PSC Partners Seeking a Cure Newsletter

Vol. 2, Issue 1, February 2006

Edited by David Rhodes and Ricky Safer

www.pscpartners.org

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

In This Issue:

Don't Miss Our Exciting Weekend in Pittsburgh!

Here's your chance to meet other PSC partners and get a new medical perspective from top PSC experts. Joanne Grieme has firmed up plans for our second annual conference for PSCers and caregivers which will take place in Pittsburgh from April 7-9, 2006. If you haven't signed up yet, please look at our incredible agenda and then log onto our home page at **www.pscpartners.org** for conference registration materials.

If you are planning to attend, but you haven't made your reservations at the hotel, please reserve now by contacting the Pittsburgh Marriott City Center online at:

http://www.stayatmarriott.com/PSC

or by calling 1 800 228-9290 and asking for the special group rate with our group code PPSPPSA. We have set aside a block of rooms at the special group rate of $89 per room per night. Once our block of rooms is filled, the Marriott will try to extend the special rate, but they can't promise this, so please reserve soon if you plan on coming. The weekend schedule is shown on page 2.

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Second Annual PSC Partners Seeking a Cure Conference Agenda

Friday April 7:

- 5:00 - 7:30 pm: Registration and Welcome Reception

Saturday April 8:

- Continental Breakfast (7:00-8:00 am)
- Opening Remarks (8:00-8:10 am) : **Don & Ricky Safer**, PSC Partners Seeking a Cure Foundation
- Presentation One (8:10-8:40 am) : PSC - An Overview - Keynote Speaker, **Dr. Keith Lindor,** Mayo Clinic, Rochester, MN
- Presentation Two (8:40-9:05 am) : Role of the Endoscopist - **Dr. Adam Slivka**, UPMC
- Presentation Three (9:05-9:30 am) : Itching in Cholestasis - **Dr. Nora Bergasa**, SUNY Downstate Medical Center
- Question & Answer Panel (9:30-10:15 am) : Above Three Speakers
- Break (10:15-10:30 am)
- Presentation Four (10:30-10:50 am) : Medical Management of PSC - **Dr. Kapil Chopra**, Mayo Clinic, Phoenix
- Presentation Five (10:50-11:10 am) : Transplant Workup & Outcomes - **Dr. Thomas Shaw-Stiffel**, UPMC
- Presentation Six (11:10-11:30 am) : Liver Transplant - **Dr. Kusum Tom,** Starzl Transplantation Institute
- Question & Answer Panel (11:30-12:15 pm) : Above Three Speakers
- Box Lunch (12:15-1:15 pm)
- Presentation Seven (1:15-1:35 pm) : IBD in PSC Patients - **Dr. Leonard Baidoo**, UPMC
- Presentation Eight (1:35-1:55 pm) : Nutrition for PSC and IBD - **Dr. Laura Matarese**, UPMC
- Presentation Nine (1:55-2:15 pm) : Update on PSC Research - **David Rhodes**, PSC Partners Seeking a Cure Foundation
- Question & Answer Panel (2:15-2:45 pm) : Above Three Speakers
- Break (2:45-3:00 pm)
- Breakout Sessions: Session 1 (3:00-3:30 pm) *Pick 1*
    * Quality of Life for Children with a Chronic Illness - **Dr. Robert Noll,** Children's Hospital of Pittsburgh
    * Organ Allocation - How the Process Works - **Nance Conney**, Starzl Transplantation Institute
    * Meditation - **Dorit Baurer**
- Breakout Sessions: Session 2 (3:35-4:05 pm) *Pick 1*
    * Stress Management - **Jerry DeNucci,** Highmark Blue Cross
    * Disability/Social Security - **Glenn Sinko**, Esq.
    * Organ Allocation - How the Process Works - **Nance Conney**, Starzl Transplantation Institute
- Evening Dinner Reception (6:00-8:00 pm) : **Chris Klug**, PSC Patient, Transplant Recipient, Olympic Medalist - To the Edge and Back

Sunday April 9:

- Continental Breakfast (7:30-8:30 am)
- Presentation (8:30-9:00 am) : Update on Dr. Chapman's Research, **Ivor Sweigler**, PSC UK Support Group
- Roundtable Discussions (9:00-10:15 am)
- Break (10:15-10:30 am)
- Roundtable Discussions (10:30-11:45 am)
- Closing Remarks (11:45-12:00 pm) : **Don & Ricky Safer**, PSC Partners Seeking a Cure Foundation

This will likely be the last announcement about this conference in our newsletter. Please visit: **http://www,pscpartners.org/Conf2006.htm** for last minute changes to the agenda.

From the AASLD web site: **https://www.aasld.org/eweb/DynamicPage.aspx?webcode=SS_Relatedmeetings**

PSC (Primary Sclerosing Cholangitis) Partners Seeking a Cure will host the organization's 2nd Annual Conference April 7-9, 2006, in Pittsburgh, Pennsylvania. Further information: Joanne Grieme, **jgrieme@zoominternet.net**

COUNTDOWN TO PITTSBURGH

I can't believe that in less than two months, our second annual conference will start in Pittsburgh! Joanne Grieme and her committee have done a phenomenal job in planning an outstanding selection of speakers and a fantastic agenda, including time for us to get together informally and share our experiences, questions, answers, advice, and concerns with each other. I, personally, am looking forward to seeing all of our PSC family who came to last year's conference in Denver, and to meeting all the new PSCers and caregivers who will attend this year. It is an uplifting weekend and a true highlight of my year.

