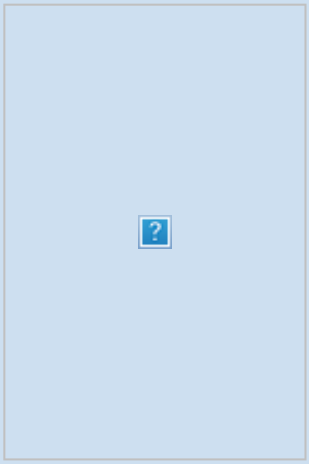
April 2010

Structural Biology: Understanding How Cells Anchor

The ability of cells to anchor to one another is fundamental to both normal development and cancer progression. In fact, when a cells' ability to anchor to (or stick to) another is disrupted, it can often result in cells spreading from a primary cancer site to other locations—also known as metastasis.



UHN's Dr. Mitsuhiko Ikura, a Tier I Canada Research Chair in Cancer Structural Biology, along with postdoctoral fellow Dr. Noboru Ishiyama and colleagues, recently uncovered important information regarding the cancer-promoting protein p120 and its role in cell adhesion. Dr. Ikura and his team changed specific regions of the p120 protein and surveyed how it interacted with another important protein known as E-cadherin—vital for ensuring cells anchor to one another and for preventing cancer progression and metastasis. The team determined how exactly the interaction of p120 and E-cadherin is crucial to stabilize cell adhesion, or cell 'sticking'.

"For the first time we've been able to determine where these two proteins intimately interact with one another and how this is important to cell adhesion," explains Dr. Ikura. "Proteins have the ability to change shape and our studies here add essential knowledge to our understanding of how cells lose the ability to achor to each other, leading to metastasis. With this knowledge, we can move forward and potentially design ways of preventing this in the future."

Ishiyama N, Lee SH, Liu S, Li GY, Smith MJ, Reichardt LF, Ikura M. Cell. 2010 Apr 2;141(1):117-28. [Pubmed abstract]. *Research supported by the Canadian Cancer Society, the Simons Foundation and the Canada Research Chairs program.*

Malaria: How Maternal Infection Contributes to Low Birth Weight

UHN and Merck Join Efforts for Cancer Research

On April 15, 2010, UHN joined Merck's global oncology research network—a group of leading international cancer research institutes working together to accelerate the development of cancer drugs for patients—as a centre of excellence for clinical trials of new anti-cancer drugs. John Milloy, Minister of Research and Innovation, and Merck Canada President Carlos Dourado were on site for the highly anticipated announcement.

Over the next five years, UHN will receive $17.5M—of which $2.6M are being invested by the Ontario government through its Biopharmaceutical Investment Program. As part of the Merck global network, PMH/OCI will aim to develop a new generation of cancer treatments based on genomics, stem cell research and personalized medicine.

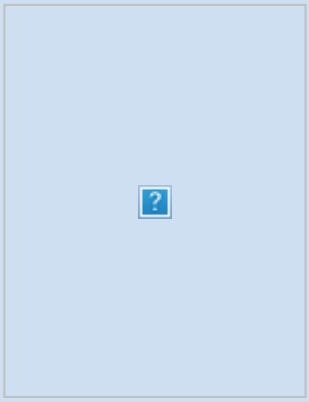
PMH's Drs. Benjamin Neel, Director of OCI and the Campbell Family Cancer Research Institute, and Dr. Malcolm Moore, Head of the Department of Medical Oncology and Hematology and the Robert and Maggie Bras and Family New Drug Development Program will be leading the partnership.

Canadian Society for Immunology Lauds VP Research

The Canadian Society for Immunology has recognized UHN's Dr. Christopher Paige—VP Research and Professor, Departments of Medical Biophysics and Immunology, University of Toronto—with the 2010 Bernhard Cinader Award. The award includes travel reimbursement, a plaque marking the honour and a cash prize. Dr. Paige will present the award lectureship "Dancing With the Bees" on Sunday April 25th at the annual meeting.

The Award, named in honor of Dr. Hardy Cinader, is awarded to an Immunologist working in Canada who exemplifies distinguished scientific leadership and accomplishments in Immunology.

Up until now, the mechanism by which malaria infection of the placenta during pregnancy induces low birth weight (LBW) has been poorly defined. Current findings by TGRI researcher Dr. Kevin Kain and colleagues have provided insight into this and, most importantly, his team may have identified clinically informative biomarkers to identify mothers at risk of delivering LBW babies. A Tier I Canada Research Chair in Molecular Parasitology, Dr. Kain explains, "Placental malaria (PM) due to infection doubles the risk of LBW causing over 100,000 preventable infant deaths per year."



