PBC connections

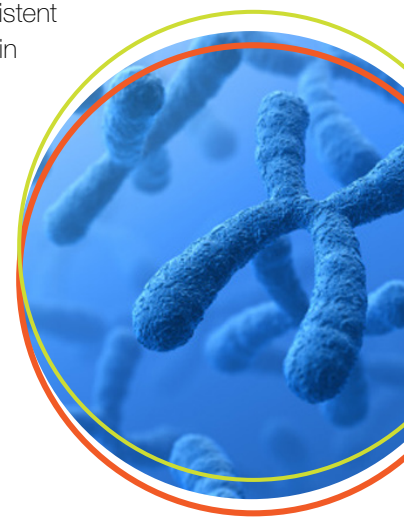
A Canadian PBC Society Newsletter

2014 • VOLUME ONE

AN UPDATE ON CANADA'S PBC GENETICS STUDY – UNRAVELLING THE CAUSES SO AS TO CONSTRUCT THE FUTURE

DR. KATHY SIMINOVITCH, PROFESSOR OF MEDICINE, University Of Toronto And Mount Sinai Hospital/University Health Network

The specific causes of primary biliary cirrhosis (PBC) are not known, but include genetic and environmental factors. Over the past five years, progress in identifying the genetic contribution to PBC has been – in a word – spectacular. This progress has been fueled by many factors, key ones being unprecedented advances in genetic technologies and biological informatics. Equally important to the PBC genetics research study initiated in Canada has been the collaborative participation of hepatologists from across this country and from sites in the USA and Europe, as well as the remarkable generosity of PBC patients in agreeing to take part in this study. Thanks to these factors, our PBC genetics research, under the initial leadership of Drs. Jenny Heathcote, Gideon Hirschfield and Kathy Siminovitch, enabled the very first discovery of genes conferring risk for PBC. Published in the New England Journal of Medicine in 2011, the results of this study identified three gene regions involved in predisposition to PBC. As is consistent with the integral role for immune cells in PBC, all three of the "risk" genes identified are involved in regulation of immune cell function. Following that study, our group has collaborated with several groups in the USA who have also recruited PBC patients for genetic studies; our combined efforts have led to the discovery of a total of 22 PBC risk genes. Most recently, we have been working with a UK-based group studying the genetics of PBC and these studies have identified several more of the genes that predispose to PBC.



Thus, in a relatively short time, we have gone from knowing very little about the genetic basis of PBC to identifying much of the genetic basis of this disease. We now know that: PBC is caused, in part, by interactions between many genes; most of these "risk" genes code for proteins that regulate our immune system function; and the genes conferring risk for PBC overlap extensively with genes causing other autoimmune diseases, such as Type 1 diabetes or celiac disease.

The current challenge is to translate this new knowledge into meaningful clinical benefit. To do so, we need to first define the precise steps or pathways whereby each PBC risk gene contributes to development of PBC. Such information will provide the understanding required to develop more effective treatments. More studies are also required to define the full spectrum of genetic "variants" underlying risk for PBC as well as those gene variants that influence the course and outcome of disease and the response to treatment in individual patients. This information will enable "customization" of therapy for each individual patient – an approach referred to as personalized medicine.

Progress in pinpointing the genetic causes of PBC has indeed been remarkable, but there are many more questions that need to be answered so as to ensure the best health outcomes for all PBC patients. With the support of the PBC Society of Canada and of PBC patients and hepatologists across the country, our group hopes to make the vision of more effective, personalized healthcare for all PBC patients a reality.

COMBINED ANTI-RETROVIRAL THERAPY FOR PATIENTS WITH PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis is associated with progressive damage to the bile ducts. When the bile ducts are damaged, bile and other substances accumulate in the liver causing progressive damage over time and eventually leading to cirrhosis. Treatment with Ursodiol leads to increased bile flow and removal of toxic substances from the liver. However, up to a third of patients with PBC do not respond to therapy that well.