If you haven't registered for the conference yet, and are considering it, please log onto our website (**www.pscpartners.org**) and click on "2006 Conference" to view the agenda and registration information. All meals are included in the price of registration.

Dr. Thomas Shaw-Stiffel has put together a star-studded group of speakers from the University of Pittsburgh Medical Center and the Starzl Transplantation Institute. We are especially pleased that Dr. Keith Lindor of the Mayo Clinic in Rochester, Minnesota will be our keynote speaker. Dr. Nora Bergasa, of the SUNY Downstate Medical Center is an expert on pruritus, and she has some new suggestions for many of us. Chris Klug is back again this year, as our keynote speaker at Saturday's dinner. (Check out "Chris Klug Foundation" on our homepage.) One change from last year is the addition of breakout sessions on Saturday afternoon, where you have a choice of sessions to attend. For parents of PSCers, we have included a session focusing on issues for children and young adults. When you look over the agenda, I think you will find something special for everyone. If you have any questions, feel free to contact:

Joanne at **jgrieme@zoominternet.net**
or Ricky Safer at **pscpartners@yahoo.com**

Here are a few general updates from PSC Partners Seeking a Cure:

- On January 5, Arne Myrabo posted some interesting historical information on the PSC online support group. Thanks to Tiffany's foresight, the online group was started in December 1998 with a total of twelve members. Our numbers keep increasing. In 2005, 322 new members joined, giving us a total of 978 registered online members. To quote Arne, "The point is, this is a great group with a tremendous amount of experience. YOU ARE NOT ALONE."

- This is another reminder that our PSC Partners Seeking a Cure brochures are available at no charge to anyone who would like to order them. Log onto our homepage to view the text of the brochure and for instructions on ordering the brochures from Barb Henshaw at:

  pscbrochures@yahoo.com

- Paula Marquardt, one of our online members, is planning a scrapbooking fundraiser for PSC Partners on May 6 at the Ephrata Recreation Center in Ephrata, PA. For more information, please contact Paula at **cmpaula@verizon.net**

- We need your help! Elissa Deitch, who has been our trusted and invaluable legal advisor, needs to step down at the end of May, when her second baby will be born. The pressures of raising two young children and continuing her legal job will fill up all her time. Her shoes are tough to fill, but if you know of a lawyer who is interested in our cause, and who might be willing to be our legal advisor or to share the load, please contact me at **pscpartners@yahoo.com**

- We greatly appreciate every donation that we receive, as they all move us closer to our goal of funding a research project, hopefully before the end of 2006. Two donations that we received in the past month have especially touched my heart.

  - We received a donation from Denver Robinson in Denmark, in memory of his wife Mette Terslose, who passed away of complications of PSC five years ago. Denver created a website in his wife's memory, and he is a very sensitive and expressive writer. Denver's dream years ago was to create a PSC foundation. When he recently found out about PSC Partners Seeking a Cure, he wrote: "I was immediately stunned by the great progress that has been made for PSCers in the last five years."

  - The daughter of one of Lee Bria's friends had an assignment for one of her college classes to speak about a non-profit organization. Afterwards, we received a lovely donation and letter from her instructor at Indiana University. "One of my Business and Professional Communication students at Indiana University spoke so eloquently and persuasively about your organization that my husband and I were moved to send a donation. Although we wish it could be more, we hope that it may help get the word out about this disease. Your organization's history is inspiring, and we hope that your mission is successfully continued in the new year."

I am encouraged to see that awareness of the goals of PSC Partners Seeking a Cure is becoming more widespread.

Sadly, it seems like many of our new members are parents whose children are dealing with PSC and IBD. I just wanted to point out that last September, the Crohn's and Colitis Foundation of America (CCFA) sponsored an important research conference focused exclusively on issues in pediatric IBD, titled"Pediatric Challenges." It was a forum for 30 leading physicians and scientists to clarify issues and set a five year agenda for pediatric IBD research. For more information about this, log onto their website at **www.ccfa.org**

Before ending, I want to mention the deep loss and profound sadness that we all are feeling after the untimely deaths of Melanie Caldwell Quinn and Bill Colfer, Jr. Our condolences go out to their families and friends. Losses such as these motivate me to work harder in our fight against PSC, whatever it takes. Hoping to see you in Pittsburgh!

Ricky Safer

Northern California PSCers Learn About Research and Donate Blood Samples

by Jennifer Soloway

On January 7, 2006, PSC researchers at University of California Davis met with about 40 PSC and PBC patients, friends and families. Doctors discussed their PSC research projects. They also recruited people with PSC and people without the disease to give blood samples for research. Finally, PSC patient Jennifer Soloway passed out the PSC Partners brochure and talked about sources of support and information. Fourteen people signed up for a new support group she is organizing in Northern California.

Doctors also answered audience questions. In response to questions on liver transplant, Dr. Christopher Bowlus said that PSC/PBC patients have the best outcomes after liver transplant compared to any other category of transplant patient. He also estimated that about 20% of PSC patients will develop PSC recurrence after transplant, but that post-transplant PSC usually progresses slowly. He pointed out that bile duct damage due to other causes can mimic PSC, and so post-transplant PSC diagnosis may not be accurate. Unfortunately, there was not time for a detailed presentation on transplants.

