



Primary Biliary Cirrhosis: Surveying Disease Genetics

Findings from a UHN-led study published in the *New England Journal of Medicine* highlight the significant association between primary biliary cirrhosis (PBC)—an autoimmune disease of the liver targeting the small bile ducts—and genetic predisposition to the disease due to genetic changes or mutations to specific genes.

Led by Drs. [Katherine Siminovitch](#) and [Jenny Heathcote](#), DNA samples from over 2,000 North American subjects, with and without PBC, were analyzed. The genomewide studies showed that changes in the *HLA*, *IL12A* and *IL12RB2* genes were strongly associated with risk for this disease.

Comments Dr. Siminovitch, "The proteins these genes produce are critical components of the immune response, so our findings confirm a major role for the immune system in development of this disease. Our study also identifies the IL12 pathway as a potential therapeutic target in PBC and because drugs that regulate this pathway are already available, our data pave the way for a new approach to treating PBC patients."

Hirschfield GM, Liu X, Xu C, Lu Y, Xie G, Lu Y, Gu X, Walker EJ, Jing K, Juran BD, Mason AL, Myers RP, Peltekian KM, Ghent CN, Coltescu C, Atkinson EJ, Heathcote EJ, Lazaridis KN, Amos CI, Siminovitch KA. N Engl J Med. 2009 May 20. [Epub ahead of print]. [PubMed abstract]. Research supported by the Canadian Institutes of Health Research, the Ministry of Research and INnovation Ontario Research Fund, the Canadian Primary Biliary Cirrhosis Society, the National Institutes of Health, the American Gastroenterological Association, and the A.J. Sigismunda Palumbo Charitable Trust.

Ovarian Cancer: Determining Safety and Efficacy

According to recent findings from an PMH-led international study, when patupilone—part of the epothilone drug family responsible for stopping cell growth—is administered once every three weeks, it results in a manageable safety profile in patients with advanced ovarian, fallopian or peritoneal cancer.

Led by Dr. [Amit Oza](#), the team—which included clinical trials nurse Lisa Tinker and Drs. Helen Mackay, Joan Murphy, Barry Rosen and Stephane Laframboise—enrolled 45 women in the study. Unlike previous studies, the OCI investigation included standardized diarrhea management, a



OCI Director Honoured with Prestigious Award

UHN congratulates Dr. Benjamin Neel on receiving one of two prestigious Premier's Summit Awards in Medical Research presented at a gala event held in MaRS Tuesday May 12, 2009.

Dr. Neel is recognized for his significant and distinguished ongoing contributions to the field of cell signaling in several human diseases, including developmental defects and cancer. The Province will provide Dr. Neel with \$2.5M in funding over the next five years towards expanding a research program to determine the detailed pathophysiology underlying developmental disorders associated with several types of childhood and adult leukemias. In addition, the award will support studies to elucidate the mechanisms underlying HER2+ breast tumor development.

Society Recognizes TWRI Researcher

UHN congratulates Dr. Karen Davis, head of the Division of Brain, Imaging and Behaviour - Systems Neuroscience at TWRI and Associate Director of the Institute of Medical Science at the University of Toronto, on being inducted as a new member of the Johns Hopkins Society of Scholars. Dr. Davis' induction recognizes her as a former postdoctoral fellow at Johns Hopkins who has gained marked distinction in her field of research.

During her three-year postdoctoral fellowship in the Pain Research Laboratory at Johns Hopkins University, Dr. Davis published 14 papers. Her research at UHN has led to the first functional magnetic resonance images of brain networks underlying the human

common side effect of patupilone, and allowed the dose to be increased to levels that show good antitumor activity. Other commonly reported patient side effects were fatigue and peripheral neuropathy.

"Our study shows improved results from a previous study in similar patients using a weekly schedule," notes Dr. Oza. "In addition to being well-tolerated by patients, patupilone administered on the three week schedule showed disease stabilization for 15.8 months and has prompted a phase III study."

Ten Bokkel Huinink WW, Sufliarsky J, Smit WM, Spanik S, Wagnerova M, Hirte HW, Kaye S, Johri AR, Oza AM. J Clin Oncol. 2009 May 18. [Epub ahead of print]. [PubMed abstract]. Research supported by Novartis Pharmaceuticals Corporation.

Arthritis: Determining How Gender Affects Disease

Approximately 2-3% of the working-age population has reported arthritis disability and findings from a TWRI-led study are providing strong evidence that gender differences may be at the root of this statistic.

"Arthritis may marginalize women and men in different ways and our findings here underscore the importance of looking more closely at differences in the employment experiences of women and men," comments study co-author Dr. Simone Kaptein.

With study lead Dr. [Elizabeth Badley](#) and colleague Dr. Monique Gignac, the team analyzed self-reported data of over 28,000 Canadians to show that women with arthritis may be more likely to leave employment, whereas men may be more likely to remain working and report negative workplace experiences. The study also shows that factors such as older age, not being married, having no children, long duration of disability, and more severe pain and disability were significantly associated with being out of the labor force.

