April 2009

Malaria: Discovering Diagnostic Tools

Currently, there are few tools that can determine which individuals infected with Plasmodium falciparum—the parasite responsible for causing malaria in humans—will progress to severe and potentially fatal complications such as cerebral malaria (CM). However, in a world first finding, TGRI investigators have discovered promising biomarkers for CM that may one day serve as a prognostic test for severe malaria, according to study lead Dr. Kevin Kain.

Dr. Kain's team collaborated with colleagues from Thailand and Uganda to analyze blood samples, from malaria-infected and non-infected Thai adults as well as Ugandan children, for changes in proteins involved in maintaining vascular integrity and the blood-brain-barrier including angiopoietin-1 (ANG-1) and angiopoietin-2 (ANG-2).

Findings show that ANG-1 and the ratio of ANG-2:ANG-1 had a sensitivity and specificity of 100% for distinguishing CM in Thai adults and 70% and 75% respectively for Ugandan children. Also, low levels of the ANG-1 protein were able to predict subsequent mortality in children.

"Specifically, we found that ANG-1 and ANG-2 proteins may play a role in the pathogenesis of CM and are accurate biomarkers to discriminate cerebral malaria from uncomplicated malaria," says Dr. Kain. "Of particular interest, they also help to predict survival in African children and may assist health care providers in triaging critically ill patients and in individualizing treatments in the future."

Lovegrove FE, Tangpukdee N, Opoka RO, Lafferty EI, Rajwans N, Hawkes M, Krudsood S, Looareesuwan S, John CC, Liles WC, Kain KC. PLoS ONE. 2009;4(3):e4912. Epub 2009 Mar 20. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, Genome Canada through the Ontario Genomics Institute, the NIH Fogarty International Centre, and the McLaughlin Centre for Molecular Medicine.*

UHN and UT Welcome New Institute

The countdown is on for the new University of Toronto Transplantation Institute opening May 4, 2009, which will create an Institute of the highest academic and clinical quality to support innovative and transformative research, education and patient care in the field of transplantation. The new institute will build upon the 20-year history of the Multi-Organ Transplant (MOT) Program's experience and leadership in transplantation excellence.

UHN's Dr. Gary Levy will act as Founding Director and will be guided by a 12-member advisory board. The Institute will be home to a growing number of international transplant experts, allow for the evolution of more innovative and interdisciplinary research, and will continue to be home to the only nationally funded training program for transplant specialists.

New Funding for UHN Researchers

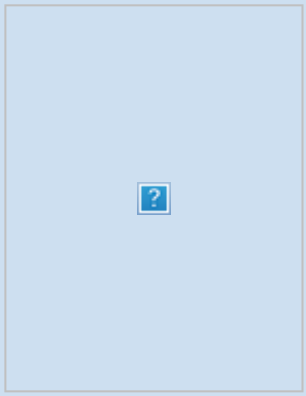
UHN would like to congratulate the following researchers on their successful proposals in recent special funding programs from the Canadian Institutes of Health Research (CIHR), the Ontario Institute for Cancer Research (OICR), and the Physicians' Services Incorporated Foundation —totaling $7.25M in new research support.

TGRI's Dr. Sharon Walmsley was successful in CIHR's *Randomized Controlled Trial* category, and Dr. David Hwang received a *Catalyst Grant* award.

Drs. Hal Berman (TGRI), Rod Bremner

Liver Cancer: A New Treatment Direction

For patients with liver metastases that are inoperable and who are not candidates for standard treatment therapies, findings from an UHN-led phase I study are 'casting light' towards a new radiotherapy treatment option that is individualized and does not cause radiation-induced liver disease.



To determine the safety and efficacy of individualized six-fraction stereotactic body radiation therapy (SBRT)—which involves delivering high doses of radiation precisely to tumor sites within the body—OCI's Dr. Laura Dawson and colleagues Drs. James Brierley, Rebecca Wong, Bernard Cummings, Jolie Ringash and Jennifer Knox recruited 68 patients with inoperable colorectal (40 patients), breast (12 patients), or other (16 patients) liver metastases.

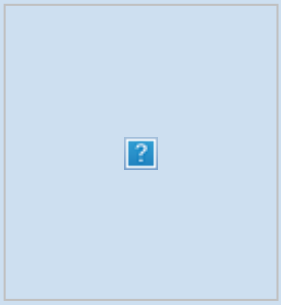
Among patients who had undergone SBRT, the one-year survival rate was 60% and overall, SBRT was well tolerated by patients with no radiation liver toxicity observed.

"What we've seen here is that with this group of patients with focal liver metastases unsuitable for standard therapies, SBRT was safe, and it led to sustained local control for the majority of patients treated" says Dr. Dawson. "Taking this into phase II and III studies will help us determine the benefits of SBRT, which may be greatest when delivered earlier in a patient's treatment course."

Lee MT, Kim JJ, Dinniwell R, Brierley J, Lockwood G, Wong R, Cummings B, Ringash J, Tse RV, Knox JJ, Dawson LA. J Clin Oncol. 2009 Mar 2. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Cancer Society, the National Cancer Institute of Canada, Elekta Oncology Systems, and the American Society of Clinical Oncology.*

Parkinson's Disease: Examining the Motor Cortex

Parkinson's Disease (PD) is a movement disorder caused by the loss of brain cells responsible for producing dopamine, a key chemical in relaying signals from one cell to another. A TWRI group has examined the consequences of preventing these specific cells from communicating to one another and how this might play a role in PD.