Dr. Bowlus is a hepatologist and Associate Professor of Medicine at U.C. Davis. He started off the meeting going over consent forms for subjects in two UC Davis studies; "The Molecular Basis of PSC" and "The Molecular Basis of Autoimmune Disease." About 20 PSC and PBC patients signed the consent forms and gave samples of blood during the meeting. Family members and friends also donated blood to be used as controls.

Dr. Bowlus explained that we need to understand PSC in order to improve diagnosis. There is no specific blood test, and so doctors making a diagnosis must piece together information from ERCP, MRCP and other tests. We also need to develop prognostic models so that we can predict the course of the disease. The final goal is to design and test new treatments. In comparison, there is a reliable blood test for PBC and after many years of research, trials for new PBC treatments are beginning.

The cause of PSC is partly genetic, partly immunological and partly environmental. But doctors still don't know how these factors combine to cause PSC. The interactions are complex. Some combinations of genetic, immune and environmental factors protect one person from getting PSC, and some other combinations cause another person to get PSC. But scientists have only identified a few of the risk and protective factors and have yet to understand how these factors balance off each other.

Dr. Bowlus is the lead scientist on the study of "The Molecular Basis of PSC". He is interested in comparing the genes of PSC patients with those who do not have PSC. He is also establishing a PSC Patient Registry and Serum/DNA Bank to assist with future PSC research at UC Davis and other research institutions.

In order to help the audience members understand genetic research and PSC, he presented a brief course in Genetics 101. We all carry two sets of chromosomes; one from dad and one from mom. The chromosomes are made of DNA. DNA is a long string of "nucleotides." Nucleotides are made of one molecule of sugar, one molecule of phosphorus and one "base". A DNA "base" is one of four chemicals; adenine, thymine, guanine, and cytosine (A, T, G, C). A, T, G, and C are the "letters" that spell out the genetic code. The sequences of bases in DNA form the "genetic blueprint" for each individual. Each string of DNA contains billions of nucleotides. The sequence varies between individuals about every 300 bases. So, there are numerous differences in the DNA in different individuals.

Genes are segments of DNA. They are the "sentences" made up of the DNA sequence letters (A, T, G, and C). The DNA gene sequence provides the instructions for (encodes) a single protein structure. Genes transmit "traits" from parents to children. Traits can include characteristics including eye and hair color, height etc. Traits can include diseases such as Cystic Fibrosis and Sickle Cell Anemia. Simple traits are those transmitted in DNA of a single gene. Complex traits result from the interaction of several genes.

Simple traits can result from recessive or dominant inheritance. For diseases caused by recessive inheritance, two copies of the defective gene (both parents are carriers) are required for a child to have the disease. Cystic Fibrosis is a disease transmitted by recessive inheritance. If a disease is caused by dominant inheritance, only one copy of the defective gene (only one parent is a carrier) is necessary for a child to have the disease. Huntington's Disease is transmitted by dominant inheritance.

If a disease is caused by complex genetics, the fact that a parent has the disease may increase the risk of disease,

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but no one gene from the parent is sufficient or required for a child to have the disease. People get PSC because of complex genetics combined with environmental factors. Researchers must look for a number of genes that may increase the likelihood of having PSC. One part of the search is to compare genes of people with PSC to controls (relatives or non-relatives who do not have PSC).

For example, suppose that gene "A" is more prevalent in PSC patients than in controls, and therefore might affect getting the disease. But this finding is only a starting point for research because "A" alone is not solely responsible for causing PSC and may not be required for every person to get PSC (people may still get PSC without the "A" gene.) In addition, these types of studies often find associations with genes that are not really involved in developing the disease. Most researchers agree that multiple studies must duplicate an association for it to be confirmed as a true association. Dr. Bowlus spent the summer in Norway trying to replicate a previous association found in the UK, unfortunately without success.

Norway is a good place to make genetic comparisons between PSC patients and controls for many reasons. There is a relatively large PSC population in Norway; nearly 400 patients have been identified. Also, most people in Norway are native Norwegians. With this homogeneous population, there are a limited number of ancestral chromosomes and so comparisons between PSC patients and controls are easier to make.

In contrast, this type of genetic research is particularly difficult in the U.S. because of the diverse population and the constant immigration of new populations into the country, which increases the gene pool diversity. People from all ethnic groups get PSC. This diversity makes it difficult to find appropriate controls that can be compared to PSC patients.

