NRx
Advances in Research at UHN

February 2015

Welcome to the February Issue of NRx

As UHN's monthly research newsletter, NRx reports on the full spectrum of leading research from UHN's five research institutes: 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:

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: Tumours Hijack Antioxidants to Survive

The Canadian Cancer Society recommends eating unprocessed and fresh foods that are rich in antioxidants rather than taking high-dose antioxidant supplements

The role of antioxidants in cancer is highly controversial. Some studies show that an antioxidant-rich diet is important for health, while others indicate that antioxidants taken in pill form can be harmful. New findings from PM Cancer Centre Senior Scientist Dr. Tak Mak add to the controversy by revealing that tumour growth may be enhanced by the presence of high levels of antioxidants.

Dr. Mak explains, "When cells grow and divide, they produce harmful oxidative byproducts. Cancer cells, which grow very quickly and therefore produce high levels of harmful oxidative byproducts, may increase the production of antioxidants to

Research News & Events

UHN Surgeon-in-Chief Appointed to Order of Canada

TGRI Senior Scientist and UHN Surgeon-in-Chief Dr. Shaf Keshavjee has been appointed an Officer of the Order of Canada—one of the country's highest civilian honours. The distinction recognizes outstanding achievements that have improved the lives of Canadians.

Dr. Keshavjee received the distinction for his innovative contributions to thoracic surgery, notably in the development of the Ex Vivo Lung Perfusion System, which has improved lung transplantation worldwide.

The process effectively preserves donor organs and extends the window of time that an organ can be removed from a deceased donor and transplanted into a recipient without tissue deterioration. Specifically, the technology enables lungs to be preserved outside of the body for over 25 hours, improving on existing limits, which require

support their survival."

In a recent article published in the journal *Cancer Cell*, Dr. Mak and his team revealed that turning off two key antioxidant pathways in an experimental cancer model delays the development and reduces the severity of a variety of cancers.

The two pathways that the researchers targeted were glutathione (GSH) and theoredoxin (TXN). Drugs capable of turning these pathways off are currently being used to treat rheumatoid arthritis. Because the drugs are approved for use in humans, they could help to fast track these findings towards new, effective treatments for cancer patients.

This work was supported by the Natural Sciences and Engineering Council of Canada, the German Research Foundation, the ATTRACT program of the Luxembourg National Research Fund, the Canadian Institutes of Health Research and the Princess Margaret Cancer Foundation. T Mak holds a Tier 1 Canada Research Chair in Inflammation Responses and Traumatic Injury.

Glutathione and thioredoxin antioxidant pathways synergize to drive cancer initiation and progression. Harris IS, Treloar AE, Inoue S, Sasaki M, Gorrini C, Lee KC, Yung KY, Brenner D, Knobbe-Thomsen CB, Cox MA, Elia A, Berger T, Cescon DW, Adeoye A, Brüstle A, Molyneux SD, Mason JM, Li WY, Yamamoto K, Wakeham A, Berman HK, Khokha R, Done SJ, Kavanagh TJ, Lam CW, Mak TW. Cancer Cell. *2015 January 21.* [Pubmed abstract]

Physical Activity: Regular Exercise not Enough

Sedentary activities and high blood sugar levels carry the same level of risk of death.

Sedentary activities—such as sitting while watching TV or working at your computer—are the fourth leading risk factor for death worldwide. To counteract this, the World Health Organization recommends that adults should participate in at least 150 minutes of moderate physical activity—such as walking or cycling—per week. However, a recent study published by TRI Senior Scientist Dr. David Alter suggests that this may not be enough to completely eliminate the negative health effects linked to sedentary activity.

Dr. Alters' research team identified 41 studies conducted in different countries worldwide that examined the relationship between the length of time spent sitting and a variety of diseases and conditions. By performing a careful statistical analysis of the results of these studies, the research team found that the longer that a person sits, the greater their risk of dying of or developing heart disease, type II diabetes or cancer. Even people who participate in regular physical activities are at risk, albeit a lower risk than those who remain inactive.

"Our results and others reaffirm the need for greater public awareness about the hazards linked to physical inactivity and justify further research to explore the effectiveness of new approaches to minimize it," says Dr. Alter.

This work was supported by the Heart & Stroke Foundation of Canada, the Canadian

transplantation to occur within four hours. Congratulations to Dr. Keshavjee.

UHN Researcher Inducted into IOM

The United States Institute of Medicine (IOM) recently announced the election of 70 new members, and TGRI Affiliate Scientist Dr. Michael Sefton was among the Institute's latest inductees. IOM members are individuals who have made major contributions to the advancement of the medical sciences, health care and public health.

