NRx

Advances in Research at UHN

July 2013

Welcome to the July Issue of NRx

NRx (formerly known as Net Results Express) is UHN's monthly research e-newsletter. Through NRx you can read about ongoing research at our five research institutes, the Ontario Cancer Institute (OCI), the Toronto General Research Institute (TGRI), the Toronto Western Research Institute (TWRI), the Toronto Rehabilitation Institute (TRI) and the Techna Institute (Techna).

In this issue you can read about research in:

We hope that you will find NRx informative and helpful. If you have feedback or questions, please contact www@uhnresearch.ca.

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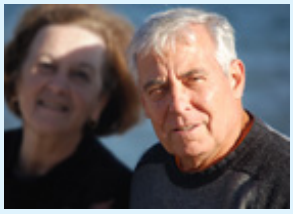
Cancer: Developing Improved Prognostics for Mantle-Cell Lymphoma



Mantle-cell lymphoma occurs four times more frequently in men than women, and patients are typically in their 60s when diagnosed.

While treatments exist for mantle-cell lymphoma (MCL), a cancer of the cells of the immune system, the condition is currently incurable. MCL leads to uncontrolled growth of defective immune cells, leading to the swelling of lymph glands that ultimately compromises the ability of the immune system to function. The aggressiveness of MCL varies widely and treatments range from observation-alone approaches for less aggressive MCL to highly invasive chemotherapies and, in the worst cases, bone marrow transplants to replace the immune systems of patients. Currently, physicians lack the ability to

Research News & Events

Epigenetics Research Gets a Financial Boost

On July 10, 2013, the Canadian Minister of Health announced an investment of $21.8M over five years towards epigenetics research, including projects led by OCI Senior Scientists Drs. Cheryl Arrowsmith and John Dick. Funding will be provided by the Canadian Institutes of Health Research in partnership with Genome BC, Fonds de recherche du Québec-Santé and the Japan Science & Technology Agency.

The project led by Dr. Cheryl Arrowsmith will use advanced technology to study the influence of the gut microbiome—the collection of genes expressed by gut microorganisms—on disease mechanisms in inflammatory bowel disease.

Dr. John Dick will co-lead with Dr. Hiromitsu Nakauchi (University of Tokyo) in a joint Canadian-Japanese project that aims to create an

confidently identify MCL severity or to predict treatment impact on progression of this disease.

In order to meet the need for higher performance prognostic tools, OCI Senior Scientist Dr. Suzanne Kamel-Reid and her colleagues Dr. Michael Crump (Medical Oncologist, Princess Margaret Cancer Centre) and Dr. Rashmi Goswami (Postdoctoral fellow, OCI) analyzed a large set of tumour samples from MCL patients. Their studies led to the identification of 14 microRNAs—molecules known to be involved in cancer severity—that were implicated in MCL aggressiveness. By combining one of the microRNAs identified (known as miR-127-3p) with existing prognostics, Dr. Kamel-Reid and co-workers were able to devise new and superior prognostic models for MCL. While clinical trials are required to test the usefulness of these models in patients, the identified microRNAs may help physicians better customize treatments to patients, and will serve as the basis for new studies into the molecular mechanisms underlying MCL severity.

This work was supported by the Irving and Mary Storfer Mantle-Cell Lymphoma Research Fund, the Princess Margaret Cancer Foundation, the Cancer Research Society, the Galloway Fund and the Ontario Ministry of Health and Long-Term Care.

MicroRNA Signature Obtained From the Comparison of Aggressive With Indolent Non-Hodgkin Lymphomas: Potential Prognostic Value in Mantle-Cell Lymphoma. Goswami RS, Atenafu EG, Xuan Y, Waldron L, Reis PP, Sun T, Datti A, Xu W, Kuruvilla J, Good DJ, Lai R, Church AJ, Lam WS, Baetz T, Lebrun DP, Sehn LH, Farinha P, Jurisica I, Bailey DJ, Gascoyne RD, Crump M, Kamel-Reid S. Journal of Clinical Oncology. *2013 Jul.* [Pubmed abstract]

Stem Cells: Pulling at Heartstrings with Biowire

Because adult heart cells cannot multiply and heart stem cells are rare, damage to the heart is difficult to heal.

During heart development, stem cells respond to local conditions to give rise to adult heart cells that are highly connected and capable of contracting in unison. Serious conditions arise when these cells are compromised, such as when heart cells are weakened (i.e. heart failure) or when they beat irregularly (arrhythmia). While researchers are exploring ways of growing personalized heart "patches" made from patients' own cells to repair failing hearts, current techniques produce immature cells that lack important characteristics of adult heart cells.

