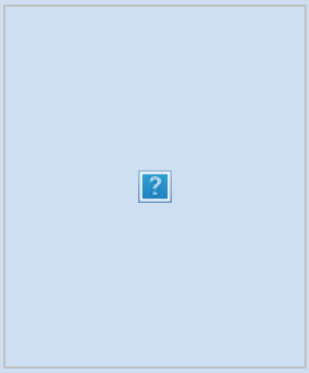
September 2009

Lung Cancer: Enhancing the Decision-Making Process

An OCI-led study may improve our understanding of treatment impact on quality of life for patients with non-small-cell lung cancer (NSCLC) undergoing adjuvant chemotherapy. Currently, only two thirds of patients with resected NSCLC are referred for potentially curative adjuvant chemotherapy, and less than half go on to receive chemotherapy, with the most widely cited reason for this being patient refusal.



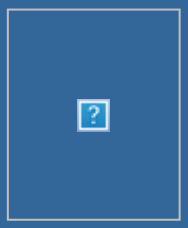
Study lead Dr. Natasha Leighl and colleagues Drs. Frances Shepherd and Andrea Bezjak examined lung cancer patients' perceptions of value pertaining to their health outcomes during and after adjuvant chemotherapy treatment. For the first 2 or 3 years, patients may have slightly lower quality-adjusted survival in exchange for longer quality-adjusted and overall survival in future.

Comments Dr. Leighl, "Simply put, if living with short-term chemotherapy-related adverse effects such as fatigue, nausea, and vomiting is worth half as much as being healthy and free from lung cancer recurrence, then adjuvant chemotherapy will pay off. Over the long term, this chemotherapy not only improves overall survival, but also improves a patient's quality of survival. These findings could help patients better understand the impact of chemotherapy on their quality of life and may serve to better inform patients during the treatment decision-making process."

Jang RW, Le Maître A, Ding K, Winton T, Bezjak A, Seymour L, Shepherd FA, Leighl NB. J Clin Oncol. 2009 Aug 10. [Epub ahead of print] [Pubmed Abstract]. *Research supported by the Canadian Cancer Society, the National Cancer Institute of Canada, the National Cancer Institute, the US Intergroup Members (Southwest oncology Group, Easter Cooperative Oncology Group, and Cancer and Leukemia Group B), and GlaxoSmithKline.*

Diabetes: New Protein Targets the Gut

UHN Researcher Wins Noble

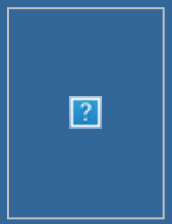


UHN congratulates Dr. Brian Wilson for being awarded the Canadian Cancer Society's 2009 Robert L. Noble Prize. The prize is awarded annually to a Canadian investigator who has made outstanding achievements in cancer research.

Dr. Wilson is being recognized for his pioneering research into various optic tools that can be used for minimally invasive cancer treatment and early diagnosis. He has been instrumental in the development of fluorescence and endoscopic imaging techniques such those used in Barrett's esophagus and colon cancer. Most recently, he has developed optical imaging to guide surgery being evaluated in clinical trials for head and neck, prostate and brain cancers.

The prize honours Dr. Noble, a leading Canadian investigator, whose 1950s research led to the discovery of the widely used anti-cancer drug vincristine.

UHN Researcher Awarded an ERA

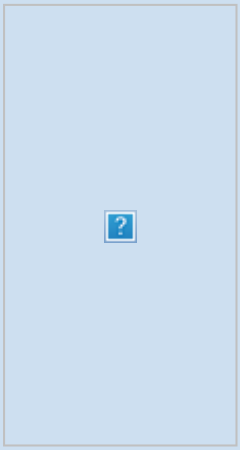


Ontario's Ministry of Research and Innovation has selected TGRI's Dr. Tony Lam as a recipient in Round 5 of the Early Researcher Award competition.

The award will support Dr. Lam's research program in understanding the physiology and molecular aspects of central nervous system sensing and its potential novel regulation of blood cholesterol levels. His work also aims to identify new molecular candidates and strategies targeting the brain to lower blood cholesterol levels in cardiovascular disease, diabetes and obesity.

Congratulations Dr. Lam!

Currently, patients with diabetes can lower their glucose through diet, exercise, anti-diabetic tablets or insulin injections. Interestingly, recent findings by Scientist Dr. Tony Lam out of TGRI may have important implications for the development of future treatment strategies to target the gut in lowering patients' glucose levels. Findings were highlighted as the cover story of the August issue of the journal *Cell Metabolism*.



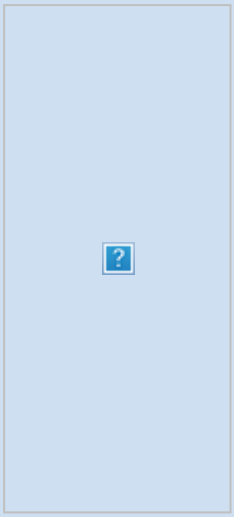
Using an animal model, Dr. Lam and colleagues discovered that activating receptors of the CCK protein hormone in the gut rapidly, and potently, lowered blood glucose levels by triggering a signal to the brain, and then to the liver to lower glucose or sugar production. Furthermore, in the same experiment, CCK failed to lower blood glucose in a high-fat diet.

