



August 2014

Welcome to the August Issue of NRx



As UHN's monthly research newsletter, NRx reports on the full spectrum of leading research from UHN's five research institutes. Located in downtown Toronto, these institutes are the Princess Margaret (PM) Cancer Centre, 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:

- [A new anticancer therapy entering clinical trials](#)
- [The link between obesity and depression](#)
- [An HIV treatment linked to low birth weights](#)
- [Nanotechnology to visualize and treat cancer](#)
- [Barriers to breast reconstruction surgery](#)
- [The discovery of a new type of motion sickness](#)

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

Christopher J. Paige, PhD, FCAHS
Vice President, Research
University Health Network

Cancer: Potential Anticancer Therapeutic Discovered



While the study focused on breast cancer, CFI-400945 also has similar anticancer activity in other types of solid tumour cancers.

An exciting new study from Dr. [Tak Mak](#) and his team describes the discovery of an effective new potential anticancer agent. The team used an approach that combined functional RNAi analysis with gene expression analysis in breast cancer-derived cell lines and in human breast cancers replicated in mice. Using these multidimensional datasets for human breast cancer, the enzyme PLK4 was identified as a candidate target among 10,000 other targets for the development of anticancer therapeutics. Their work also showed that an aggressive form of basal breast cancer was dependent on PLK4 for survival and that depleting it induced cell death.

Research News & Events

UHN Researchers Receive Early Researcher Awards

Congratulations to Drs. [Catherine O'Brien](#) and [Marcelo Cypel](#) on receiving Early Researcher Awards (ERAs) from the Ontario Ministry of Economic Development and Innovation. The ERA program helps promising, recently appointed Ontario researchers to build their research teams of undergraduates, graduate students, post-doctoral fellows, research assistants, associates and technicians.



Dr. O'Brien is a PM Scientist, with a research focus in cancer stem cells, colorectal cancer and new anticancer therapies. The ERA will support

her research into the identification of new adjuvant therapeutics to be used in combination with cetuximab—a targeted therapeutic that is used to treat colorectal cancer.

"This finding led to the identification of CFI-400945, a selective and orally active inhibitor of PLK4, which was shown to have significant antitumour activity as a single agent in a variety of preclinical tumour models," says Dr. Mak, a PM Senior Scientist and the Director of The Campbell Family Institute for Breast Cancer Research. In addition, this antitumour activity was observed in tumour models with a PTEN gene deficiency. PTEN, a tumour suppressor, is known to be defective in as many as half of all advanced solid tumour cancers.

"If clinical testing supports our hypothesis that PTEN is a predictive biomarker for CFI-400945, we will have another way to tailor personalized cancer medicine based on an individual's genetics," says Dr. Mak. The next phase of research for this new drug is evaluation in human cancer patients, and a Phase I clinical trial initiated early this year is currently ongoing at the Princess Margaret Cancer Centre and University of California, Los Angeles.

This study was supported by the Canadian Institutes of Health, Genome Canada and the Princess Margaret Cancer Foundation. T Mak is a Tier 1 Canada Research Chair in Inflammation Responses and Traumatic Injury.

Functional characterization of CFI-400945, a PLK4 inhibitor, as a potential anticancer agent. Mason JM, Lin DCC, Wei X, Che Y, Yao Y, Kiarash R, Cescon DW, Fletcher GC, Awrey DE, Bray MR, Pan G, Mak TW. Cancer Cell. Jul 2014. [[PubMed abstract](#)]



Dr. Cypel is a TGRi Scientist with a research focus in lung transplantation, specifically the use of artificial lung devices in addition

to gene and cell therapy to monitor and repair injured organs prior to transplant. The ERA will support his research into the ongoing development of a novel lung preservation approach known as normothermic *Ex Vivo* Lung Perfusion, which will increase the number of available lungs for life-saving transplantation procedures.

UHN 2014 Inventors of the Year

For the first time, UHN's Inventor of the Year award is being presented to two researchers: Dr. [Tak Mak](#) (and the Campbell Family Drug Development Team), for the development of multiple new cancer therapeutics that are currently in clinical trials; and Dr. [Ralph Dacosta](#), for his development of a handheld imaging device that can detect bacterial infections in wounds. This award, sponsored through UHN's Technology Development and Commercialization Office, is presented to UHN researchers who have demonstrated an outstanding ability to apply biomedical research towards the creation of new, inventive and patient-oriented technologies, products and therapeutics.