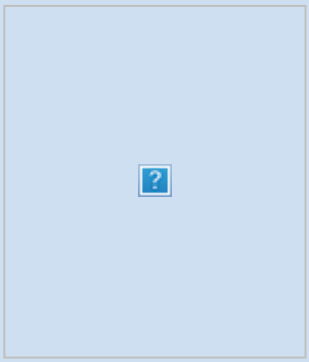
Using a mouse model of PM, the team showed that infected mice had abnormal levels of angiopoietin proteins 1 and 2 (ANG- 1 and ANG-2)—critical regulators of blood vessel formation—including decreased ANG-1, increased ANG-2 and ANG-2:ANG-1 ratio in the placenta and blood. The team then focused their attention towards malaria-exposed pregnant women and found ANG-1 and ANG-2 levels proportionately similar to those detected in mice. Interestingly, when these infected women were treated, ANG-1 levels recovered to normal.

"We've also found that women with PM who delivered LBW infants had increased ANG-2:ANG-1 ratios compared to uninfected women delivering normal birth weight infants," says Dr. Kain. "Our results suggest that the ANG-2:ANG-1 ratio may be informative as a biomarker in screening new moms who may be at risk for LBW infants. Future studies are still needed to determine if malaria-associated angiopoietin dysregulation could, in fact, predict LBW outcome."

Silver KL, Zhong K, Leke RG, Taylor DW, Kain KC. PLoS One. 2010 Mar 1;5(3):e9481. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, Genome Canada through the Ontario Genomics Institute, the National Institute of Allergy and Infectious Diseases, the National Institutes of Health and the Canada Research Chairs Program.*

Lymphoma: Opening the Door to New Research and Treatments

OCI and Campbell Family Institute scientist Dr. Gil Privé, working in collaboration with OCI's Dr. Cheryl Arrowsmith and groups at the Weill Cornell Medical College and the University of Maryland, has discovered a small molecule that selectively blocks the activity of BCL6—the cancer-causing protein found in diffuse large B-cell lymphoma (DLBCL), the most common form of non-Hodgkins lymphoma.



"We're very excited by these findings because they help open new avenues for cancer cell therapeutics. We have shown that a certain class of proteins called transcription factors can be targeted with drugs. Prior to our work, we knew that many transcription factors had important roles in cancer, but we did not have the tools to do anything about it. Our results demonstrate that we can target transcription factors with drug therapy," explains co-lead Dr. Privé.

Congratulations Dr. Paige!

UHN Awarded Two Canada Research Chairs

UHN congratulates Drs. John Dick and Tony Lam on their recent Canada Research Chair (CRC) awards.

The successful renewal of Dr. Dick's Tier I CRC in Stem Cell Biology will provide $1.4M over the next seven years towards his program, which uses immune-deficient mice to study normal and leukemic human stem cells. His research is helping to develop improved therapies for several major diseases and novel commercial products that support the biotechnology industry.

TGRI's Dr. Lam was awarded a new Tier II CRC in Obesity, which will help to further our understanding of obesity and related disorders. Specifically, Dr. Lam's CRC award will significantly expand our understanding of the processes involved in obesity and will offer important insights into how the central nervous system reacts to high-fat-induced obesity. This could help lead to the eventual development of new treatments for obesity and diabetes.

These two researchers were among the 18 awarded new or renewal CRCs across the University of Toronto in this round.

Ministry Recognizes Vision Science Research Excellence

TWRI's Dr. Christopher Hudson, Scientist in the Division of Visual Science and the Department of Opthalmology and Vision Sciences, has been awarded $2.4M in the Ministry of Research and Innovation's (MRI) Research Excellence (RE) Round 4 towards a program entitled "Retinal Oxygen Saturation, Blood Flow, Vascular Function and High Resolution Morphometric Imaging in the Living Human Eye".

With key private sector partners, Dr. Hudson and nine colleagues from the University of Waterloo and University of Toronto will develop retinal imaging instruments that will allow for the early detection and improved management of the three most common causes of age-related vision loss: macular degeneration, glaucoma and diabetic retinopathy.

Specifically, the team will build, develop and validate new quantitative non-invasive imaging technologies to: comprehensively assess the blood supply to the back of the eye, a diagnostic capability currently severely limited; and assess oxygen transport to the back of the eye, a diagnostic capability that currently does not exist.

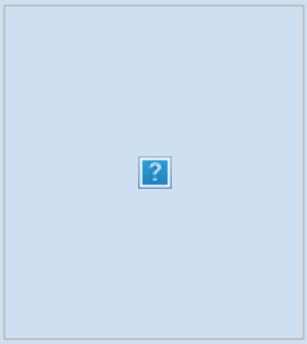
Using an investigational strategy based on the three-dimensional structure of BCL6, the team screened over one million compounds to find which ones could effectively bind to BCL6. Eventually, the team discovered a small molecule that was able to bind to BCL6 and prevented it from working with other surrounding proteins. This small molecule selectively killed cancer cells that had elevated levels of BCL6 protein in several models of DLBCL. Moreover, lab studies determined that this small molecule is non-toxic in normal cells.

