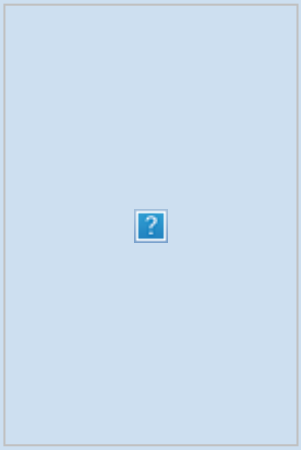
July 2010

Influenza A: Identifying New Cell Population to Battle Infection

Recent findings out of the Arthritis and Autoimmunity Research Centre (AARC) and TGRI uncover a new population of immune cells—late-activator antigen presenting cells (LAPC)—that may play a pivotal role in regulating resistance against pulmonary influenza A virus infections. The influenza A virus primarily affects organs and tissues responsible for breathing; and once infected, these viruses grow rapidly in number (within hours of first exposure) sending the immune system into a tail spin.



As explained by study lead and AARC Director Dr. Eleanor Fish, "For influenza virus infections, our bodies are equipped with two very distinct responses, known as T1 and T2 immunity. Our study specifically looked at T2 immunity within the context of disease cause and progression. We chose this route of study primarily because our understanding of the mechanics behind this T2 response is still in its infancy."

Using an animal model of influenza A infection, Dr. Fish and her team conducted an in-depth investigation, revealing the novel LAPC cell population, as well as showing how these cells differ and are unique from other well-known immune cells. Importantly, the study also explained how LAPCs modulate influenza A infection to coax our T2 immune response into action.

"Collectively, our findings here show that LAPCs have wide-spread involvement in different virus infections and they appear to have distinct roles in the immune response to virus infections. For flu infection, LAPCs leave the lungs much later than other virus fighting cells and trigger different responses," says Dr. Fish. "Future studies looking at the function of LAPCs in different virus infections and how they respond to different pathogens may provide us with new therapeutic targets for the treatment for a host of infections, including influenza A virus."

Yoo JK, Galligan CL, Virtanen C, Fish EN. J Exp Med. 2010 Jul 5;207(7):1435-51. Epub 2010 Jun 14. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research and the Canada Research Chairs Program.*

Immunity and Disease: Applying Cell Therapy to Combat Infectious Disease

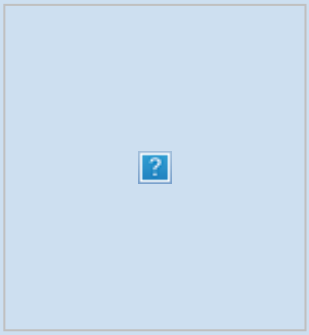
UHN Publication Receives International Recognition

The 2009 UHN Research Report has received a Bronze Award from the League of American Communications Professionals (LACP) Vision Awards, a global annual report competition for excellence within the Health Care—Providers & Services category.

In the world's largest annual report competition—with more than 4,000 overall entries received from organizations across 25 countries on five continents—less than one out of every five entries received award-level recognition. Scoring 95 out of a possible 100, the UHN Research Report received a perfect score in multiple categories including: Letters to Shareholders, Report Narrative, Message Clarity and Information Accessibility.

This report is a collaboration between the Office of the Vice President, Research Communications and Research Support Services.

Sepsis—frequently called 'blood poisoning'—is the number one cause of death in critically ill patients and is caused by overwhelming infection. Currently, sepsis remains without an effective specific treatment strategy; however, new findings out of UHN, St. Michael's Hospital and the University of Ottawa harness the immune-regulating power of stem cells to improve clinical outcome in this devastating disease.



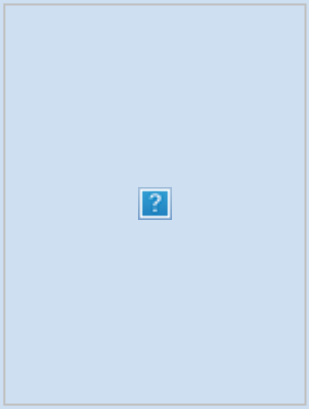
Co-led by TGRI's Dr. W. Conrad Liles and the University of Ottawa's Dr. Duncan Stewart, a series of molecular investigations found that administering mesenchymal stem (stromal) cells (MSCs)—stem cells from the bone marrow—to mice with sepsis (and receiving appropriate antimicrobial therapy) significantly reduced mortality in comparison to mice who did not receive MSC treatment. Studies also went on to show that MSCs significantly reduced the level of proteins that are responsible for promoting inflammation, which is a critical component of sepsis.

"MSCs were able to up-regulate or 'turn on' genes involved in positive immune action, specifically killing invading bacteria," explains Dr. Liles. "Our studies show that, by reducing inflammation and promoting the eradication of bacteria, MSC therapy may be an effective tool, in partnership with current therapies, to reduce sepsis-related morbidity and death. This study demonstrates the potential for therapeutic use of MSCs for sepsis and provides the basis for launching a clinical trial in patients with sepsis."