At the University of Alberta in Edmonton, **Dr. Andrew Mason** studies are beginning to shed light on the possible causes and the potential for radical new therapies. The current theory is that PBC is triggered by an environmental agent that could be bacteria, a virus or an environmental chemical. Family studies have shown that people who have a sibling with PBC have a 10x higher risk of developing the disease. This means that there is likely an inherited genetic susceptibility. While genetic studies have linked several genes with the development of PBC, Dr. Mason's research group has been working on the idea that primary biliary cirrhosis is in fact a form of viral cholangitis (inflammation of the bile ducts). His laboratory has been studying an animal model of PBC that has bile duct infection with a virus similar to one found in PBC patients. Using this model, he has discovered that viral infection causes similar liver damage seen in patients with PBC and the disease can be blocked by antiviral therapy.

Dr. Mason has conducted several antiviral studies to develop novel and well-tolerated therapies for patients with PBC. The first pilot study used Combivir, which is a combination of lamivudine and zidovudine that have been used to treat patients with hepatitis B virus and human immunodeficiency virus infection. These studies showed improvement in liver biopsies. When the pathologist reviewed biopsies before and after Combivir, he found less bile duct injury, less inflammation and more bile ducts present in the biopsy after treatment. In a follow up international multi-center randomized controlled trial, PBC patients treated with Combivir for 6 months showed a mean reduction of alkaline phosphatase levels of more than 65 IU/mL from their baseline levels. This was a significant but not substantial improvement in liver tests used to monitor PBC.

"The increased number of bile ducts seen in patients after Combivir treatment may be important but need to be confirmed in other studies" says Dr. Mason. *"On the whole, the Combivir studies were disappointing because the improvement in symptoms and liver tests was not that great".*

Subsequently his laboratory has used animal models to test other anti-viral medications and found that the combination of Truvada and Kaletra could block the development of the PBC-like disease. At the Canadian Digestive Disease Week held in Toronto in February 2014, Dr. Mason reported the his early experience with treating patients in a randomized controlled trial for 6 months with Truvada and Kaletra.

"In this study, we observed a significant biochemical improvement with alkaline phosphatase levels improving by more than 120 IU/mL. So that's nearly double what we saw with Combivir."

However, therapy was not that well tolerated and the frequency of side effects in PBC patients on Kaletra was higher than that reported for HIV. Over half the patients complained of nausea, vomiting, weight loss or abdominal pain that resulted in patients not being able to take all the doses of Kaletra.

The long-term extension study is still in progress and collecting follow up data on symptoms, liver tests and liver biopsies. Dr. Mason commented *"We are encouraged with the incremental improvement in liver tests using stronger combinations of anti-retroviral treatment but I don't think we can use Kaletra in PBC patients because of the side effect profile. Hopefully this study will serve as a proof of principle that antiviral therapy can improve the disease process. We are looking at better tolerated treatments for future PBC studies."*

Funding Agencies: *Canadian Institutes for Health Research, Canadian Liver Foundation.*

FIBROSIS IN PRIMARY BILIARY CIRRHOSIS

DR. ANGELA CHEUNG MD, FRCPC

For our winter meeting on November 23, 2013, **Dr. Angela Cheung** presented a talk on fibrosis in PBC, including a discussion about the different stages of fibrosis and their effects on the body.

What does the liver do? The liver has over 500 functions, the most important of which include the production of specific proteins, excretion of bile, regulation of blood clotting systems, immune system regulation, and the clearance of toxins and drugs. Nearly all blood flows through the liver, making it one of the central organs in the body.

What is fibrosis? The chronic liver inflammation caused by PBC leads to scarring of the liver, otherwise known as fibrosis. Any process that causes significant damage to the liver will lead to fibrosis. We used to think liver fibrosis was irreversible, but we now know that isn't true. There are 4 stages in PBC, each defined by the level of liver injury and fibrosis: Stage 1: Inflammation, Stage 2: Increase in the number of small bile ducts, Stage 3: Scarring (early to moderate scarring), Stage 4: Cirrhosis (severe scarring).

