Sandi, her fight with PSC, and how she copes with life.

"Sick but Determined Woman Reaches Out" quotes her as well as liver specialists. It's a good informational article about living with PSC. Sandi's upbeat attitude comes through.

The article is on our website and here's the URL: <http://www.pscpartners.org/donate>.



Calling All Potential 2012 Conference Hosts

Here's your chance to hold the 2012 Conference in your hometown. If you might be interested in being our co-host for the 2012 conference, please click on: <http://www.pscpartners.org/conferencelocations>.

After you have gathered all the necessary information, please fill in our online form and return it to Ricky Safer no later than January 15, 2011. If you have any questions, please write to her at contactus@pscpartners.org.

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Note: Donors who achieve a PSC Partners Foundation Level Sponsorship may be listed twice in this acknowledgement list.

Thanks to Those Who Organized Successful Letter Writing Campaigns!

We know it's up to us to fund research for PSC, and one fantastic way is through letter writing campaigns. Writing to friends, family, and colleagues, can bring in contributions to support our research and educational programs.

These members raised a lot through several letter campaigns and we're grateful for their efforts:

Sheldon and Robin Wohl

Deb Wente

Joanne Hatchett

Jill Dittrich

Cindy Rogers

Karen Pearlman

Eileen Pearlman

Transplant Center

Donate Life America Survey Results Indicate Improving Support for Organ Donation

An online survey of 5,100 adults in January 2010, found that increasing numbers of Americans favor organ donation:

- ◆ Three fourths of adults want their donation wishes followed, regardless of family desires.
- ◆ More than three fourths of adults know there are fewer organs donated than are available.
- ◆ Unfortunately, almost half of participants incorrectly believe there is a black market in the US where people can buy or sell organs.
- ◆ Nearly 37 percent believe, however, that the allocation system for organs is fair.

Note to Readers:

Articles in this newsletter have been written by persons without formal medical training. Therefore, the information in this newsletter is not intended nor implied to be a substitute for professional medical advice.

Please consult with your doctor before using any information presented here for treatment. Nothing contained in this newsletter is intended to be for medical diagnosis or treatment. The views and opinions expressed in the newsletter are not intended to endorse any product or procedure.



PSC Partners Seeking a Cure is a 501(c)3 nonprofit foundation that endeavors to find a cure for Primary Sclerosing Cholangitis.

The three-fold purpose of the **PSC Partners Seeking a Cure** foundation is to: raise funds for research on the causes and cures of PSC, promote PSC and organ donation awareness, and provide education and support to PSC patients and their families.

Ricky Safer is the principal contact person for the PSC Partners Seeking a Cure Foundation. Reach her at: contactus@pscpartners.org

Tax-deductible donations can be sent to: PSC Partners Seeking a Cure, 5237 South Kenton Way, Englewood, CO 80111 with a check made out to: PSC Partners Seeking a Cure.

Website

www.pscpartners.org

PSC Partners Seeking a Cure Board Members

Dike Ajiri, Lee Bria, Tom Butler, Becky Long, Dr. Gregory Everson, Rachel Gomel, Joanne Grieme, Chris Klug, Scott Malat, David Rhodes, Ricky Safer, and Deb Wentz

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The Duct Newsletter

Editor: Pat Bandy (newsletter@pscpartners.org)

Contributors to this issue: Pat Bandy, Meegan Carrey, Mele Ohuafi, Karen Pearlman, Sandi Pearlman, Julianne Vasichek, David Rhodes, Ricky Safer