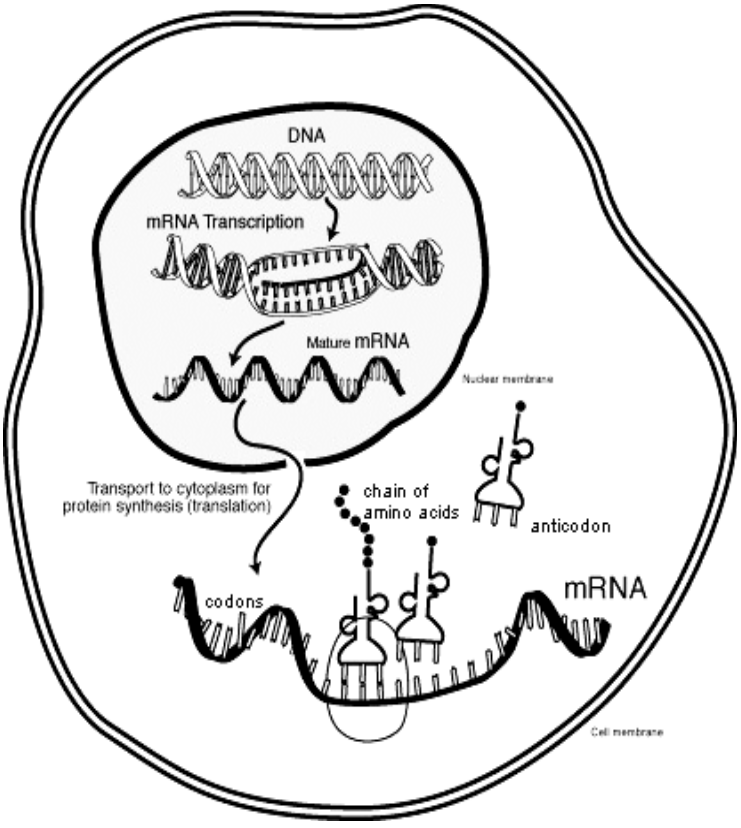
U.C. Davis is starting a PSC DNA/serum Bank to obtain and preserve genetic data from the diverse population of Northern California. In about 6 months, 72 PSC patients have been identified and most have agreed to participate. Dr. Bowlus is working with other research centers to recruit more patients and controls for the DNA Bank. Siblings and parents of PSC patients make the best controls, but genetic information from children of patients and non-relatives is also useful.

The next speaker, Dr. Christopher Aoki, summarized his research, which focuses on PSC and the immune system. He explained that our immune system is designed to identify and eliminate foreign objects that are harmful to the body (antigens). In autoimmune disease, the immune system fails to distinguish antigens from our own proteins and attacks certain parts of the body as if they were antigens.

Autoimmune disease can be identified by direct evidence, indirect evidence or circumstantial evidence. There is only circumstantial evidence that PSC is an autoimmune disease. This evidence includes:

- Patients with PSC have higher incidences of known autoimmune disease (UC, Crohn's and other autoimmune diseases).
- Patients with PSC have similar codes on their genes important to the function of their immune system.
- Patients with PSC have a high amount of antibodies that attack normal human tissue.
- On liver biopsies, the cells that are important to the immune system are found near areas of inflammation.
- There are some case reports that immunosuppressants may be beneficial in patients with PSC.

Dr. Aoki pointed out that PSC has been designated an "orphan" disease because it is relatively rare, little is



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known about it, and there are very few investigators in the field. His approach to learning more about the disease is to look at the immune system.

He recently completed a study of peripheral blood mononuclear cells, which are a broad group of cells that are active participants in the immune system. DNA, which exists in the nuclei of most cells, contains instructions for making proteins and this information is transmitted by messenger RNA (mRNA). RNA is a molecule very similar to DNA. The mRNA moves out of the cell nucleus and into the cell's cytoplasm where a protein is made following the DNA's instructions. Dr. Aoki collected blood from people who have and from people who do not have PSC and isolated mRNA from peripheral blood mononuclear cells. This mRNA was screened on a chip that can detect abnormal expression of over 50,000 different known mRNA sequences. Dr. Aoki did not summarize the preliminary findings of this study, but preliminary data were presented at an American Association for the Study of Liver Disease conference and confirmation/publication is currently underway. The results of this study give us clues to possibly important genes and proteins that may be involved in PSC, which may lead to better diagnostic tools or possible targets for therapy in the future.

Because autoantibodies are circumstantial evidence of autoimmune disease, Dr. Aoki is studying the autoantibody most common in PSC patients; p-ANCA. It is unknown if p-ANCA is important to disease or if it is merely a marker of the disease. Dr. Aoki is trying to find the antigen that triggers the p-ANCA autoantibody. Finding the antigen may make it easier to prove the importance or lack of importance of p-ANCA to PSC.

Dr. Hershan Johl, a hospitalist, was the last speaker. He is studying non-genetic causes of PSC. These could include, among other things, environmental exposures, diet and infections. Environmental studies would attempt to identify who exactly is at risk and how risk factors affect the course of PSC. He noted that very little is known about environmental conditions that might affect PSC. We know that smoking reduces the risk of getting PSC but, because of the severe health risks of smoking, doctors urge PSC patients not to start smoking. Trials using nicotine to treat PSC showed no benefit.

A small study done in the UK concluded that tonsillectomy may reduce risk of PSC and that appendectomy may increase the risk of PSC, but delay onset of ulcerative colitis.

Dr. Johl explained how the PSC registry at UC Davis will be a useful tool for studying environmental effects on PSC. The registry will include a representative U.S. population, drawing a diverse group of PSC patients from Northern California. Information can be gained on how PSC progresses, helping with development of a prognostic model. Information can also be obtained to help identify environmental risk factors for developing PSC and altering its progression.

The meeting adjourned for lunch and blood sample donations. Two major messages can be drawn from the presentations. The first is that research at UC Davis is at a basic level. Researchers are now getting information that will lay the foundation for future research. The second is that it is essential for as many patients as possible to participate in PSC research. Existing patient cohorts are very small and are not ethnically diverse. The more PSCers participate in PSC studies, patient registries and DNA/serum banks, the more reliable results will be, and hopefully effective treatments will come sooner. If you would like to participate in the UC Davis PSC Patient Registry, kits are available for shipping samples, as there is no geographic limitation. Please contact Marcy Crees at: **mlcrees@ucdavis.edu**

PSC Patients Blood Samples Needed for Research

There is a serious shortage of subjects for PSC research. The more PSCers participate in research, the more reliable the results and the more likely treatments will be found.