Mei SH, Haitsma JJ, Dos Santos CC, Deng Y, Lai PF, Slutsky AS, Liles WC, Stewart DJ. Am J Respir Crit Care Med. 2010 Jun 17. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, Northern Therapeutics, NSERC Doctoral Canada Graduate Scholarship and Ontario Graduate Scholarship, the Weston Foundation, the McLaughlin Centre for Molecular Medicine and the Canada Research Chairs Program.*

Hodgkin Lymphoma: Taking a Closer Look at Heart Disease Risk and Cancer Treatment

PMH's Dr. David Hodgson and colleagues from across the province have found strong evidence pointing towards a high risk of cardiac hospitalization (CH) following mediastinal radiation therapy (RT)—radiation to the area between the lungs where the heart, esophagus and windpipe are located—and doxorubicin-based chemotherapy in Hodgkin lymphoma (HL) patients, especially among those patients with pre-existing heart disease. These findings have important implications for medical teams when weighing treatment options, and in the follow-up of these patients.



The team conducted a population-based study of over 3,900 patients throughout Ontario who were diagnosed with HL from 1988 to 2003. A detailed analysis of a random sample of over 1,000 patients found that the relative cardiotoxicity of different treatments depended on the presence or absence of pre-existing cardiac disease. Other conventional cardiac risk factors—such as high blood pressure and diabetes—were also major

contributors to the risk of cardiac complications, and the combination of doxorubicin chemotherapy and mediastinal RT was associated with a significantly higher risk than just doxorubicin chemotherapy alone.

"These findings are an example of the fact that the complications of cancer treatments do no occur in isolation, but vary from one person to the next depending on their pre-existing health," comments Dr. Hodgson. "An effort to reduce the cardiac exposure to radiation in patients with pre-existing cardiac disease is necessary, and medical teams should carefully monitor and treat cardiac risk factors following HL treatment."

Myrehaug S, Pintilie M, Yun L, Crump M, Tsang RW, Meyer RM, Sussman J, Yu E, Hodgson DC. Blood. 2010 Jul 1. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research and Cancer Care Ontario.*

Lupus: Closely Monitoring Heart Disease Risk in Patients

Dr. Murray Urowitz, a Senior Scientist at the Toronto Western Research Institute and member of AARC, with TWRI/AARC collaborator Dr. Dafna Gladman and their fellow currently in Australia, have discovered important new findings highlighting the variability of cholesterol and blood pressure (BP) in patients with systemic lupus erythmatosus (lupus or SLE)—an autoimmune disease affecting the body's connective tissue, resulting in damage to internal organs, joints and skin.

"This study bears significant clinical importance because patients with SLE are at an increased risk of coronary artery disease (CAD), and understanding how the levels of total cholesterol (TC) and BP change over time will greatly assist medical teams to better understand risk factors and improve patient care," explains Dr. Urowitz.

Sampling over 26,000 measurements of TC, and systolic and diastolic BP (SBP and DBP) from greater than 1,200 patients over a nine-year follow-up period, the study determined that over time, 64.7% of patients varied between having normal and elevated cholesterol levels, while 46.4% of patients varied between having normal or abnormally high BP, emphasizing the need for vigilant monitoring of lipid levels during active disease and treatment with corticosteroids. Also of note, patients using antimalarials had lower TC, SBP and DBP levels. "Other independent factors related to TC and BP were smoking and hormone replacement therapy," says Dr. Urowitz.

"We have provided strong evidence showing the important concept of TC and BP variability over time, which makes a strong case for finding summary measures that better capture cumulative exposure to these risk factors over time. Future studies will work towards an even greater in-depth understanding of the complex relationship between various CAD risk factors in SLE."

Nikpour M, Gladman DD, Ibanez D, Harvey PJ, Urowitz MB. Arthritis Res Ther. 2010 Jun 30;12(3):R125. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Centre for Prognosis Studies in The Rheumatic Diseases, the Smythe Foundation, Lupus Flare Foundation, Ontario Lupus Association, The Lupus Society of Alberta, the Arthritis Centre of Excellence and the Geoff Carr Lupus Fellowship.*

Parkinson's Disease: Understanding the Anatomy

of Movement

Over a prolonged period of time, patients undergoing treatment for Parkinson's disease (PD) with the drug commonly known as L-DOPA—a chemical related to dopamine used to increase levels of dopamine in the brain—commonly experience motor complications such as dyskinesia, or involuntary or uncontrolled body movements. However, recent findings out of TWRI are helping scientists better understand the mechanics behind dyskinesia and where future treatments could be targeted to prevent it.

Dr. Jonathan Brotchie and his colleagues used a large animal model of PD and a series of in-depth molecular and physiological investigations to show that two areas in the brain intimately involved in motor control (the striatum and motor cortex middle layers) have increased levels of 5-HT2A receptors—brain proteins responsible for passing important information between cells. Moreover, the study provides evidence showing the pathway that information travels to promote L-DOPA induced dyskinsia.

Comments Dr. Brotchie, "Our findings are adding important new knowledge of how prolonged L-DOPA use could promote dyskinesia in patients with PD. Building on these anatomical findings, future studies are necessary to see if, and how, chemicals blocking 5-HT2A from working could help prevent dyskinesia."

Huot P, Johnston TH, Winkelmolen L, Fox SH, Brotchie JM. Neurobiol Aging. 2010 Jun 17. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Cure Parkinson's Trust, the Krembil Neuroscience Fund, the Edmond J. Safra Philanthropic Foundation and the Parkinson's Society, Canada.*