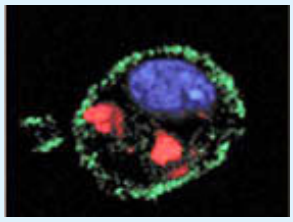
Dr. Sefton is a leader in the fields of tissue engineering, biomaterials, biomedical engineering and regenerative medicine. He pioneered the technique of surrounding living cells with artificial polymers. The encapsulated cells can then be transplanted into a host without being detected by its immune system. The technique could be used, for example, to deliver insulin-producing cells into diabetic patients. Dr. Sefton's research also focuses on the engineering of different materials that are compatible with the human body to improve artificial organs and implanted medical devices, such as stents.

IOM was established in 1970 and serves as a national resource for independent, scientifically-informed analyses and recommendations on health issues. Congratulations to Dr. Sefton on being selected to join this prestigious Institute.

Institutes of Health Research, the Public Health Agency of Canada and the Toronto Rehab Foundation.

Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA. Annals of Internal Medicine. *2015 January 20.* [Pubmed abstract]

Osteoarthritis: Eating Away at the Joint



In cells undergoing autophagy, specialized structures called autophagosomes (red in the microscope image above) use acids to break down unwanted cellular components.

Osteoarthritis (OA) is characterized by the erosion of joint cartilage (the tough elastic material that protects the ends of bones). This damage is caused by inflammation, which can lead to joint stiffness and swelling that can be debilitating. The mechanisms responsible for joint inflammation and cartilage destruction in OA are not fully known; however, a recent study led by TWRI Scientist, Dr. Mohit Kapoor, has revealed one of the processes responsible.

Using an experimental model of OA, Dr. Kapoor and his team discovered that PPARγ—a factor that governs genes that respond to inflammation and joint destruction—is critical to keep the disease under control. PPARγ promoted autophagy, a self-protective process in which debris are recycled within cells. When PPARγ function was lost, joint inflammation and cartilage destruction increased—two effects that when combined accelerated the progression and severity of OA.

This study suggests that therapeutics capable of promoting PPARγ function may be effective for OA. These anti-inflammatory drugs, known as PPARγ agonists, are already approved for treating diseases like diabetes. As such, they represent an accessible option for improving the quality of life of people with OA.

This work was supported by the Canadian Institutes of Health Research, the Canadian Arthritis Network/The Arthritis Society and the Toronto General & Western Hospital Foundation. Image modified from "Pan et al. Cathepsin S deficiency results in abnormal accumulation of autophagosomes in macrophages and enhances Ang II-induced cardiac inflammation. PLoS One. 2012. 7(4):e35315".

PPARγ deficiency results in severe, accelerated osteoarthritis associated with aberrant mTOR signalling in the articular cartilage. Vasheghani F, Zhang Y, Li YH, Blati M, Fahmi H, Lussier B, Roughley P, Lagares D, Endisha H, Saffar B, Lajeunesse D, Marshall WK, Rampersaud YR, Mahomed NN, Gandhi R, Pelletier JP, Martel-Pelletier J, Kapoor M. Annals of Rheumatic Disease. *2015 January 8.* [Pubmed abstract]

Heart Disease: Harmful Effects of Intense Exercise

Regular physical exercise is beneficial to our wellbeing. It not only improves cardiovascular health but also boosts

Dr. John Floras Named a Fellow of the CAHS

Dr. John Floras, TGRI Senior Scientist and Tier 1 Canada Research Chair in Integrative Cardiovascular Biology, has been elected to the Fellowship of the Canadian Academy of Health Sciences (CAHS). Considered one of the highest honours for Canadians in the health sciences community, election into the Fellowship occurs through a nomination and peer-review process that demonstrates Dr. Floras' internationally renowned leadership and broad range of achievements.

The award recognizes Dr. Floras' contributions to our understanding of hypertension, heart failure, sleep apnea, and the role of heart function on the kidneys and lungs. He has published approximately 250 articles that have been cited close to 10,000 times—evidence of the impact and significance of his work. Dr. Floras has also recently been honoured with the Research Achievement Award from the Canadian Cardiovascular Society (2011) and a Lifetime of Service to the Science of Medicine Award from the Hellenic Cardiological Society (2013).

Dr. Padraig Warde made Honorary Fellow

In honour of his outstanding achievements in radiation oncology, Clinical Researcher at PM Cancer Centre Dr.

Endurance athletes are at risk for atrial fibrillation even though they do not suffer from traditional risk factors of the disease such as obesity or high blood pressure. Photo by Raniel Diaz (Flickr).

the immune system, promotes brain regeneration and effectively combats conditions such as diabetes and obesity. However, high intensity endurance exercise can have a negative impact on heart health by increasing susceptibility to atrial fibrillation—a very common condition that is associated with irregular heartbeats, palpitations and shortness of breath.