Obesity and Depression: Two Sides of the Same Coin?



Body weight may influence the body's ability to respond to antidepressant drugs.

Major depressive disorder is often associated with obesity, suggesting that they may be linked. A handful of previous studies have tried to examine whether a person's body weight or body mass index (BMI)—a measure of body weight relative to body length—is able to predict response to antidepressant therapies, but have failed to provide conclusive results. A limitation of these previous studies is that BMI data were grouped into broad categories (eg, normal, overweight or obese), thus potentially concealing

subtle differences.

The research team led by Dr. [Roger McIntyre](#), Clinical Researcher at TWRI, used a more direct approach. Rather than grouping patients into categories, they simply recorded the body weight and BMI of people with depression, and then initiated treatment with the antidepressant fluoxetine. Patients' response to treatment was assessed using two different depression questionnaires and rating scales. This approach revealed that higher body weight and BMI before treatment were associated with having a worse response to the drug.

Currently, different BMI cutoff points are used to define overweight and obese categories depending on ethnicity. This study highlights that current BMI category definitions may result in loss of information and explain the inconsistent results seen in the past.

This work was supported by the Kai-Syuan Psychiatric Hospital, the National Science Council of Taiwan and the Toronto General and Western Hospital Foundation.

Both body weight and BMI predicts improvement in symptom and functioning for patients with major depressive disorder. Lin CH, Chen CC, Wong J, McIntyre RS. Journal of Affective Disorders. 2014 June. [\[PubMed abstract\]](#)

HIV: Hormone Linked to Low Birth Weights



Without treatment, the risk of HIV transmission from a breastfeeding mother to her child is estimated to be between 20 and 45%.

Human immunodeficiency virus (HIV) can be transmitted from mother to child during pregnancy, labour, delivery and breastfeeding. This can be prevented by treating mothers with a combination of drugs known as combination antiretroviral therapy (cART). Recently, it has been shown that pregnant women treated with a type of cART known as protease inhibitor-based cART (PI-cART) are more likely to have premature babies with low birth weights. How or why this occurs is still unclear.

TGRI Assistant Scientist, Dr. [Lena Serghides](#), has provided some insight into this phenomenon by revealing that a hormone important to normal births, known as progesterone, may be involved. Dr. Serghides found that the administration of PI-cART in an experimental model of pregnancy was associated with decreased progesterone levels and lower birth weights of offspring. Birth weights were improved by providing mothers with additional progesterone during their pregnancy. Moreover, researchers observed a similar trend in pregnant, HIV-infected women: those treated with PI-cART had lower progesterone levels and gave birth to babies with lower birth weights, in comparison to those treated with another cART and to mothers without HIV infection.

Dr. Serghides says "While the mechanisms that lead to progesterone reduction remain to be elucidated, our study provides vital information that could translate into more informed treatment choices for HIV-positive pregnant women and new ways to protect the health of their children."

This work was supported by funding from the Ontario HIV Treatment Network, the Canadian Institutes of Health Research, the Canadian Foundation for AIDS Research and the Toronto General and Western Hospital Foundation.

HIV protease inhibitor use during pregnancy is associated with decreased progesterone levels; a potential mechanism contributing to fetal growth restriction. Papp E, Mohammadi H, Loutfy MR, Yudin MH, Murphy KE, Walmsley SL, Shah R, Macgillivray J, Silverman M, Serghides L. The Journal of Infectious Diseases. 2014 July 16. [\[PubMed abstract\]](#)

Cancer: Nanoparticles to Visualize and Treat Tumours

Photothermal therapy is a promising treatment option in cancer. It exploits the ability of certain small "nanoparticles" to be incorporated specifically into tumours. Upon targeting laser light to the tumour location, these



Tak Mak is a Senior Scientist at PM Cancer Centre and Director of The Campbell Family Institute for Breast Cancer Research. The

most recent cancer therapeutic developed by his research team, known as CFI-400945, has been shown to be effective in preclinical models against a particularly difficult to target "triple-negative" breast cancer. The drug is currently being tested at the PM Cancer Centre and the University of California, Los Angeles in Phase I clinical trials, and joins two other drugs developed by Dr. Mak's team that are also being clinically tested.



