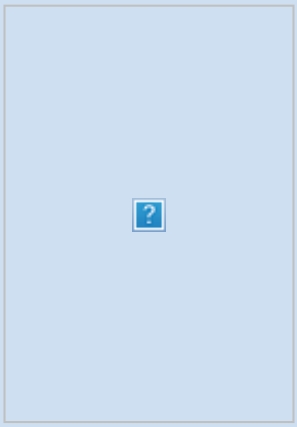
May 2008

Regenerative Medicine: Growing Heart Cells for Repair

In a groundbreaking study, a UHN-led international team of researchers has successfully grown human heart progenitor cells—immature heart cells—from embryonic stem cells, a major step towards creating functioning heart tissue.



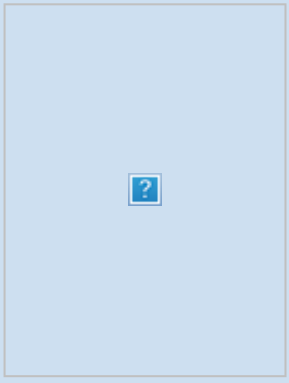
Study author Dr. Gordon Keller, Director of the McEwen Centre for Regenerative Medicine, and colleagues treated cultures of embryonic stem cells with a combination of growth-promoting proteins. The team was able to direct the stem cells to grow into three types of heart cells: cardiomyocytes, endothelial cells and vascular smooth muscle cells.

The finding represents a means of efficiently and effectively making different types of heart cells for basic and clinical medical research. Says Dr. Keller, "The immediate impact is significant: it will allow us to test for potential toxic effects of new drugs in petri dishes. Over the longer term, it may represent a new strategy for repairing damaged tissues after heart attack."

Nature 2008 [Epub April 23]. [Pubmed abstract]*. Research supported by the National Institutes of Health/National Heart Lung and Blood Institute.*

Diabetes: Revealing a Three-Pronged Approach to Treatment

Exciting new findings out of UHN have revealed a three-organ sensory network relaying vital information responsible for the regulation of glucose levels.



"It's a completely new circuit, which begins with the intestines serving as a remote-control device that signals the brain to regulate glucose production," says Dr. Tony Lam, TGRI Scientist and study lead of the paper, which appeared in *Nature*.

Dr. Lam and colleagues used a mouse model to show for the first time that an axis of communication exists between the gut, brain, and liver whereby the accumulation of fats in the upper intestine triggers a wave of information to pass to the brain and then off to the liver. This signals the liver to decrease glucose production and maintain appropriate levels of blood glucose.

Notes Dr. Lam, "It's far easier to design drugs to "hit" the gut than either the liver or the brain, with the latter being especially difficult to target

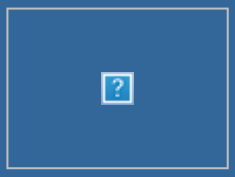
OCI Researcher Receives Prestigious Award

UHN congratulates Dr. Frances Shepherd on receiving a prestigious Premier's Summit Awards in Medical Research at a gala event April 29, 2008.

Dr. Shepherd is recognized for her substantial and distinguished contribution to the field of lung cancer. The province will provide $2.5M in funding over the next five years towards expanding investigations into the areas of screening, detection and early prevention; population and patient genomic profiling; and correlative molecular research in lung cancer.

Celebrating PMH!

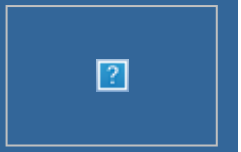
On Thursday May 1, 2008, PMH cancer program and OCI staff, volunteers and physicians, PMH Foundation staff and Cancer Care Ontario leadership commemorated Princess Margaret Hospital's 50th anniversary.



The festivities highlighted the care, education and research that has taken place at PMH over the past 50 years and featured the successes and milestones that have been reached.

Krembil Research Day

The Krembil Research Institute (Krembil) is holding its annual Research Day at 89 Chestnut Street on Wednesday, May 21, 2008.



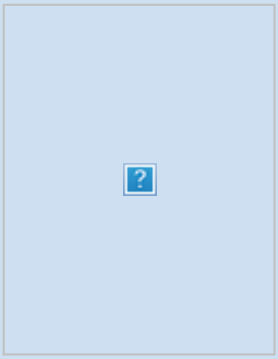
All Krembil investigators, trainees and staff, and TWH clinical researchers are invited to attend the event which will feature posters and abstracts of leading research underway at the institute.

because of the blood-brain barrier. So this new finding is very significant for potential diabetes treatment."

