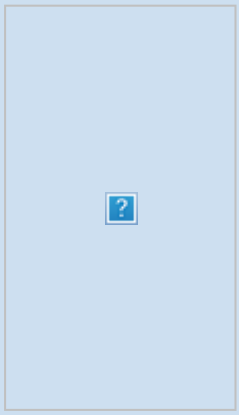
October 2009

Atherosclerosis: Understanding the Beginnings of Disease

The development of lesions that thicken artery walls due to the build-up of cells and fatty materials, such as cholesterol, is known as atherosclerosis. While the exact mechanisms behind how atherosclerotic lesions form are currently unknown, important study findings from a team of investigators at TGRI may ultimately change this.



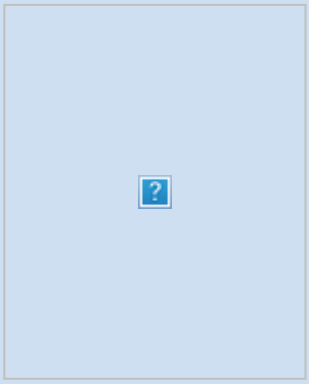
Dr. Myron Cybulsky and his team paired a specific cell labeling technique with state-of-the-art microscopy to survey how immune cells accumulate in artery walls to form the initial lesions of atherosclerosis. They found that in response to a high-fat diet, immune cells in the artery wall divide and more immune cells are recruited from the blood into the artery wall. Over time, both divided and recruited immune cells accumulate in the artery, ingest fatty materials, and thus thicken the wall. Previously, it was not appreciated that immune cells divide in early stages of atherosclerosis.

"By adding an additional molecular layer of investigations to the previously mentioned imaging studies, we were able to show that the GM-CSF protein, which is normally involved in several immune-cell functions, is responsible for immune cell division in early lesions," explains Dr. Cybulsky. "These findings provide evidence for future treatments targeting GM-CSF to specifically prevent immune cell division that contributes to the inception of atherosclerosis."

Zhu SN, Chen M, Jongstra-Bilen J, Cybulsky MI. J Exp Med. 2009 Sep 14. [206(10):2141-2149]. [Pubmed abstract]. *Research supported by the Heart and Stroke Foundation of Ontario.*

Cardiology: Learning the Benefits of Salt

A TGRI team led by Dr. Vivek Rao and colleagues has identified a novel pretreatment strategy in an animal model that can improve the movement of blood and preserves cardiac blood vessel function following transplantation. These findings could potentially lead to improved early and late survival after cardiac transplantation.



The team pretreated donor hearts with a hypertonic saline solution (HTS)—a simple salt solution—immediately before transplantation and then maintained the organs in cooler conditions for approximately six hours before transplantation. Findings show that in comparison to hearts that were not treated with HTS, HTS-pretreated donor hearts had limited injury to cells lining the interior surface of blood vessels and enhanced recovery in

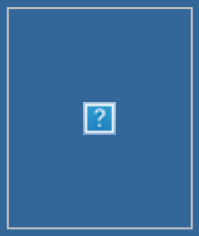
Canada Research Chairs Renewed

UHN congratulates Drs. Claire Bombardier and Allen Volchuk on the successful renewal of their Canada Research Chairs (CRC).

Dr. Bombardier, a Tier I Chair in Knowledge Transfer for Musculoskeletal Care, will use her seven-year, $1.4M Chair to bridge the gap between research evidence and clinical practice, with application to chronic musculoskeletal conditions. In addition, Dr. Bombardier was awarded funds from the Canada Foundation for Innovation (CFI) to establish the program's "Post-Marketing Surveillance Infrastructure for Arthritis: Supporting the Optimal Use of Therapies and Best Practices for Rheumatologic Care in Canada".

TGRI's Dr. Allen Volchuk, a Tier II Chair in Diabetes, will use molecular investigations to advance basic knowledge about how the processes involved in insulin secretion can lead to Type II diabetes and to work towards developing novel drugs to target specific insulin secretion pathways.

UHN Lupus Researcher Recognized



TWRI's Dr. Murray Urowitz is the recipient of the 2009 Evelyn V. Hess Award from the Lupus Foundation of America. Dr. Urowitz is being recognized for his contributions to advancing our understanding of the pathophysiology, etiology, epidemiology, diagnosis and treatment of lupus.

The prestigious award—presented annually at the American College of

ventricles after transplantation.