"Our work will help advance the development of targeted drugs to fight this cancer," says Dr. Privé. "On a larger scale, our findings show that proteins like BCL6 can be targeted with drugs. This opens the door to a new arena of cancer research and we expect that we will be able to apply these methods to other types of cancer."

Cerchietti LC, Ghetu AF, Zhu X, Da Silva GF, Zhong S, Matthews M, Bunting KL, Polo JM, Farès C, Arrowsmith CH, Yang SN, Garcia M, Coop A, Mackerell AD Jr, Privé GG, Melnick A. Cancer Cell. 2010 Apr 13;17(4):400-11. [Pubmed abstract]. *Research supported by the Samuel Waxman Cancer Research Foundation, the Canadian Cancer Society, the Princess Margaret Hospital Foundation, the Campbell Family Institute for Cancer Research, the National Cancer Institute, the Leukemia and Lymphoma Society, the University of Maryland Computer-Aided Drug Design Center and the Ontario Ministry of Health and Long Term Care.*

Lung Cancer: Economic Analysis of Targeted Therapy

For patients with non-small cell lung cancer (NSCLC) who are no longer candidates for standard chemotherapy, a remaining treatment option is the drug erlotinib—a molecule designed to stop or block the actions of the epidermal growth factor receptor (EGFR)—which has been shown to improve quality of life and increase survival.



Study lead and OCI researcher Dr. Natasha Leighl explains, "Using data from a previous NSCLC clinical trial, our research focus shifted towards understanding the economic impact of a targeted therapy like erlotinib on the health care system."

With Drs. Ming-Sound Tsao and Frances Shepherd and others, the team reviewed the total costs incurred in treating patients recruited to the trial. Overall, the findings show that although the drug is expensive, treatment could be made more cost-effective by selecting a specific sub-set of patients who would benefit most from the drug.

"According to accepted guidelines, treatment of patients with NSCLC who have never smoked or who have high EGFR copy number in their tumour samples may be more cost-effective," comments Dr. Leighl. "Overall, our study adds support for the use of predictive molecular tests to identify patients for whom treatment would be most appropriate and most cost-effective. This will hopefully assist in making targeted therapies more accessible to lung cancer patients worldwide."

Bradbury PA, Tu D, Seymour L, Isogai PK, Zhu L, Ng R, Mittmann N, Tsao MS, Evans WK, Shepherd FA, Leighl NB; on behalf of the NCIC Clinical Trials Group Working Group on Economic Analysis. J Natl Cancer Inst. 2010

Congratulations Dr. Hudson!

Mar 3;102(5):298-306. Epub 2010 Feb 16. [Pubmed abstract]. *Research supported by Division of Hematology/Oncology, Princess Margaret Hospital, University of Toronto, NCIC Clinical Trials Group, OSI Pharmaceuticals and the Canadian Cancer Society.*

Parkinson's Disease: Learning the Long-Term Effects of Deep Brain Stimulation

Recent findings from an international team of investigators led by TWRI researchers provide strong evidence confirming the long-term efficacy of deep brain stimulation (DBS) in particular regions of the brain for patients with advanced Parkinson's disease (PD).

TWRI's Drs. Elena Moro, Andres Lozano, Anthony Lang and collaborators from France, Sweden, Germany, Spain, Italy, the Netherlands and the UK, undertook a review of 51 patients who received either subthalamic nucleus (STN) or globus pallidus internus (GPi) DBS following a minimum of five years of treatment. Overall, study findings showed improvements in their motor skills with either STN- or GPi-DBS. Both groups of patients also experienced marked decreases in the frequency of involuntary movements due to anti-PD medications (dyskinesias).

"Although this study was not a comparison between the two brain targets, patients who underwent GPi DBS experienced less adverse effects, whereas STN DBS provided more motor improvement," comments Dr. Moro. "We have confirmed that DBS in both regions of the brain are effective in improving motor PD signs with sustained benefit at the 5 to 6 year follow-up mark. Future studies will work towards understanding why STN-DBS patients may experience better outcome of motor signs while GPi-DBS patients experience fewer adverse effects."

Moro E, Lozano AM, Pollak P, Agid Y, Rehncrona S, Volkmann J, Kulisevsky J, Obeso JA, Albanese A, Hariz MI, Quinn NP, Speelman JD, Benabid AL, Fraix V, Mendes A, Welter ML, Houeto JL, Cornu P, Dormont D, Tornqvist AL, Ekberg R, Schnitzler A, Timmermann L, Wojtecki L, Gironell A, Rodriguez-Oroz MC, Guridi J, Bentivoglio AR, Contarino MF, Romito L, Scerrati M, Janssens M, Lang AE. Mov Disord. 2010 Mar 8. [Epub ahead of print]. [Pubmed abstract]. *Research supported by Medtronic.*