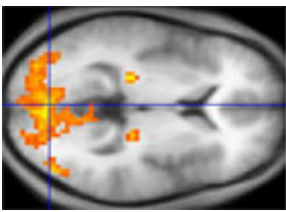
Ralph DaCosta is a Scientist at PM Cancer Centre and Techna Faculty in Photonics. His work within cancer imaging has led to the development of

a new device that could transform how chronic wounds are treated. The device, called PRODIGI, enables health care providers to rapidly track the number of bacteria in wounds at the patient's bedside thus providing physicians with an accurate diagnosis with which they can customize patient treatments.

Brian Wilson Presented with Biomedical Optics Award



PM Cancer Centre Senior Scientist, Dr. [Brian Wilson](#), has been awarded the 2014 Britton Chance Biomedical Optics



Magnetic resonance imaging (used above, to visualize labelled cells within the brain) relies on magnetic fields and radiowaves to create accurate images of the body.

nanoparticles convert the light into heat energy and kill the tumour cells. Currently, gold nanoparticles are being used for photothermal therapy, but they are non-biodegradable and therefore raise questions as to their toxicity after long-term use.

An emerging alternative nanoparticle is the porphyrin, which is biodegradable and equally as effective as gold in transferring light into heat energy. The research team of Dr. [Gang Zheng](#), Techna Team Lead and PM Senior Scientist, recently created a porphyrin loaded with the metal, manganese (Mn³⁺). They found that

Mn³⁺-porphyrins are non-toxic, highly stable and have excellent photothermal properties. Furthermore, the addition of Mn³⁺ actually allows these nanoparticles to be visualized using magnetic resonance imaging. This has important implications as Mn³⁺-porphyrins can be used to simultaneously visualize tumours and apply treatment in real time, which leads to increased accuracy and efficiency of photothermal therapy.

The porphyrin created by Dr. Zheng's team is a highly customizable particle that could be used to target a variety of difficult to treat cancers, thus representing a valuable new tool for development of new therapies.

This work was supported by the Ontario Institute for Cancer Research, the Natural Sciences and Engineering Research Council of Canada, the Canadian Institutes of Health Research, the Canada Foundation for Innovation and the Princess Margaret Cancer Foundation. G Zheng holds a Joey and Toby Tanenbaum / Brazilian Ball Chair in Prostate Cancer Research.

An MRI-sensitive, non-photobleachable porphyrin photothermal agent. MacDonald TD, Liu TW, and Zheng G. Angewandte Chemie International Edition. 2014 May 19. [[Pubmed abstract](#)]

Breast Cancer: Choosing Reconstruction with Surgery



IBR with a silicone implant such as those pictured above can improve quality of life and emotional well-being following a mastectomy.

Approximately one third of women with breast cancer will undergo a surgical procedure called a mastectomy to remove one or both breasts as part of their treatment. For those at high risk of developing breast cancer, the procedure is often carried out as a preventative measure. Immediate breast reconstruction (IBR), where the surgeon rebuilds the breast in the same procedure as the mastectomy—sometimes sparing the skin and nipple—is one option to help improve quality of life for breast cancer survivors. However, it has been reported that IBR is under used.

PM Clinical Researcher Dr. [Toni Zhong](#) examined procedure information from the Canadian Institute for Health Information (CIHI) database to identify factors that influence the IBR choice and access to the procedure. The team found that patients receiving mastectomy without reconstruction

Award by SPIE (the International Society for Optics and Photonics). The award is presented annually to one outstanding researcher within the field of biomedical optics who has made pioneering contributions to innovative biophotonic technologies.

Dr. Wilson serves as Director of the Laboratory of Applied Biophotonics at UHN, where his research is focused on the development of new cancer therapeutics that use laser and optical technologies. With a strong translational focus, Dr. Wilson's research program has led to the creation of new photodynamic therapies (eg, light-sensitive drugs), imaging techniques (including the use of optical imaging to guide surgery) and nanotechnologies for the treatment and diagnosis of cancer.

The award honours his high quality contributions to the field of biomedical optics over more than 30 years. Congratulations Dr. Wilson!