"Our findings lead us to believe that HTS treatment may represent a simple, cost-effective method of improving clinical outcomes after cardiac transplantation," comments Dr. Rao. "Future studies will look to investigate HTS treatment in both sexes and the effects, if any, this treatment may have on other organs."

Badiwala MV, Ramzy D, Tumiati LC, Tepperman ED, Sheshgiri R, Prodger JL, Feindel CM, Rao V. Circulation. 2009 Sep 15;120(11 Suppl):S206-14. [Pubmed abstract]. *Research supported by the Heart and Stroke Foundation of Ontario.*

Stroke: Protein Suppression Prevents Brain Cell Death

After cardiac arrest, the brain is deprived of oxygen, which causes brain cells to die typically within a few days. Findings published from the lab of TWRI's Dr. Michael Tymianski are helping investigators prevent the death of brain cells.

"Once brain cells die, the damage is irreversible and patients are left with lifelong disabilities," explains Dr. Tymianski. "If we can better understand how to prevent cell death following stroke, we could help reduce or remove these disabilities."

As reported in the journal *Nature Neuroscience*, the team used a gene therapy approach in an animal model to specifically block the production of TRPM7—a protein responsible for causing cell death—in the hippocampus, a region of the brain responsible for high level functions such as learning, memory and emotion. By selectively blocking TRPM7 in the hippocampus (a region very sensitive to oxygen deprivation), the team was able to prevent irreversible brain cell death following a stroke.

"We are excited by this very promising research as it leads us a step closer to better care for the millions of people worldwide that are affected by strokes," comments Dr. Tymianski. "These findings are not only important for stroke victims but potentially also for patients with Alzheimer's and Parkinson's disease, in which cells die after they have been deprived of oxygen."

Sun HS, Jackson MF, Martin LJ, Jansen K, Teves L, Cui H, Kiyonaka S, Mori Y, Jones M, Forder JP, Golde TE, Orser BA, Macdonald JF, Tymianski M. Nat Neurosci. 2009 Oct;12(10):1300-7. Epub 2009 Sep 6. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, the US National Institutes of Health, the Canadian Stroke Networks, and the Krembil Seed Fund.*

Neurology: Mapping Nerve Changes in the Brain

Rheumatology National Scientific Meeting —honours Dr. Hess' outstanding contributions to lupus research.

Congratulations, Dr. Urowitz!

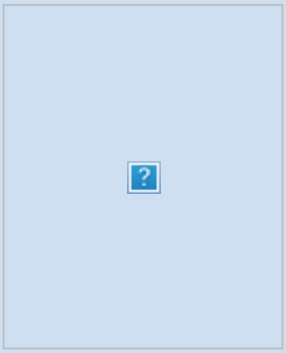
UHN Researcher Wins CIHR Award

Dr. Nizar Mahomed, a TWRI Scientist in the Division of Health Care & Outcomes Research, is one of eight recipients of the Canadian Institutes of Health Research (CIHR) – Canadian Medical Association Journal (CMAJ) Top Canadian Achievements in Health Research awards.

In this inaugural award round, Dr. Mahomed is being recognized for leading 35 hospitals that introduced new procedures for hip and knee surgery. These procedures have reduced wait times, cut rehabilitation stays and dramatically improved patient outcomes.

The award recognizes Canadian researchers whose discoveries and innovations have had the biggest impact on the health of Canadians and those around the world.

Recent results from a team of TWRI investigators is helping to determine if the brain landscape changes following upper limb surgical repair of cut nerves. Severe nerve injuries—as a result of various accidental and work-related injuries—require surgery after they have been cut.



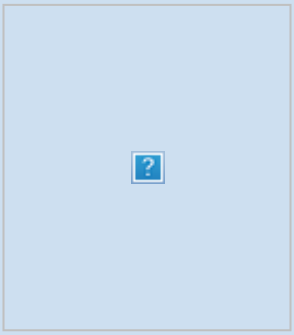
UHN investigator Dr. Karen Davis, Dr. Dimitri Anastakis and PhD student Keri Taylor used powerful magnetic resonance imaging techniques to assess functional structural changes in the brains of 14 patients who had surgical repair of major nerves in the arm that had been completely cut. These patients had impaired function of the repaired nerves, reduced grey and white matter (major structural components of the brain), and functional changes in key areas of the brain that process information related to touch and pain. Many of these brain changes correlated with the severity of sensory loss.