Please donate blood samples to both the Mayo Clinic and University of California Davis research projects.

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U.C. Davis has a established a PSC Patient Registry and DNA/Serum Bank that will be available to all researchers. To participate, contact Marcy Crees at:

mlcrees@ucdavis.edu

People without PSC may also participate as controls. Siblings and parents make the best controls. UC Davis will provide kits for sending blood samples, as there are no geographic limitations.

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Mayo Clinic is also collecting blood samples for genetic research. Data will be available for other researchers. PSC patients who want to participate should log on to:

http://clinicaltrials.mayo.edu

and type PSC in the search box.

Mayo Clinic will provide kits for sending blood samples, as there are no geographic limitations.

Fundraising Update

Thank you to everyone who helped us get our fundraising off to a flying start in 2005.

Our Kroger program is winging its way to the $2,000 mark. As of Dec. 31, 2005, we have brought in $1,788.38 from our combined grocery shopping. So far we have purchased a combined total of over $35,000 in groceries from Kroger! This is a great total considering that we did not start this amazing fundraiser until June of 2005. Just imagine what we can do this year! Want to help? If you or someone you know can use a Kroger rechargeable grocery card, just email me at: **ldbria@comcast.net**. We have only just started this program and already this has added $100.00 of lift beneath our foundation wings.

Do you shop at a Hiller's Market? We also have a small program with a local grocery store here in Ann Arbor called Hillers. Their program also gives 5% on groceries but has not yet gone to plastic gift cards. Right now they use paper certificates, but if you happen to live and shop in my area , I would be happy to get some Hiller grocery certificates to you. This was an additional lift to the foundation of $75.00 in 2005.

Walkers for PSC needed! Our first annual walk is here!

Our 2006 Virtual Walk is here and we are looking for walkers to join us in the fight to beat PSC. So far we have 32 registered walkers with more promised to come. It's fun and it's easy. Registration is $20.00 and you will receive a kit with everything you need to join us. The kit comes with your blank slate , a plain white tee shirt with a burgundy PSC Partners Seeking a Cure printed on it, and a black permanent marker. [Be bold! Add some color markers!] You also receive a set of directions, signature sheets and a return envelope for donations.

We are walking our shirts through our neighborhoods, local businesses and the workplace. Each person can donate any amount and sign with the permanent marker on the shirt. Donations will help us raise money for research and all the signatures will be a show of support to our members. If you are coming to our conference in Pittsburgh, please bring your shirt to display. If you can't attend the conference, please send us a picture of your shirt to display. What a morale booster this will be! If you can't get out to gather signatures, consider writing an inspiring message on your shirt with your signature so that we can add your message of support to our display.

This one is for everyone. All can participate and help the fight against PSC. Please see our website **www.pscpartners.org** for the registration form. Register before Feb. 25th so that I can be sure to have enough shirts. Questions? You can call me at 734-665-7999 or email me at **ldbria@comcast.net**

I can't wait to see all the familiar faces in Pittsburgh from last year and to meet all the new members who have joined us.

Lee Bria

News About Our Recycling Fundraising Effort:

Our AAA Environmental program has raised $272.42 through December. You have sent in 333 ink jets, cell phones and laser printers, of which 268 have earned money for us. This is a remarkable job done by those who have participated in this venture. Thank you for working together in this fight. The “whatever it takes” part is the $272 dollars that will be earmarked for research towards a cure. A reminder to everyone of our 1000 members; it does not cost any of us to raise this money. The hardest job you will have with recycling will be sealing the envelopes and walking to your mail box. So if you have already participated in this effort, please continue to do so, and to those of you new to the group, please look around the office or ask your neighbors for an ink jet or cell phone donation. You can order your self addressed, postage paid envelopes from:

www.aaaenvironmentalinc.com

or call them toll free at 866-332-2234 and please give them our code **PSCPARTNE001** (no breaks in the spelling please and no R at the end.) Just a reminder, no Epson cartridges can be used, and the Laser Printer Cartridge program has been suspended for the time being. If you have been collecting these, please hold on to them until further notice.

Tim Wholey

Time to Stock Up on Wristbands -- April is National Donate Life Month!

One of the easiest ways to promote awareness and raise money for PSC Partners Seeking a Cure is selling our wristbands. With "Give Life" imprinted on the green bands, they are a hot and meaningful fashion accessory for Spring. You can order them by going to **www.pscpartners.org** and clicking on wristbands. They cost $2.00 each plus shipping and handling. Larger quantities are available at a discounted price.

Dana Miletic

Good news! As another donation vehicle, we have opened a brokerage account at LPL Financial Services. Now, in addition to your cash gifts to PSC Partners Seeking a Cure, you can gift appreciated stocks which we can then sell and turn into cash. The tax benefit to you is enormous. Let’s say, for example, you bought 100 shares of XYZ at $10 per share, and it has now appreciated to $30 per share. Instead of selling it and paying capital gains taxes on the $2,000 profit, you can transfer the shares electronically to our account at LPL. You can then take a tax deduction for the full market value of the security on the date of transfer WITHOUT incurring any capital gains tax. Here’s how to do it. Just instruct your broker to use the following wire transfer instructions for the securities you wish to donate:

Linsco Private Ledger DTC #0075
For credit to: PSC Partners Seeking a Cure
LPL account #7392-9459