Donna Stewart Honoured for Contributions to Women's Health



TGRI Senior Scientist Dr. [Donna Stewart](#) was recently appointed a Member of the Order of Canada in recognition of her distinguished contributions to women's health. Her research in this field has generated more than 350 research publications; a number of which have provided profound insights into women's mental health, social determinants of health,

were more likely to come from lower income or immigrant neighbourhoods. Furthermore, the likelihood that the reconstruction procedure was carried out was much higher at teaching hospitals or those institutions where two or more plastic surgeons were on staff, and patients undergoing IBR were more likely to travel longer distances to get the procedure. "As well as socioeconomic factors, the undersupply of plastic surgeons in Ontario may be a factor in the low rates of IBR; only 40 of Ontario's 193 hospital sites met the two or more plastic surgeon criteria," says Dr. Zhong.

This work was supported by the Canadian Breast Cancer Foundation, Cancer Care Ontario, the Institute for Clinical Evaluative Sciences, the Ontario Ministry of Health and Long-Term Care and The Princess Margaret Cancer Foundation.

Barriers to immediate breast reconstruction in the Canadian universal health care system. Zhong T, Fernandes KA, Saskin R, Sutradhar R, Platt J, Beber BA, Novak CB, McCready DR, Hofer SO, Irish JC, Baxter NN. Journal of Clinical Oncology. 2014 July. [PubMed abstract]

Motion Sickness: What You Hear Matters



The vestibular system, part of the inner ear (pictured), comprises three semicircular canals (in purple) that enable motion and balance to be perceived in three dimensions.

Motion sickness can lead to distressing symptoms that include nausea, dizziness and fatigue. While the underlying cause of this condition is not known, it often occurs when sensory perceptions do not match (for example, when visual cues conflict with perceptions of balance originating from the vestibular system of the inner ear).

While motion sickness is often experienced by travellers, a related condition known as simulator sickness can occur when using gaming and virtual reality systems. Simulator sickness can occur in the absence of physical movement and is therefore said to be "visually induced"; however, very little is known about whether simulated

sounds contribute to this condition.

To explore the role of sound, TRI postdoctoral fellow Behrang Keshavarz in collaboration with TRI Scientist Dr. [Jennifer Campos](#) led a study in which 20 participants were placed in an immersive virtual reality dome ([iDAPT's StreetLab](#)). Participants were exposed to a series of visual or audio cues to simulate perceptions of rotating and were also asked to tilt their heads at various points, to further enhance the simulation.

As expected, visual cues were found to be highly effective at inducing simulator sickness; surprisingly, 25% of participants also experienced the condition when exposed to sound alone. Dr. Keshavarz comments, "This finding reveals the existence of a new type of motion sickness—one caused purely by sound. This insight will help us design better simulation technologies that account for and help minimize the effects of motion sickness."

This work was supported by the Toronto Rehab Foundation.

Demonstrating the potential for dynamic auditory stimulation to contribute to motion

interpersonal violence and psychological aspects of reproductive health.

Dr. Stewart continues to contribute to the field of women's health as the Director and inaugural Chair of Women's Health at UHN and the University of Toronto, where she is responsible for research, education, policy and health service delivery in this field.

The Order of Canada is awarded to leaders from all sectors of Canadian society and recognizes lifetime outstanding achievements, dedication to the community and service to Canadians.

Andres Lozano Named University Professor at UofT



TWRI Senior Scientist Dr. [Andres Lozano](#) has been honoured by the University of Toronto with a prestigious appointment to

University Professor—a rank attained by only 2% of tenured faculty. Dr. Lozano's groundbreaking work in surgery, deep brain stimulation (DBS) and high-intensity focused ultrasound (HIFU) have opened new treatment pathways for many patients who had otherwise run out of options for Alzheimer's, Parkinson's and severe depression. The designation recognizes these research achievements, as well as his commitment to education.

He is the first neurosurgeon to receive this distinction for academic excellence, and the fifth at UHN, joining Drs. Tirone David, Tak Mak, Donna

sickness. Keshavarz B, Hettinger LJ, Kennedy RS, Campos JL. PLoS One. 2014 July 1. [[Pubmed abstract](#)]

Stewart and James Till.



NRx is brought to you by UHN Research Communications.

We hope you have enjoyed receiving this message. If you have any feedback, please email www@uhnresearch.ca.

To access archived issues of NRx, visit uhnresearch.ca/news/netresultsexpress

Some images adapted from the image archives of stock.xchng.ca, Wikimedia Commons and Wikipedia.