"We see the majority of injuries in 16-35 year olds, and many of these patients suffer years of disability and economic difficulties," says Dr. Davis. "The more we understand the consequences of nerve injury, the more we will come to know about the mechanisms of how the brain changes to deal with this trauma and its relation to sensory function. This is important because it may help to develop new treatment strategies and intervention programs."

Taylor KS, Anastakis DJ, Davis KD. Brain. 2009 Sep 8. [Epub ahead of print]. [Pubmed abstract]. *Research supported by The Physicians' Services Incorporated and a joint seed grant from the University of Toronto Centre for the Study of Pain/AstraZeneca.*

Oral Cancer: Identifying microRNAs as Potential Biomarkers

Oral squamous cell carcinoma (OSCC) is one of the most common types of head & neck cancers, and some of these cancers may develop from pre-malignant lesions such as oral leukoplakia—lesions which present as 'white patches' and are classified based on clinical and histological assessments. A recent OCI study has discovered a potential microRNA signature associated with disease progression—which may be an effective tool to help assess pre-malignant lesions at risk for developing cancer.



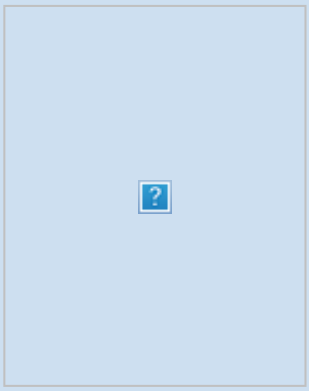
microRNAs are small RNA molecules that regulate protein expression. As explained by study lead Dr. Suzanne Kamel-Reid, the team analyzed sequential progressive leukoplakias and same-site OSCC patient samples, collected between 1991-2005, from UHN and the Faculty of Dentistry at the University of Toronto. These samples were used to identify microRNA alterations as potential biomarkers that can accurately predict which leukoplakia will most likely transform to cancer at the time of diagnosis.

Study findings showed that increasing abundance of three microRNAs (miR-21, miR-181b and miR-345) were associated with progressive stages from dysplasia to invasive cancer. Specifically, the over-expression of these microRNAs may be an early event during oral cancer progression. As a direct result of these findings, future studies will aim to develop a "multi-

microRNA expression analysis tool," which, together with clinical and histological analyses, could help medical teams determine which leukoplakias have a higher risk of progressing into cancer, ultimately improving treatment and patient survival.

Cervigne NK, Reis PP, Machado J, Sadikovic B, Bradley G, Galloni NN, Perez-Ordonez B, Pintilie M, Jurisica I, Gilbert R, Gullane P, Irish J, Kamel-Reid S. Hum Mol Genet. 2009 Sep 23. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Galloway Fund administered through the University Health Network and the Cancer Research Society (Canada).*

Nasopharyngeal Cancer: Targeting New Disease Proteins



An important therapeutic opportunity to improve clinical outcome for patients with nasopharyngeal cancer (NPC) is on the horizon thanks to the collaborative efforts of Canadian, French and Chinese investigators. Led by UHN, the team has discovered a protein involved in NPC which may help in disease prognosis, the establishment of therapeutic targets and a better understanding of the mechanism of disease.

Comments study lead Dr. Fei-Fei Liu, "The Plk1 protein is important for cell growth and is commonly expressed in many different human cancers. Specifically, we wanted to understand how and why Plk1 is important in NPC, and whether it could be a potential biomarker for this disease."

Using a series of molecular tests, the team compared Plkl levels from biopsy samples from NPC and non-NPC patients. The findings show that Plk1 is over-expressed in 70% of human NPC and is significantly associated with a higher likelihood of relapse, suggesting that Plk1 is an important mediator of NPC growth and disease progression.

"When we disrupt Plk1 in cancer cells, it causes a lot of problems with cell growth eventually leading to cell death," says Dr. Liu. "When we use this approach in combination with radiation therapy, we are able to significantly impair tumor formation and prolong survival in mice. These are very exciting findings because we now understand that not only can we use Plk1 as a potential indicator of disease progress, but we can also target it in combination with radiation therapy to stop cancer growth in its tracks."

Shi W, Alajez NM, Bastianutto C, Hui AB, Mocanu JD, Ito E, Busson P, Lo KW, Ng R, Waldron J, Sullivan BO, Liu FF. Int J Cancer. 2009 Sep 8. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research and the Elia Chair in Head & Neck Cancer Research.*

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