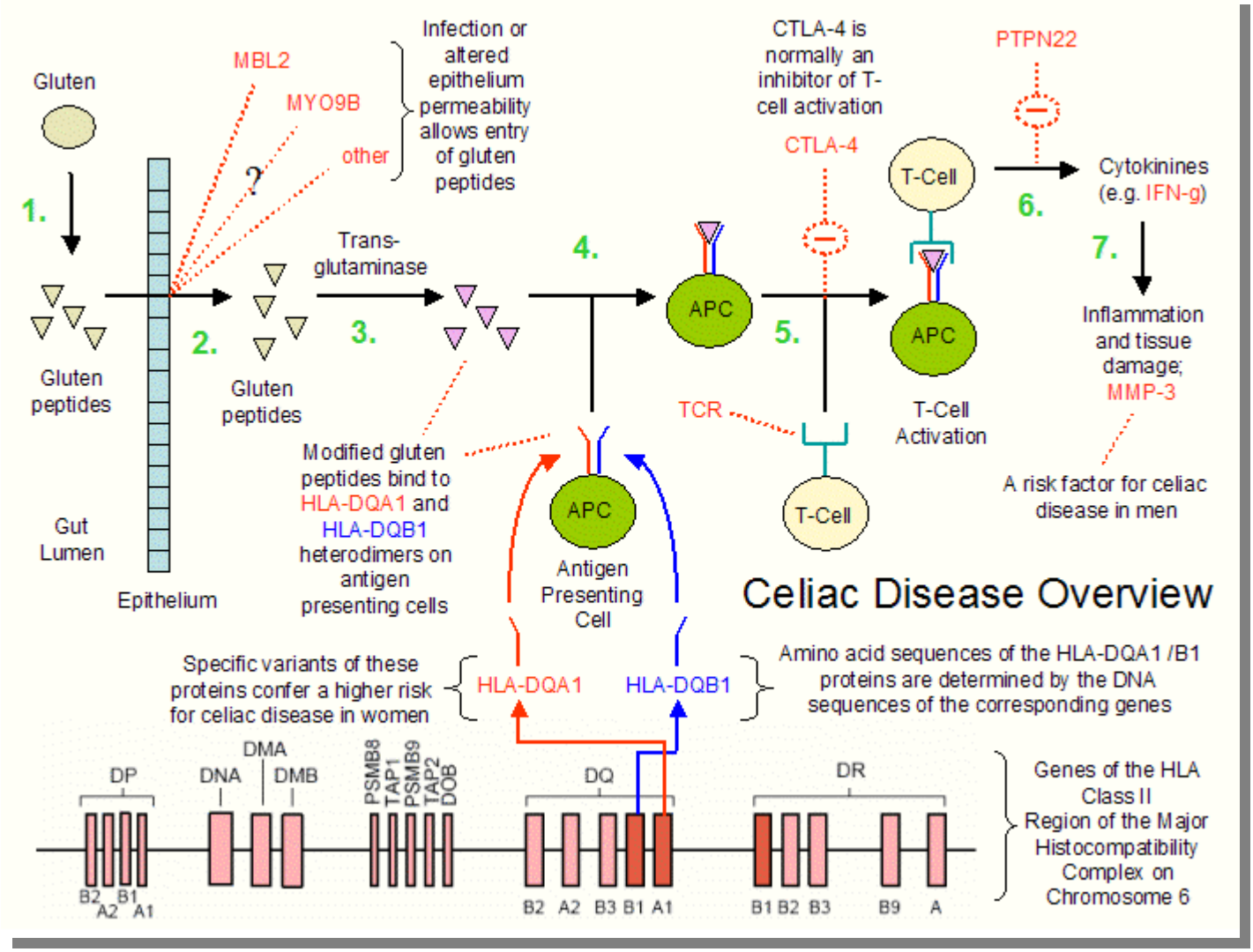
As always, please consult your tax advisor before making contributions of securities. Thank you again to all our donors who continue to support us in our fight against PSC.

Ricky Safer

Autoimmune Disease Articles: Celiac Disease (continued)

by David Rhodes

We started this series of articles in the last issue of this newsletter (Vol. 1, Issue 10; December 2005) with a narrative consideration of celiac disease. Here we present a simplified cartoon describing the key steps and major players thought to be involved in celiac disease. This will serve as a framework for considering rheumatoid arthritis in our next issue.



Key Steps

1. Gluten is digested into small peptides.

2. Infection, or a genetic defect in intestinal membrane permeability, allows gluten peptides to cross the epithelium.

3. The gluten peptides are acted on by trans-glutaminase, which converts the peptide glutamine residues to glutamate residues, making them more immunogenic.

4. The modified gluten peptides bind to HLA-DQA1/HLA-DQB1 heterodimers on antigen presenting cells (APC).

5. The APC present gluten peptides to T-cells, which then become 'activated'. This process is normally inhibited by CTLA-4, which acts as a 'brake' on T-cell activation.

6. Activated T-cells produce cytokines (e.g. interferon gamma (IFN-g)) which then trigger inflammation. These steps are greatly simplified in this diagram.

7. Inflammation can enhance the prduction of matrix metalloproteinases (MMPs), which cause further tissue damage.

Key Players

HLA-DQA1 and HLA-DQB1

Specific variants of these genes produce proteins that have an ability to bind to modified gluten peptides. The modified gluten peptides are presented to **T cells** by antigen presenting cells (**APC**).

Kagnoff MF 2005 Overview and pathogenesis of celiac disease. Gastroenterology 128: S10-S18.