"Our findings reveal a novel role for the CCK hormone and suggest that CCK-resistance in the gut may contribute to high blood sugar levels in response to high-fat feeding," says Dr. Lam. "Understanding how to overcome CCK-resistance in the gut so that blood sugars can be lowered could be a new therapeutic approach to diabetes and obesity."

Cheung GW, Kokorovic A, Lam CK, Chari M, Lam TK. Cell Metab. 2009 Aug;10(2):99-109. [Pubmed Abstract]. *Research supported by the Canadian Institutes of Health Research.*

Neurology: Changing Current Beliefs

Findings published in 2003 reported a new mechanism whereby the passage of impulses from a neuron to its target could be enhanced. Study lead Dr. Elise Stanley explains, "They found that a protein called PDLIM5 served as an anchor attaching an enzyme (PKC) to calcium channels that serve as the gatekeepers for the release of neurotransmitters from nerve endings." This finding gained considerable attention when later it was reported by others that defects in PDLIM5 may play a role in several severe psychiatric 'mood' disorders, such as schizophrenia, bipolar disease and depression. It became, therefore, critically important to fully understand the normal function of this protein.



In 2007, Dr. Stanley's team set out to expand on the original discovery. However, after exhaustive preliminary studies using biochemical, morphological and physiological approaches, they were forced to conclude that the original findings were incorrect. Because of the clinical significance of this protein as a possible pathological factor in psychiatric disorders, Dr. Stanley decided that the findings, though contrary, needed to be published to ensure that the scientific record is accurate, allowing researchers to find the real function of PDLIM5.

She explained, "In a way, this study serves as role model where contrary findings are of equal, and possibly greater, significance for the course of medical research than the more usual positive discoveries." The Stanley laboratory will continue to study PDLIM5 but has returned to first principles to determine the biology of this interesting protein.

Unique UHN Resource Featured Nationally

UHN's Centre for Global eHealth Innovation is one of the featured stories in this month's

InnovationCanada.ca publication, the Canada Foundation for Innovation's (CFI) monthly publication highlighting uniquely Canadian research resources.

Partially funded by the CFI, the Centre for Global eHealth Innovation has been operating since 2004 and contains a $6M test-bed laboratory and has become what founders believe is the largest hospital-based human factors 'usability' institution in the world. The idea is both to help industry make better devices and to pinpoint the best equipment for hospitals that are in the market for new machines.

To read more about the facility and the exciting new pain-medication pump developed in conjunction with the British Company Smiths Medical, visit innovationcanada.ca or ehealthinnovation.org.

OGI Invests in UHN-SickKids Finding

The Ontario Genomics Institute (OGI) has invested in a research project working towards improving the patient outcomes for hematopoietic stem cell (HSC) transplants, commonly referred to as bone marrow transplants. The team has received funding through OGI's Pre-Commercialization Business Development Fund (PBDF).

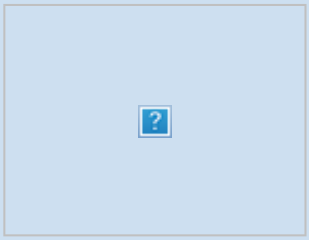
Project leads Drs. John Dick (UHN), his Research Associate Jean Wang, and SickKids investigator Dr. Jayne Danska have identified variants in a protein called SIRPalpha that contributes to the interaction between transplanted blood stem cells and the recipient's bone marrow environment. The research team has begun a retrospective genetic analysis of association between SIRPalpha genetic variants and outcomes of HSC transplants in 200 pairs of donors and recipients.

With a panel of new genetic tests they have developed, the team will continue to develop and validate prognostic genetic tests in HSC transplant donors and recipients and evaluate the predictive power of the detected variations. Understanding the underlying individual genetic variations, and the molecular interactions they affect, may also provide insights that may lead to more effective new anti-rejection therapies.

Gardezi SR, Weber AM, Li Q, Wong FK, Stanley EF. PDLIM5 is not a neuronal CaV2.2 adaptor protein. Nat Neurosci. 2009 Aug;12(8):957-8; author reply 958. [Pubmed Abstract]. *Research supported by Canada Research Chairs Program and the Canadian Institutes of Health Research.*

Cancer: Chemical Screen Identifies New Potential Drug Use

A recent OCI study conducted in the lab of Drs. Aaron Schimmer and John Dick has shown that ciclopirox olamine (CPX)—a drug currently approved for the treatment of fungal infections—has previously unrecognized anti-cancer capabilities in leukemia and myeloma (cancer in the bone marrow).