"Education was significantly associated with being in the labor force for men and women as well as the financial ramifications of retirement, losing medication coverage, and extended health care benefits," notes Dr. Badley. "Future studies with greater knowledge of gender's role in arthritis will be important when establishing workplace interventions."

Kaptein SA, Gignac MA, Badley EM. Arthritis Rheum. 2009 May 15;61(5):605-13. [PubMed abstract]. Research supported by the Great-West Life, London Life, and Canada Life, and by the Ontario Ministry of Health and Long-Term Care Health System-Linked Research Unit.

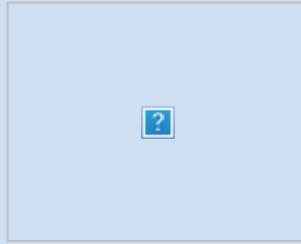
pain experience and the first images that visualize the impact of deep brain stimulation for Parkinsonian tremor. Her work has significantly increased the understanding of pain, attention and plasticity associated with neurological and psychiatric disease.

Congratulations, Dr. Davis!



Lung Transplantation: Tackling the Topic of Rejection

Understanding the mechanics behind chronic rejection following a transplant is critical to developing improved outcomes in all organ transplant fields. Findings from UHN researchers Drs. [Shaf Keshavjee](#), [Mingyao Liu](#), [Thomas Waddell](#) and [David Hwang](#) reveal a novel finding: that lymphoid neogenesis—the growth of new lymph tissue in the lung graft itself—following transplant plays a role in the immune response after lung transplantation.



Explains study lead Dr. Keshavjee, “If we can more clearly understand the underlying mechanisms of organ rejection, we can work towards lowering the incidence of this in patients who are in need of a transplant and hopefully prolong the survival of the graft.”

Using a series of investigations on human and mouse lung samples, the TGRI team discovered that new tissue growth in human samples of obliterative bronchitis—a late form of transplanted lung airway obstructive lung disease—was composed of specific immune cells, providing strong evidence to suggest that lymphoid neogenesis occurs in transplanted lungs similar to that seen in rejected human kidneys, livers and hearts.

Findings from the animal study were complimentary to the human tissue study. Mice receiving transplants from different breeds of mice had large numbers of new lymphoid tissues in comparison to samples transplanted between the same breed.

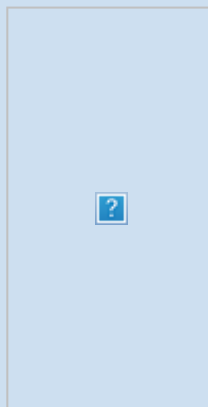
“In addition, there appears to be a period of time where lymphocyte aggregates are reversible, which suggests a maturation process,” comments Dr. Keshavjee. “The discovery of this particular type of tissue growth is important to our understanding of organ rejection and how we can prevent it in the future.”

Sato M, Hirayama S, Hwang DM, Lara-Guerra H, Wagnetz D, Waddell TK, Liu M, Keshavjee S. J Immunol. 2009 Jun 1;182(11):7307-16. [[Pubmed abstract](#)]. Research supported by the Canadian Cystic Fibrosis Foundation and the Wyeth Pharmaceuticals/Canadian Institutes of Health Research Rx&D Industrial Partner Program.

Esophageal Cancer: Identifying Markers of Disease

Cancer researchers led by OCI’s Dr. [Geoffrey Liu](#) have discovered two commonly inherited genetic variations in patients with esophageal cancer that may be relevant to determining tailored treatments for the disease.

In collaboration with Harvard School of Public Health’s Dr. David Christiani, genetic studies were conducted on samples from 371 patients with esophageal cancer on two known genetic variations—one in p53, another in a downstream gene, MDM2 (which controls cell growth). The less common genetic variation in p53 was strongly associated with an 11.8 month median survival compared with the common genetic form, that was associated with a 29.1 month median survival. The less common variant in MDM2 was strongly associated with a 10.3 month median survival, compared to patients carrying the more common form of the genetic variant (49.4 months).



"This suggests that these specific genetic variations are strongly associated with a shorter overall and progression-free survival," says Dr. Liu. "Using a simple blood test, health care teams could determine these specific genetic changes and add to the prediction of prognosis in esophageal cancer, identifying high-risk subgroups that may benefit from new therapeutic strategies."

Cescon DW, Bradbury PA, Asomaning K, Hopkins J, Zhai R, Zhou W, Wang Z, Kulke M, Su L, Ma C, Xu W, Marshall AL, Heist RS, Wain JC, Lynch TJ Jr, Christiani DC, Liu G. Clin Cancer Res. 2009 May 1;15(9):3103-9. Epub 2009 Apr 21. [PubMed abstract]. Research supported by the National Institutes of Health, Doris Duke Charitable Foundation, Alan B. Brown Chair in Molecular Genomics, Posluns Family Foundation and the Canadian Institutes of Health Research.



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