MBL2

The mannose binding lectin gene (MBL2) has been implicated as a celiac disease susceptibility gene.

Boniotto M, Braida L, Spano A, Pirulli D, Baldas V, Trevisiol C, Not T, Tommasini A, Amoroso A, Crovella S 2002 Variant mannose-binding lectin alleles are associated with celiac disease. Immunogenetics 54: 596-598.

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The mannose-binding lectin may determine susceptibility to a number of infectious diseases:

Eisen DP, Minchinton RM 2003 Impact of mannose-binding lectin on susceptibility to infectious diseases. Clin. Infect. Dis. 37: 1496-1505.

MYO9B

The myosin IXB (MYO9B) gene has recently been reported to be associated with celiac disease susceptibility.

Monsuur AJ, Bakker PI, Alizadeh BZ, Zhernakova A, Bevova MR, Strengman E, Franke L, Slot RV, Belzen MJ, Lavrijsen IC, Diosdado B, Daly MJ, Mulder CJ, Mearin ML, Meijer JW, Meijer GA, Oort EV, Wapenaar MC, Koeleman BP, Wijmenga C 2005 Myosin IXB variant increases the risk of celiac disease and points toward a primary intestinal barrier defect. Nat. Genet. 37: 1341-1344.

However, a follow-up study was unable to confirm this association:

Hunt KA, Monsuur AJ, McArdle W, Kumar PJ, Travis SP, Walters JR, Jewell DP, Strachan DP, Playford RJ, Wijmenga C, van Heel DA 2006 Lack of association of MYO9B genetic variants with coeliac disease in a British cohort. Gut Jan 19 [Epub ahead of print].

Transglutaminase

The enzyme transglutaminase is responsible for modifying gluten peptides to make them more immunogenic. So far, however, polymorphisms in the transglutaminase gene have not been detected that might be responsible for celiac disease susceptibility:

Aldersley MA, Hamlin PJ, Jones PF, Markham AF, Robinson PA, Howdle PD 2000 No polymorphism in the tissue transglutaminase gene detected in coeliac disease patients. Scand. J. Gastroenterol. 35: 61-63.

TCR

Polymorphisms in the T-cell antigen receptor (TCR) genes have so far not been observed to be associated with celiac disease:

Roschmann E, Wienker TF, Gerok W, Volk BA 1993 T-cell receptor variable genes and genetic susceptibility to celiac disease: an association and linkage study. Gastroenterology 105: 1790-1796.

CTLA-4

The cytotoxic T lymphocyte antigen-4 (CTLA-4) gene is strongly implicated as a celiac disease susceptibility gene. See for example:

Mora B, Bonamico M, Indovina P, Megiorni F, Ferri M, Carbone MC, Cipolletta E, Mazzilli MC 2003 CTLA-4 +49 A/G dimorphism in Italian patients with celiac disease. Hum. Immunol. 64: 297-301.

King AL, Moodie SJ, Fraser JS, Curtis D, Reid E, Dearlove AM, Ellis HJ, Ciclitira PJ 2002 CTLA-4/CD28 gene region is associated with genetic susceptibility to coeliac disease in UK families. J. Med. Genet. 39: 51-54.

Djilali-Saiah I, Schmitz J, Harfouch-Hammoud E, Mougenot JF, Bach JF, Caillat-Zucman S 1998 CTLA-4 gene polymorphism is associated with predisposition to coeliac disease. Gut 43: 187-189.

There is evidence that the CTLA-4 gene encodes a protein that acts as a 'brake' on T-cell activation, and this would explain the involvement of CTLA-4 in a number of different autoimmune diseases:

Pearce SH, Merriman TR 2006 Genetic progress towards the molecular basis of autoimmunity. Trends Mol. Med. Jan 10 [Epub ahead of print].

Gough SC, Walker LS, Sansom DM 2005 CTLA4 gene polymorphism and autoimmunity. Immunol. Rev. 204: 102-115.

PTPN22

The PTPN22 gene has received much attention in the last 12 months because variants of it have been found to be associated with a number of autoimmune diseases.

Brand O, Gough S, Heward J 2005 HLA , CTLA-4 and PTPN22: the shared genetic master-key to autoimmunity? Expert Rev. Mol. Med. 7: 1-15.

It is thought to encode a phosphatase that normally acts as a 'brake' on T-cell signaling. However, thus far, it has not been linked to celiac disease:

Rueda B, Nunez C, Orozco G, Lopez-Nevot MA, de la Concha EG, Martin J, Urcelay E 2005 C1858T functional variant of PTPN22 gene is not associated with celiac disease genetic predisposition. Hum. Immunol. 66: 848-852.

IFN-g

Interferon-gamma (IFN-g) is implicated in the early signalling events in activated T-cells that result in inflammation.:

Nilsen EM, Jahnsen FL, Lundin KE, Johansen FE, Fausa O, Sollid LM, Jahnsen J, Scott H, Brandtzaeg P 1998 Gluten induces an intestinal cytokine response strongly dominated by interferon gamma in patients with celiac disease. Gastroenterology 115: 551-563.

Some evidence suggests the involvement of the IFN-g gene as a celiac disease susceptibility gene:

Rueda B, Martinez A, Lopez-Nevot MA, Mas-Fontao A, Paco L, Ortega E, Fernandez-Arquero M, Urcelay E, Concha EG, Martin J 2004 A functional variant of IFNgamma gene is associated with coeliac disease. Genes Immun. 5: 517-519.