Nature. 2008 [Epub April 9]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research.*

Malaria: Learning to Block Host Immune Responses

TGRI researchers in collaboration with McGill University and Pennsylvania State have come one step closer to blocking the progression of cerebral malaria (CM) by taking control of the immune system.



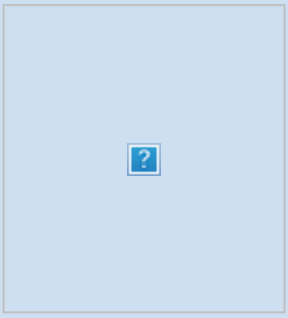
UHN scientists Dr. Kevin Kain and Dr. Conrad Liles examined mice either naturally lacking or genetically engineered to lack the C5 gene (which encodes a complement system component, an essential factor in the immune response) and found they were protected from CM. Furthermore, blocking C5 with an anbitody protected mice susceptible to CM.

"CM is the most severe and fatal form of malaria and there are currently no effective treatments for it," says Dr. Kain. "The complement system appears to play a very important role in the development of CM and blocking this system may be key to CM treatments in the future. This is now testable since an FDA-approved antibody to block C5 has currently become available."

J Exp Med. 2008 Apr 21 [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research (CIHR) Team Grant in Malaria, Genome Canada through the Ontario Genomics Institute, and the National Institute of Allergy and Infectious Diseases*

Arthritis: New Wave of Treatment May Require Caution

COX-2 inhibitors—which may be used to treat patients with pain, fever and inflammatory diseases like arthritis—increase the risk of heart attack. New findings from UHN show that a potential replacement for COX-2 inhibitors may carry a previously unrecognized cardiovascular risk.



In collaboration with researchers in Sweden, Germany and the United States, the UHN-led study shows that blocking the enzyme mPGES-1, which functions downstream from COX-2, leads to impaired recovery of the left ventricle and abnormal growth of heart cells after a myocardial infarction. This results in left ventricular dilation and impaired left ventricular function, factors that may impair a patient's ability to recover.

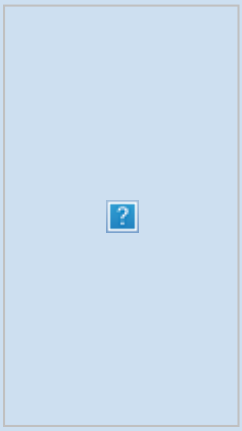
"Inhibitors of mPGES-1 are currently in development as a new class of painkillers, and may be taken by millions of patients who previously took COX-2 inhibitors. Our results indicate that patients at risk for infarction who are prescribed mPGES-1 inhibitors should be monitored closely, as these new drugs may adversely affect their ability to recover from a heart

attack," says Dr. Barry Rubin, study lead.

Circulation. 2008 Apr 1;117(13):1701-10. Epub 2008 Mar 17. [Pubmed abstract]. *Research supported by the Canadian Institutes for Health Research, the Heart and Stroke Foundation of Canada, the Canadian Heart failure Network and Tailored Advanced Collaborative Training In Cardiovascular Science for Research Fellows Partnership Program, Physicians of Ontario through the PSI Foundation, German Research Association, Swedish Medical Research Council, King Gustaf V 80 Years Foundation, Swedish Rheumatism Association, Erik och Edith Fernstroms Foundation for Medical Research, Borje Dahlin Foundation, and the Karolinska Institutet.*

Parkinson's Disease: Discovering New Treatment Modalities

Krembil researchers testing new drugs against Parkinson's Disease—a neurodegenerative disease causing loss of muscular coordination and strength—have discovered a compound capable of neural restoration and protection.



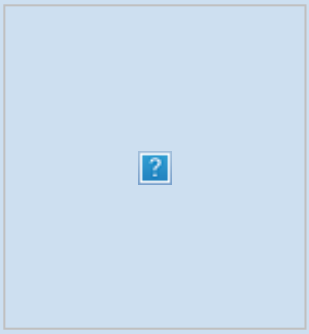
Led by UHN scientist Dr. Jonathan Brotchie, the team conducted a series of experiments on cells and mice previously treated with MPP+ and MPTP, compounds known to induce brain cell damage similar to that seen in Parkinson's patients. Damaged cells then treated with the compound PYM50028 showed a decrease in the number of damaged cells, and an increase in proteins promoting and enhancing brain cell growth.