How do we measure fibrosis? In the past, the only way to measure the degree of scarring in the liver was through biopsy (ultrasound is generally not helpful for looking at the degree of scarring in the liver). Fibroscan can now be used instead of liver biopsy. It allows for the regular assessment of fibrosis without an invasive liver biopsy. Because scarring takes a long time to form, it is usually not helpful to perform a fibroscan too often (i.e. less than a year apart). The Fibroscan is akin to a special type of ultrasound that uses a combination of regular ultrasound waves and mechanical shear waves in order to give you and your doctor an idea of how much fibrosis is present. By measuring the distance between the two types of waves, the shear wave velocity can be calculated. This is used to calculate the stiffness of the liver, which in turn correlates with the degree of scarring in your liver. Like liver biopsy, the Fibroscan only samples a small area of your liver (1cm x 4cm), but it is much less painful (i.e. it is not painful at all!).

What are the complications of cirrhosis? Cirrhosis is the last stage of fibrosis in the liver. The complications of cirrhosis include: 1.) decreased liver function and 2.) portal hypertension. When assessing liver function, we look at three main tests: 1.) Bilirubin (which is excreted by the liver), 2.) Albumin (which is produced by the liver), and 3.) INR (also produced by the liver). Another consequence of PBC is portal hypertension. Portal hypertension occurs when blood flow is directed away from the liver. When blood flow is redirected away from the liver, this can cause the spleen to enlarge, and it also causes the formation of varices (abnormally large blood vessels in the esophagus, stomach or rectum). Portal hypertension may also cause ascites (fluid buildup in the abdomen). Portal hypertension may also cause hepatic encephalopathy (confusion). This is because the liver removes toxins from the blood, and if blood is redirected away from the liver, those toxins can build up in the blood and then in the brain.

It is important to recognize that cirrhosis is a spectrum. Early cirrhosis is called compensated cirrhosis (when there is normal liver function), and late cirrhosis is called decompensated cirrhosis (when there is abnormal liver function with portal hypertension). One thing that bears mentioning is that PBC is unique - it can cause portal hypertension even if cirrhosis is not present (usually varices rather than ascites or encephalopathy). This process is called nodular regenerative hyperplasia. This process also makes the liver architecture abnormal, but unlike cirrhosis it does not involve fibrosis.

How is cirrhosis prevented and treated? Ursodeoxycholic acid (Urso) is used to prevent cirrhosis, which has improved overall survival in patients with PBC. Cirrhosis in PBC is now less common than before. Only 6% of patients will develop advanced cirrhosis after 10 years, while 22% will develop cirrhosis after 20 years. Even if patients do develop cirrhosis, patients can live with early cirrhosis for many years, even decades.

Is there anything else I can do to help my liver? Believe it or not, drinking two to three cups of caffeinated coffee a day has been shown to help decrease or stabilize liver fibrosis. Milk thistle, on the other hand, has not been shown to be helpful.

What is will the future bring for PBC research? With your help, doctors working in the area of PBC will continue to try and find newer and better treatments for PBC. Not only is it important to find newer treatments to prevent fibrosis, but it is also important to find new treatments for the symptoms of PBC such as fatigue and itch.

EVENTS

JOIN US FOR TWO IMPORTANT EVENTS

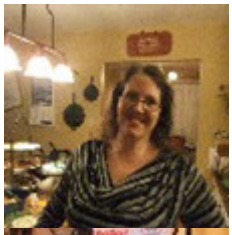
ANNUAL GENERAL MEETING

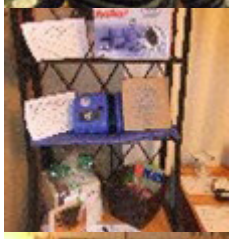
The Annual General Meeting will be held at 10:00 a.m. on **Saturday, April 5, 2014** in the All Purpose Room at 8 Covington Road, Toronto. Invitations and proxy forms will be going out shortly by mail or e-mail, if you haven't already received one. Please mail in your proxy forms if you can't attend but, if at all possible, **please come!**

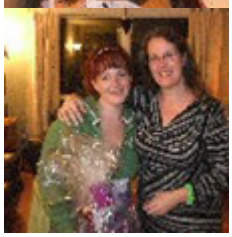
THEY'RE OFF!