To address this problem, TGRI Assistant Scientist Dr. Sara Nunes de Vasconcelos has developed a new method using a string or filament known as a "biowire". Published in *Nature Methods*, the approach recreates several physical, mechanical and electrical cues within the developing heart environment to allow for the maturation of stem cell-derived heart cells. The resulting cells mimic a number of adult cell characteristics: they are rod-shaped, can beat in unison and can be "paced" using electrical cues, do not multiply as much as immature cells and are more electrophysiologically mature. Dr. Nunes de Vasconcelos stresses that, "While further refinements are required to create true adult-like heart cells, the biowire technology serves as a promising platform to refine our epigenetic "roadmap" of different cell types within the blood system and leukemia.

Cancer Research Funding to Improve the Lives of Patients

The Ontario Institute for Cancer Research has pledged $52M in funding to support translational research that aims to improve the entire spectrum of cancer care, from prevention and early diagnosis, to diagnosis and treatment.

Successfully funded projects include OCI Senior Scientist Dr. Robert Rottapel's "Innovation in Target Validation Program", which will use high-throughput technologies to streamline the identification of cancer targets, particularly those for ovarian cancer. Also funded is Dr. John Dick's "Cancer Cell Program" for the use of cutting-edge technology to identify and characterize cancer stem cells, which are thought to be responsible for initiating and maintaining cancer. These projects have the potential to improve cancer diagnosis, to address the resistance of cancers to therapy and to develop more effective, personalized cancer therapies.

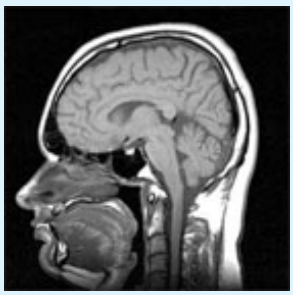
UHN's 2012 Research Report Honoured with Silver Award

ability to create functional heart cells for use in regenerative therapeutics and in drug screening platforms."

Funded by the Ontario Ministry of Research & Innovation's Ontario Research Fund–Global Leadership Round in Genomics and Life Sciences, National Sciences and Engineering Research Council of Canada (NSERC) Strategic Grant, Canadian Institutes of Health Research (CIHR) Operating Grant, NSERC-CIHR Collaborative Health Research Grant, NSERC Discovery Grant, NSERC Discovery Accelerator Supplement and a National Institutes of Health grant.

Biowire: a platform for maturation of human pluripotent stem cell-derived cardiomyocytes. Nunes SS, Miklas JW, Liu J, Aschar-Sobbi R, Xiao Y, Zhang B, Jiang J, Massé S, Gagliardi M, Hsieh A, Thavandiran N, Laflamme MA, Nanthakumar K, Gross GJ, Backx PH, Keller G, Radisic M. Nature Methods. *2013 Jun.* [Pubmed abstract]

Neuroscience: Revealing How Depression Therapies Work



Studies that examine the activity of individual brain cells may help uncover the functions of different areas of the brain.

The subcallosal cortex (SCC) is an area of the brain that has been identified as playing a key role in emotional responses. However, until now, evaluating how SCC affects major depression has only been possible using brain imaging. In a new study, TWRI Senior Scientist Dr. Andres Lozano examined the activity of individual brain cells in patients shown emotionally evocative images that varied in pleasantness, while undergoing deep brain stimulation therapy for depression.

Results showed that the individual brain cells responded to visual images depending on the type of emotion the images evoked. In particular, brain cells in the SCC of depressed patients responded to negative or unpleasant visual images more than to pleasant or neutral images.

Explains Dr. Lozano, "Overall these results may help explain the effectiveness of depression therapies. By modulating SCC brain activity these therapies may reduce overactive and preferentially negative emotional processing."

This work was supported by the by the Surgeon-Scientist Program, Department of Surgery, University of Toronto, and the Canadian Institutes of Health Research. Dr. Lozano is a Tier I Canada Research Chair in Neuroscience.

Neuronal Coding of Implicit Emotion Categories in the Subcallosal Cortex in Patients with Depression. Laxton AW, Neimat JS, Davis KD, Womelsdorf T, Hutchison WD, Dostrovsky JO, Hamani C, Mayberg HS, Lozano AM. Biological Psychiatry. *2013 Jun 14.* [Pubmed abstract]

Neurological Disease: Improving Brain Function with Stem Cells

UHN's 2012 Research Report, entitled 'Connected', was recognized by the League of American Communications Professionals (LACP) with a Silver Award in the 2012 Vision Awards Annual Report Competition. Written and designed by UHN Research Communications, with support from other departments including Research Program & Planning Analysis, Research Financial Services and Research Facilities Planning & Safety, this report competed in the "Health Care - Providers and Services" category and received a total score of 97 out of a maximum 100 points. "The level of creativity exhibited in the report judged for UHN Research Communications is outstanding, which is supported by excellent clarity in communicating this year's key messages" said Christine Kennedy, LACP Managing Director.

To view the 2012 report, click here.

Demyelination in diseases such as cerebral palsy, stroke, spinal cord injury and multiple sclerosis leads to motor impairment and disability.