A recent study by TGRI Senior Scientist Dr. Peter Backx has shed light on how intense exercise exerts this effect. The study showed that while exposure to highly intense exercise did improve heart function it also led to structural changes in the two upper chambers of the heart (atria). These changes, which involved formation of excess connective tissue in the heart and increased numbers of inflammatory cells, were associated with increased vulnerability to atrial fibrillation. Furthermore, the changes were dependent on the activity of a protein known as TNFα (tumour necrosis factor alpha), which is a key factor in inflammation.

Explains Dr. Backx, "Although preliminary, our study suggests that inhibiting TNFα could minimize the harm caused to the heart's atria by intense exercise. To this end, we have ongoing collaborations with Dr. Goodman (University of Toronto) and Drs. Dorian and Connelly (St. Michael's Hospital) to identify individuals at higher risk of developing exercise-associated atrial fibrillation and who would benefit most from such treatments."

This work was supported by the Canadian Institutes of Health Research, the American Heart Association, the National Institutes of Health and the Toronto General & Western Hospital Foundation.

Increased atrialarrhythmia susceptibility induced by intenseendurance exercise in mice requires TNFα. Aschar-Sobbi R, Izaddoustdar F, Korogyi AS, Wang Q, Farman GP, Yang F, Yang W, Dorian D, Simpson JA, Tuomi JM, Jones DL, Nanthakumar K, Cox B, Wehrens XH,Dorian P, Backx PH. Nature Communications*. 2015 January 19.* [Pubmed abstract]

Heart Failure: Inexpensive Test May Save Lives

Acute heart failure (requiring immediate treatment) and chronic heart failure (slow developing) are facets of the same disease: both occur when the heart cannot keep up with the

Acute heart failure syndrome (AHFS) is a form of heart failure that requires urgent treatment and admission to a hospital's emergency department. The underlying causes of AHFS vary widely and include worsening chronic heart failure, a heart attack or extreme hypertension. Given the mix of patients admitted to hospitals for AHFS, the assessment of these patients can be challenging.

A recent study by TGRI Scientist Dr. Douglas Lee may change this. His team analyzed blood sugar readings taken for over 16 thousand AHFS patients admitted to emergency departments across Ontario. By comparing these readings with

Padraig Warde was named an Honorary Fellow of the Faculty of Radiologists of the Royal College of Surgeons in Ireland. The Fellowship is the College's highest distinction.

Dr. Warde's program is focused on clinical and translational research into prostate and testis cancer. Congratulations to Dr. Warde.

body's demands.

patient outcomes, the team found that blood glucose measurements could be used to predict those who are at greatest risk for further hospitalization or early mortality. Surprisingly, the team also found that random blood sugar measurements at the time of emergency department presentation could be used to identify those patients that are at greatest risk of developing diabetes.

Dr. Lee states, "These results provide physicians with a more refined tool for identifying, from the full spectrum of acute heart failure patients, those who are at greater risk of early death and future hospitalization. Furthermore, measuring blood sugar levels at this stage could help predict which patients are likely to develop diabetes, thus enabling preventative measures to be started earlier."

This work was supported by the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Ontario, and the Toronto General & Western Hospital Foundation. JV Tu holds a Tier 1 Canada Research Chair in Health Services Research.

Presentation blood glucose and death, hospitalization, and future diabetes risk in patients with acute heart failure syndromes. Sud M, Wang X, Austin PC, Lipscombe LL, Newton GE, Tu JV, Vasan RS, Lee DS. European Heart Journal. *2015 January 8.* [Pubmed abstract]

HPC4Health Brings Cloud Computing to Health Research

UHN and SickKids have joined efforts to create High-performance Computing for Healthcare (HPC4Health), a service that provides researchers and clinicians with cloud-based high performance computing. The resource-sharing model will be secure and will satisfy personal health information privacy requirements.

HPC4Health is a necessary resource for scientists in today's world of big data. This huge volume of data is created by increasingly complex research modalities, such as molecular analyses and medical imaging, and requires high performance computing servers and storage solutions to keep pace. HPC4Health will address this need, ultimately serving to fast track medical research and to improve clinical decision making.

The infrastructure will be housed at the new Peter Gilgan Centre for Research and Learning at SickKids. It will be accessible to all Toronto hospitals and there are plans to eventually expand access to the service across Canada. HPC4Health was made possible by support from Compute Ontario, Compute Canada, the Canada Foundation for Innovation, The Princess Margaret Cancer Foundation and SickKids Foundation. For more information, please visit the HPC4Health website.

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