Our annual fundraising *Day at the Races* will be on June 1 this year. Once again we will be in the Northern Dancer Room at Woodbine Racetrack, Toronto, enjoying a fabulous buffet lunch, great view of the races, the availability of Woodbine staff to help place bets, a silent auction and a 50/50 draw, all for the same price as last year. If you can help by providing an item for the silent auction, please contact Barbara Badstober by phone at 416-440-0917 or toll-free at 1-866-441-3643, or by e-mail at **info@pbc-society.ca**. **This is a fun day for members, family and friends, so set aside the date and plan on coming.**

FUNDRAISING







PRIVATE FUNDRAISING EVENT IN PETERBOROUGH

A private and very successful fundraising event was held February 22, 2014 at my home in Peterborough. This was my first fundraising event and reached out to friends and small businesses within the community and surrounding community. I was overwhelmed with donations of items and services that went to a silent auction and draws, and also asked that a minimum donation of $10 be made at the door to enter the event. I also had two representatives, one from Scentsy and one from Lia Sophia here on hand to take orders with a portion of their proceeds also going towards my final tally. There were many exciting things to choose from for the silent auction from a complete mani/pedi to hand crocheted infinity scarves, to a sign I made myself that said Don't Stop Believin, several different artist's pieces, rings, a one hour massage... and so much more! It was a very fun and successful evening, so much so that the next event we are planning is going to be a public one and I already have a fellow PBCer as a partner! Welcome aboard Laurie Campkin-Lightowlers!! I also had a lot of support and help with this first event from my husband Brad and a couple of great friends Erica and Jamie. The grand total for my first fundraising event was $700!! A huge success!! We are looking forward to holding more fundraising events in the future and will make sure to notify the Canadian PBC Society of the next one. - *Vickie Heard*

CanadaHelps.org
Giving made simple.

CANADA HELPS

What We Do CanadaHelps is a registered charity with a goal to make giving simple. Through CanadaHelps.org, anyone can donate online to any registered Canadian charity. We have proudly facilitated over $100 million in charitable donations through our website since it was launched in 2000. **For Donors** CanadaHelps is a one-stop-shop for giving. We made donating online easy and secure.

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RESEARCH INTO THE USE OF GRAPEFRUIT JUICE IN REDUCING PRURITUS IN PBC - CALGARY AREA PARTICIPANTS NEEDED!

Researchers at the University of Calgary's Faculty of Medicine are attempting to study the use grapefruit juice to reduce itchy skin in people with PBC. The study will compare two types of grapefruit juice to determine which is more effective. Unfortunately we are having difficulty in enrolling the number of subjects needed to enable the study to proceed.

Who are we looking for? People 18 years or older with established PBC and a history of pruritus, and on a stable dose of Ursodeoxycholic Acid for at least 6 months.

What is involved and for how long? The study will last 5 weeks and will involve the consumption of grapefruit juice and five visits to the clinic. During the visits the doctor will examine you and carry out some tests. You will also be asked to fill out questionnaires.

Will you benefit? Participation may be of no direct benefit to you, but you will help to determine which grapefruit preparation, if any, will help reduce the itching associated with PBC. The study agent (grapefruit juice) will be provided free of charge and you will be reimbursed for parking costs during your clinic visits.

For more information and to participate, please call: Itsabo John Oshiomogho, Clinical Research Assistant (403) 210-6951 or jioshom@ucalgary.ca

DOUBLE-BLIND PHASE OF INTERCEPT'S PHARMACEUTICALS PHASE III TRIAL OF OBETICHOLIC ACID (OCA) IN PBC TO COMPLETED IN DECEMBER – RESULTS ARE EXPECTED BY EARLY APRIL 2014

This is a very exciting time! Intercept's 'POISE Trial' of their drug, obeticholic acid (OCA), is the first time a drug has reached Phase III since Urso was developed over 20 years ago. (Typically, Phase III is the last stage of a drug's development before obtaining regulatory approval.) The double-blind phase of Intercept's POISE study was completed at the end of 2013 and results of this data are planned to be announced at the annual, international meeting of the European Association for the Study of the Liver (EASL) in London, early next month. At present, the results of the study are unknown – so we don't know if there might be a new drug to treat PBC available before too long.