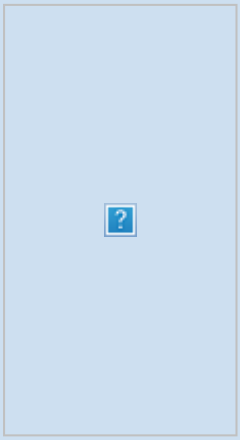
Led by Dr. Aaron Schimmer, the team identified CPX when screening a library for off-patent drugs with previously unrecognized anti-cancer activity.Specifically, the team wanted to study agents that inhibited the protein survivin—a regulator in cell growth and death—to determine whether it is preferentially expressed in malignant cells in comparison to non-cancerous cells. Studies of cancer cells show that CPX decreased tumour cell growth and the viability of malignant leukemia, myeloma and solid tumour cells, as well as AML cells, from patient samples without injuring non-cancer cells. Moreover, when CPX was administered in a mouse model of leukemia, CPX was found to selectively target and kill cancer cells, decreasing tumour weight and volume.

"In cancer cells, the survivin protein is heightened, contributing to dangerous cell growth. We showed that CPX significantly decreases these levels and in the context of future clinical trials, following survivin proteins could be a marker of biological response to the drug," notes Dr. Schimmer. "Future large scale studies are required to determine whether CPX's application—as a new cancer therapeutic—are feasible. With the help of the Leukemia and Lymphoma Society and Kansas University, we have developed CPX for clinical trial. The first clinical trial of CPX as an anti-cancer treatment will start at the Princess Margaret Hospital at the end of this month."

Eberhard Y, McDermott S, Wang X, Gronda M, Venugopal A, Wood TE, Hurren R, Datti A, Batey RA, Wrana J, Antholine WE, Dick J, Schimmer AD. Blood. 2009 Jul 9. [Epub ahead of print] [Pubmed abstract]. *Research supported by the Leukemia and Lymphoma Society, the Canadian Institutes of Health Research, the Ontario Institute for Cancer Research and a Premier's Summit Award both with funds from the Province of Ontario, Genome Canada through the Ontario Genomics Institute, a Canada Research Chair, the Canadian Cancer Society and the Terry Fox Foundation.*

Malaria: Identifying New Treatment Options

Malaria is a serious global health priority—case-fatality rates for severe malaria remain high despite potent antimalarial drugs. New treatment strategies are urgently needed.



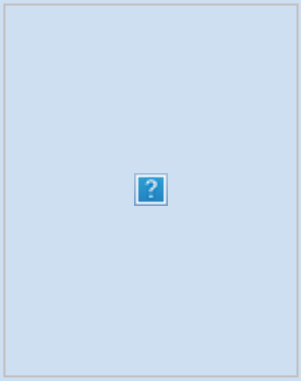
In a TGRI-led clinical trial study by researchers Drs. Kevin Kain and Conrad Liles, and colleagues in Thailand, the safety and efficacy of rosiglitazone, a drug normally used for diabetes, was assessed as a novel treatment for malaria. The team found that the 70 patients who were administered rosiglitazone twice daily for four days experienced significantly enhanced clearance of malaria parasites and had reduced inflammatory responses to infection, high levels of which are associated with adverse and fatal outcomes.

"In this randomized, double-blind study, we discovered that rosiglitazone was well-tolerated by patients with malaria," comments study lead Dr. Kain. "This is the first study to use this class of drugs as an adjunctive therapy for malaria. This is an important finding because rosiglitazone works by directly modifying the host's immune system to clear the malaria parasite, rather than by simply killing the parasite. These findings set the stage for larger clinical trials to determine if these drugs can improve survival in severe malaria."

Boggild AK, Krudsood S, Patel SN, Serghides L, Tangpukdee N, Katz K, Wilairatana P, Liles WC, Looareesuwan S, Kain KC. Clin Infect Dis. 2009 Sep 15;49(6):841-9. [Pubmed Abstract]. *Research supported by the Canadian Institutes of Health Research, Genome Canada through the Ontario Genomics Institute, and the Canada Research Chairs program.*

Neurology: Learning How to Prevent Ocular Cell Death

Patients with glaucoma, age-related macular degeneration, diabetic retinopathy and other visual impairments may have a new direction of treatment in the future thanks to recent findings out of TWRI. The death of retinal ganglion cells (RGCs)—or visual processing cells linking the eye to the brain—is in part responsible for these visual ailments.



In a study led by TWRI investigator Dr. Lyanne Schlichter, the team discovered that two ion channels play important roles in promoting RGC death in rats. A series of experiments showed that when specific potassium channels (Kv1.1, Kv1.3)—proteins that help relay signals between brain cells—were blocked or removed from retinal ganglion cells, factors promoting cell death were reduced and RGCs remained intact.

"This study provides the first evidence that targeting these Kv channels might have therapeutic potential for treating central nervous system diseases or insults that promote brain cell death," notes Dr. Schlichter. "Because several potent blockers of one of these channels (Kv1.3) have been identified and are being tested for immune suppression, these findings on RGCs in rats might be more rapidly translated into clinical trials."

Koeberle PD, Wang Y, Schlichter LC. Cell Death Differ. 2009 Aug 21. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, the Heart and Stroke Foundation, and the Krembil Scientific Development Seed Fund.*