Many neurological diseases are characterized by a damaging process called demyelination that leads to the loss of myelin, an insulating layer around nerve cells in the brain which is essential for proper function. A recent study from TWRI Senior Scientist and McEwen Centre for Regenerative Medicine investigator Dr. Michael Fehlings and his team shows exciting new evidence that neural precursor cells (NPCs)—stem cells from the adult brain—are able to address the dysfunction associated with demyelination in an experimental model.

The team used an experimental mouse model that is genetically unable to produce myelin. When transplanted into specific areas in the brains of these mice, the NPCs changed into a type of cell that re-insulated nerve cells with myelin. This remyelination was also associated with improved function of nerve cells in that area. "This study describes, for the first time, the functional characteristics and anatomical integration of transplanted NPCs in the demyelinated brain," states Dr. Fehlings. "Further exploration of stem cell therapy for remyelination is required to potentially translate the benefits of this strategy into clinical practice."

This work was supported by NeuroDevNet, The Ontario Brain Institute, Canadian Institutes of Health Research and Heart and Stroke Foundation of Canada.

Effects of adult neural precursor-derived myelination on axonal function in the perinatal congenitally dysmyelinated brain: optimizing time of intervention, developing accurate prediction models, and enhancing performance. Ruff CA, Ye H, Legasto JM, Stribbell NA, Wang J, Zhang L, Fehlings MG. Journal of Neuroscience. *2013 Jul 17;33(29):11899-11915.* [PubMed abstract]

Cancer: Understanding *BRCA1* in Breast Cancer

Many cases of breast and ovarian cancers that run in families are associated with altered BRCA1 genes.

An altered form of a gene called *BRCA1* is found in 5-10% of breast cancers, and is associated with an increased risk of developing ovarian cancer. OCI Senior Scientist and Director of the Campbell Family Institute for Breast Cancer Research Dr. Tak Mak and OCI Affiliate Scientist Dr. Mona Gauthier have provided outstanding new insight into this clinically important genetic change.

The researchers discovered the mechanism by which the *BRCA1* gene controls the production of highly unstable molecules known as reactive oxygen species (ROS). Because ROS cause cellular damage, healthy cells possess several safeguards to regulate ROS. Changes to the *BRCA1* gene compromise the cell's ability to control ROS levels, leading to accumulation and damage that can cause cancer. The researchers found that BRCA1's role is to interact with and stabilize a protein called Nrf2. Furthermore, they found that estrogen acts to protect damaged cells by

stabilizing Nrf2, further increasing the chance that these cells can become cancerous, grow and spread.

The critical influence of estrogen helps explain why *BRCA1* leads specifically to breast and ovarian cancer. This new understanding of *BRCA1*'s role as a sensor and regulator of ROS in breast cancer is a major advancement that will help guide treatment strategies.

This research was supported by a European Molecular Biology Organization Long-Term Fellowship, the Canadian Institutes of Health Research and the Ontario Ministry of Health and Long-Term Care.

BRCA1 interacts with Nrf2 to regulate antioxidant signaling and cell survival. Gorrini C, Baniasadi PS, Harris IS, Silvester J, Inoue S, Snow B, Joshi PA, Wakeham A, Molyneux SD, Martin B, Bouwman P, Cescon DW, Elia AJ, Winterton-Perks Z, Cruickshank J, Brenner D, Tseng A, Musgrave M, Berman HK, Khokha R, Jonkers J, Mak TW, Gauthier ML. The Journal of Experimental Medicine*. 2013 Jul 15.* [Pubmed abstract]

Osteoarthritis: Returning to Work after Joint Replacement

Osteoarthritis is the leading cause of disability in working-age people. Artificial knee implants (pictured) can help restore function.

Surgery to replace a knee or hip joint can relieve pain and improve mobility for people with severe osteoarthritis. Total joint replacement is increasingly an option for those under 65 and the total number of surgeries is increasing. Because many of these people are still in their working years, it is important to know when they can return to work and whether they face any challenges. To answer these questions, TWRI Senior Scientists Drs. Aileen Davis, Elizabeth Badley and Monique Gignac surveyed 190 total hip replacement and 170 total knee replacement patients to evaluate their ability to return to work.

More than half of those surveyed returned to work within three months of surgery and experienced fewer limitations than pre-surgery. The work limitations encountered were not purely physical or related to the function of the joint, but included issues with concentration and transportation to and from work. A quarter of those receiving a total knee replacement returned to work within one month, but reported more pain and experienced work limitations that were similar to those before surgery. "This study raises interesting considerations for determining the optimal time to return to work," Dr. Davis says, "And also presents important information to help employers understand that people with osteoarthritis can continue to participate in the workforce."

This work was supported by the Canadian Institutes of Health Research.

Return to work and workplace activity limitations following total hip or knee replacement. Sankar A, Davis AM, Palaganas MP, Beaton DE, Badley EM, Gignac MA. Osteoarthritis and Cartilage*. 2013 June 15.* [Pubmed link]

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