The POISE trial enrolled 217 patients across 59 centers in 13 countries. All eligible patients have now entered the open label long-term extension phase of the trial where they will continue to receive OCA for several years. In Canada, the study is being conducted at the University of Toronto by Dr. Hemant Shaw and at Hôpital Saint-Luc/CHUM in Montreal by Dr. Catherine Vincent. Canadian centers have played a key role in the PBC studies with OCA and Toronto entered the largest number of patients in the Phase 2 program. Intercept continues with its plans to submit an application for approval of OCA in PBC hopefully by the end of this year, if the results of the POISE trial are positive.

Additionally, the long term phase of Intercept's earlier Phase II trial of OCA is currently ongoing with about 20 patients, including some in Canada, continuing to receive OCA. Several people have been on OCA for well over 4 years. Longer-term therapy with OCA continues to appear safe and tolerable in PBC patients, and the previously reported improvements in liver enzyme tests, including alkaline phosphatase, have been maintained.

More information about the ongoing Phase III POISE trial and Intercept can be found at:

- ClinicalTrials.gov (a registry clinical studies conducted in the United States and around the world): **http://clinicaltrials.gov/ct2/show/NCT01473524?intr=%22INT-747%22&rank=4**
- Intercept's website: **http://www.interceptpharma.com/primary_biliary_cirrhosis.php**

regional connections

ALBERTA NORTH

For more information, please contact **Shauna Vander Well**: AlbertaN@pbc-society.ca or 780-962-6217

ATLANTIC

For more information, please contact **Judi Pemberton**: atlantic@pbc-society.ca or 902-798-5554

BRITISH COLUMBIA

We've had a cool winter this season, but nothing like the rest of Canada, and we are fine with that. Our annual social lunch in Fall 2013 was great fun and attended by about half of the Vancouver area folks. Everyone is feeling well for the most part and it was really good to connect with each other and hear how each member has been doing. We will plan our next luncheon for Fall 2014 and welcome anyone with PBC and family members and friends. An announcement will be made closer to the date.
A Happy, Healthy New Year to you all.

For more information, please contact **Kathryn Swift**: bc@pbc-society.ca

GOLDEN HORSESHOE REGION

For more information, please contact: **Karen Isbister**: kisbister@cogeco.ca or 905-336-3502 and **Jackie Gay**: gingerjack@cogeco.ca or 905-937-1081

MANITOBA

Greetings from Manitoba! The land of cold and snow! Yes, I know it is like this over most of the country but there are only 14 days left until spring. How is that for optimism!

A few of us met for lunch in the fall. It was the last time we saw Alvina Block who passed away in December. Although we only met her twice, we found her to be a remarkable woman, who gained a Ph. D. in Canadian history at age 70 and was an accomplished pianist.

On another sad note, the husband of a long time member Kathy, died recently. Our sympathies go out to both these families.

On a happier note a new member, Brenda, has been told that she does not have PBC. It had been a tentative diagnosis. We are so pleased for her and hope our friendship will continue nonetheless.

There are concerns about the cost of some medications which are no longer covered by PharmaCare here in Manitoba. It can be a financial burden for those finding themselves in that position. Have some in other provinces experienced similar issues?

We have a supper meeting planned for March 14 with 11 people already committed.

Love to all my PBC sisters and probably a few brothers, Carol

For more information, please contact **Carol Seburn**: Manitoba@pbc-society.ca or 204-254-5226

OTTAWA

For more information, please contact **France Foucoult**: ffoucoult@hotmail.com

QUÉBEC

For more information, please contact **Francine Lamontagne**, Répresentante Québec, Société canadienne de la PBC: quebecrep@pbc-society.ca

SOUTHWESTERN ONTARIO

For more information, please contact **Betty Van Luven**: bvanluven@rogers.com

TORONTO

A meeting was held at the Toronto Yorkdale Holiday Inn on Saturday, November 23, 2013 with Dr. Angela Cheung as guest speaker. Dr. Cheung is Senior Researcher at the Francis Liver Clinic, Toronto Western Hospital, one the leading centres of research into PBC. A snowstorm limited attendance, but about 20 members, family and friends heard Dr. Cheung review the progress and treatment of fibrosis in PBC, followed by a question and answer session.

For more information, please contact: info@pbc-society.ca or 416-440-0917 or toll-free 1-866-441-3643