"Compound PY50028 is a small molecule drug that increases growth factor synthesis. It can be administered orally, making an exciting non-invasive method of restoring neural growth. This obviously holds tremendous potential for treatment of this disease and it is currently in clinical development" says Dr. Brotchie.

FASEB J. 2008 Mar 25 [Epub ahead of print]. [Pubmed abstract]. *Research supported by The Krembil Foundation, Michael J. Fox Foundation, and Cure Parkinson's Trust.*

Pituitary Cancer: Defining Growth Mechanisms

Recent findings from UHN highlight a new potential oncogene, or cancer-causing gene, as the link between the opposing effects of two major systems in the pituitary gland, say lead researchers Drs. Shereen Ezzat, Sylvia Asa and colleagues.



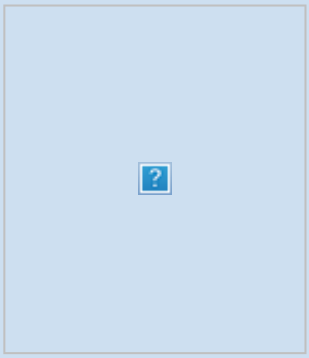
The oncogene MAGE-A3 has emerged as the common target of a type of receptor protein FGFR2 and the female hormone estrogen. FGFR2 prevents cancerous growth in pituitary cells while estrogen enhances MAGE-A3 production, which is correlated with invasive disease.

"The centrality of MAGE-A3 underscores the importance of a type of cell signalling network referred to as methylation. Changes in methylation have long been observed in pituitary cancers. Our work pinpoints a specific set of components in this pathway which hold the precise balance between opposing signals. By silencing MAGE-A3, we can prevent events that trigger cancer cell growth," says Dr. Ezzat.

Clin Cancer Res. 2008 Apr 1;14(7):1984-96. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research and the Toronto Medical Laboratories.*

Lung Cancer: Immune Cells Impact Survival

TGRI researchers Drs. Marc de Perrot, Michael Johnston, Shaf Keshavjee, Li Zhang, with research fellow Masaki Anraku and OCI's Dr. Ming-Sound Tsao have found evidence that elevated levels of CD8+ T cells in patients with malignant pleural mesothelioma—cancer of the lining surrounding the lungs—are associated with better survival.



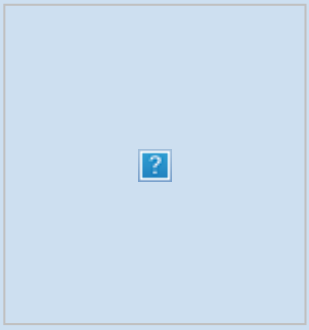
Samples from thirty-two patients diagnosed with this cancer were tested for the distribution of specific immune cells. Those patients with high levels of CD8+ tumor-infiltrating lymphocytes—a white blood cell that helps fight infection—had longer disease-free survival and lower incidents of mediastinal node disease.

Explains Dr. de Perrot, "We may be able to stimulate the immune system to increase the production of these CD8+ T cells. By targeting these cells specifically, we could improve control and prolong survival."

J Thorac Cardiovasc Surg. 2008 Apr;135(4):823-9. [Pubmed abstract]. *Research supported by the American Association for Thoracic Surgery (Second Andrew G. Morrow Research Scholarship)*

Prostate Cancer: New Predictor May Improve Screening

Serum PSA is a common screening tool for prostate cancer, and 20% of patients diagnosed with a precancerous lesion may develop cancer.



Efforts by OCI researchers have led to a new test to further refine the prognosis of these men. A small-scale study by Drs. Joan Sweet, Neil Fleshner, graduate student Jocelyn Stewart and colleagues has shown that lesions testing positive for another compound—AMACR—are five times more likely to be diagnosed with prostate cancer in later biopsies.

"If these results also hold true in large-scale studies, physicians may be able to use PSA and AMACR testing to better screen and treat men with higher risk of prostate cancer."

J Urol. 2008 Mar 14 [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Prostate Clinical Research Program at the Princess Margaret Hospital.*