MMP-3

The matrix metalloproteinases (MMPs), such as stromelysin-1 (MMP-3), are a family of enzymes important in resorption and remodeling of the extracellular matrix. The degradation of this matrix may play a role in the villous atrophy characteristic of celiac disease. Polymorphism in the MMP-3 gene may contribute to susceptibility to celiac disease, particularly in males. This is different from the HLA susceptibility alleles (see **HLA-DQA1 and HLA-DQB1**, p 8) that confer a higher risk in females:

Mora B, Bonamico M, Ferri M, Megiorni F, Osborn J, Pizzuti A, Mazzilli MC 2005 Association of the matrix metalloproteinase-3 (MMP-3) promoter polymorphism with celiac disease in male subjects. Hum. Immunol. 66: 716-720.

Other

Not all celiac susceptibility genes have been identified. Identification of additional genes remains of considerable interest to the celiac disease research community.

Update on Inflammatory Bowel Disease Genetics

by David Rhodes

There were several important developments in inflammatory bowel disease genetics since our last newsletter issue. Dr. G.T. Ho and colleagues reported on the association of ulcerative colitis (UC) and polymorphisms (variants) of the Multidrug Resistance 1 (MDR1) gene. The association with UC was shown to be strongest with the phenotype of extensive disease in the European population studied. The MDR1 gene encodes a transporter (specifically an ABC transporter (where "ABC" stands for "ATP-Binding Cassette")), that is also known as the P-glycoprotein 170:

> Ho GT, Soranzo N, Nimmo ER, Tenesa A, Goldstein DB, Satsangi J 2006 The ABCB1/MDR1 gene determines susceptibility and phenotype in ulcerative colitis: discrimination of critical variants using a gene-wide haplotype tagging approach. Hum. Mol. Genet. Jan 24 [Epub ahead of print].

The MDR1 gene is localized on chromosome 7 (7q21.1). In the Spanish population, distinct MDR1 gene polymorphisms are associated with both ulcerative colitis and Crohn's disease:

> Urcelay E, Mendoza JL, Martin MC, Mas A, Martinez A, Taxonera C, Fernandez-Arquero M, Diaz-Rubio M, Concha EG 2006 MDR1 gene: susceptibility in Spanish Crohn's disease and ulcerative colitis patients. Inflamm. Bowel Dis. 12: 33-37.

However, in the Japanese population, polymorphisms in the MDR1 gene seem to be specifically associated with late-onset UC:

> Osuga T, Sakaeda T, Nakamura T, Yamada T, Koyama T, Tamura T, Aoyama N, Okamura N, Kasuga M, Okumura K 2006 MDR1 C3435T polymorphism is predictive of later onset of ulcerative colitis in Japanese. Biol. Pharm. Bull. 29: 324-329.

An important nuclear receptor that regulates the expression of the above MDR1 transporter gene, is the pregnane X receptor (PXR), localized on chromosome 3 (gene map locus 3q12-q13.3). Dr. M.M. Dring and colleagues have recently shown that polymorphisms in the PXR gene are associated with inflammatory bowel disease, particularly extensive UC, in the European population:

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

The pregnane X receptor (PXR) not only controls expression of the MDR1 gene, but also several enzymes of bile acid detoxification. This receptor is activated by rifampin (rifampicin), which is often used to control pruritus in primary sclerosing cholangitis (PSC) patients.

Dr. W.G. Newman and colleagues have confirmed that the discs large homolog 5 (DLG5) gene, localized on chromosome 10 (gene map locus 10q23), contributes to risk of Crohn's disease in the Canadian population:

> Newman WG, Gu X, Wintle RF, Liu X, van Oene M, Amos CI, Siminovitch KA 2006 DLG5 variants contribute to Crohn disease risk in a Canadian population. Hum. Mutat. Jan 31 [Epub ahead of print].

The DLG5 gene encodes a protein that is thought to be involved in maintaining the structure of epithelial cells and transmitting extracellular signals to the membrane and cytoskeleton.

Dr. F. Friedrichs and colleagues further report that polymorphisms in the DLG5 gene may be particularly important in determining Crohn's disease risk in men:

> Friedrichs F, Brescianini S, Annese V, Latiano A, Berger K, Kugathasan S, Broeckel U, Nikolaus S, Daly MJ, Schreiber S, Rioux JD, Stoll M 2006 Evidence of transmission ratio distortion of DLG5 R30Q variant in general and implication of an association with Crohn disease in men. Hum. Genet. Jan 31 [Epub ahead of print].

It will be of future interest to see if any of these genes are associated with susceptibility to PSC.

UPDATE ON DONATIONS TO PSC PARTNERS SEEKING A CURE

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We'd also like to thank Dave and Judy Rhodes for their very generous in-kind donation in 2005. They covered all our costs to the Wintek Corporation, the computer company that houses our two www domains (**www.psc-literature.org** and **www.pscpartners.org**). Thanks also to Lee Bria for her continuing in-kind donations.

A big thank you to our newest sponsors:

Gold level sponsors:	The Grover Family Foundation, Inc. (Deb and John Wente)
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Thank you, everyone, for your continuing generosity!!!!

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Quotations

The poorest man would not part with health for money, but the richest would gladly part with all their money for health.

Charles Caleb Colton

Health is a blessing that money cannot buy.

Izaak Walton

Additional Contact Information

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

pscpartners@yahoo.com

Submitting Newsletter Articles

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

rhodesdavid@insightbb.com

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