"We wanted to look at the motor cortex—the region of the brain responsible for directly controlling muscles that produce movement—and what happens to communications between brain cells in PD," explains study lead Dr. Robert Chen.

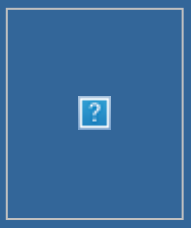
Working with 11 patients 'on' and 'off' of PD medications, the team stimulated the motor cortex during short (SICI) or long (LICI) intervals of 2, 100 and 150 milliseconds. The team found that while there was no difference in SICI for groups, LICI and more importantly, the influence of LICI on SICI were significantly reduced in PD.

"These findings showed that in PD, a form of communication between brain cells known as presynaptic inhibition is disturbed," says Dr. Chen. "This

(TWRI), Robert Bristow (OCI), Geoffrey Liu (OCI), Suzanne Trudel (OCI), and Ming-Sound Tsao (OCI) received support from OICR.

Drs. Angela Cheung (TGRI) and Charmaine Lok (TGRI) received funding support from the Physicians' Services Incorporated Foundation.

UHN Investigator 'Featured Expert' in Nature



The highly respected science publication *Nature* has chosen TGRI 's Dr. John Dick as the 'Featured Expert' in this month's *Nature Reports Stem Cells* for the significant contributions he has made to leukemia research, in particular, for discovering the first cancer stem cell and developing an assay widely used to identify blood stem cells.

The report highlights Dr. Dick's research areas, an interview session regarding careful assays for cancer stem cells, and recommended papers to review in the field of cancer stem cells.

For more information and to view the full report, visit Nature.com.

could ultimately be contributing to the movement symptoms, such as bradykinesia and akinesia, which are common in PD. This doesn't appear to be corrected by current medications and as such, future studies will investigate how we can alleviate this."

Chu J, Wagle-Shukla A, Gunraj C, Lang AE, Chen R. Neurology. 2009 Mar 3;72(9):842-9. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, the Canada Foundation for Innovation, and the Ontario Innovation Trust.*

Neurology: A Different Way of Seeing the Brain

A new way to visualize blood vessels in the brain may be possible—thanks to findings from a TWRI team led by Dr. David Mikulis—that overcomes current restrictions.

Conventional imaging of abnormal brain blood vessels requires the injection of contrast agents into the blood carried by arteries supplying the brain. The images show defects in the column of blood caused by abnormalities that actually lie within the blood vessel wall. The problem is that the defects in the blood column can look similar even when caused by very different blood vessel wall diseases. The new advance uses a more powerful magnetic resonance imaging (MRI) system that is able to image the blood vessel wall directly thus enabling a more accurate diagnosis of the disease that is affecting the blood vessel.

TWRI investigators, including researchers from Johns Hopkins Hospital, recruited 37 patients with various blood vessel diseases that were affecting the brain's blood vessels, including atherosclerosis, dissecting (tears in blood vessel walls) aneurysms, and inflammation using a powerful form of MRI, specifically 3T MRI, demonstrating higher-definition and improved image clarity of blood vessels in the brain.

"The 3T MRI technology was quite useful in providing clear imaging of blood vessel wall architecture that was specific to the disease," says Dr. Mikulis. "The ability to make a more accurate diagnosis will allow physicians to initiate more timely and definitive treatment preventing brain injury from deficits in blood flow (stroke). Future studies will examine a broader range of patients to determine how sensitive, specific and predictive a tool like 3T MRI can be, in terms of the best treatment strategy for each patient."

Swartz RH, Bhuta SS, Farb RI, Agid R, Willinsky RA, Terbrugge KG, Butany J, Wasserman BA, Johnstone DM, Silver FL, Mikulis DJ. Neurology. 2009 Feb 17;72(7):627-34. [Pubmed abstract]. *Research supported by the Department of Medical Imaging at the University Health Network and The University of Toronto.*

Breast Cancer: Revisiting Cancer Diagnoses with Biopsy

OCI researchers have conducted the first prospective study comparing original breast cancer tumors with a biopsy of newly suspected metastasized tumors that may change the way oncologists currently treat patients—using only data collected from original tumors.

Dr. Mark Clemons and colleagues evaluated 29 biopsies of recurrent tumors taken from patients whose breast cancer had spread to bone, skin, lymph nodes, lung or liver. Biopsy results were then compared to original cancer results by evaluating estrogen, progesterone, and Her2 receptors. Oncologists use these receptors to decide which drug treatments to give patients.

While 15 patients had unchanged receptors, 10 patients had results that had changed, three patients now had benign disease, and one patient had a different type of cancer that required an entirely different treatment. "Cancers may change over time and not respond to treatment that was appropriate for the original cancer," says study lead Dr. Mark Clemons. "These early findings are leading us in a new direction as we understand more about why some women don't respond to treatment so we can change our treatment strategy appropriately."

Simmons C, Miller N, Geddie W, Gianfelice D, Oldfield M, Dranitsaris G, Clemons MJ. Annals of Oncology Advance Access [Epub ahead of print]. March 18, 2009. [Pubmed abstract]. *Research supported by the Canadian Breast Cancer Foundation, Ontario Chapter.*