The Krembil

March 2016

Introducing *The Krembil*: the official newsletter of the Krembil Research Institute (formerly the Toronto Western Research Institute). *The Krembil* informs the Toronto Western Hospital community, external stakeholders and interested community members about the exciting news and innovative research happening at the Krembil Research Institute.

In this issue you can read about:

Donald Weaver, PhD, MD, FRCPC, FCAHS
Director, Krembil Research Institute
University Health Network

News

Krembil Annual Research Day Fast Approaching

The Krembil Research Institute (Krembil) will be holding its 16th annual Research Day on Wednesday, May 18, 2016. The event will feature the latest in research advances and innovative technologies from Krembil's basic science and clinical researchers. It will also be an opportunity for Krembil's trainees to showcase their research achievements. This year's Research Day will be held at the Chestnut Residence and Conference Centre on 89 Chestnut Street.

This year's Keynote Speaker will be Dr. Betty Diamond, Investigator and Head of the Center for Autoimmune and Musculoskeletal Diseases at The Feinstein Institute for Medical Research. Dr. Diamond's research focuses on the autoimmune disease, systemic lupus erythematosus. A distinguished scientist, her studies have provided valuable insights that inform the creation of new therapies to treat autoimmune diseases.

Krembil appointed Scientists, Clinician Investigators, Clinical Researchers, trainees and staff are welcome to attend the event. It is also open to members from the Department of Chemistry at the University of Toronto. There is no registration fee, but you must complete online registration if you are planning to attend Krembil Research Day. Registration, abstract submission and additional information can be found on the Krembil Research Day Website.

The deadline for general registration is Friday, April 29, 2016 at 4pm.

The deadline for abstract submission is Thursday, March 31, 2016 at 4pm.

Krembil Senior Scientists Announced as Canada Research Chairs

The Honourable Kirsty Duncan, Minister of Science, recently announced a total of 305 new and renewed Canada Research Chairs (CRCs). Two of the CRCs were bestowed on Senior Scientists at the Krembil Research Institute: Dr. Donald Weaver received a Tier 1 CRC, and Dr. Antonio Strafella had his Tier 2 CRC renewed.

Dr. Weaver is a neurologist and medicinal chemist whose research focuses on drug discovery for protein misfolding disorders, including Alzheimer disease and progressive supranuclear palsy. He uses chemistry and computational modelling with the aim of developing candidate molecules and drugs that are capable of halting the progression of neurodegenerative disease.

Dr. Strafella is a neurologist with expertise in movement disorders and functional brain imaging. He uses advanced imaging techniques like positron emission tomography to measure changes in the brain of people with Parkinson disease, particularly those that are associated with impulse control such as pathological gambling, hypersexual behaviour, compulsive shopping and binge eating.

The CRC program stands at the center of a national strategy to enhance Canada's international reputation as a leader in research and development. It was created in 2000 to help Canada attract and retain some of the world's most brilliant scientific minds. Through research excellence in the fields of engineering, natural sciences, health sciences, humanities and social sciences, CRC award holders enhance our quality of life and build our nation's economy. They also help build the next generation of scientists through student supervision, teaching and mentoring junior researchers.

Research

Lupus: Matters of the Heart

Over a third of the patients with systemic lupus erythematosus develop lupus nephritis (LN), a severe inflammation of the kidneys that leads to loss of kidney function and eventually death. These patients are often treated with a class of drugs, called angiotensin converting enzyme (ACE) inhibitors, which reduce proteinuria, one of the markers of impaired kidney function.

ACE inhibitors are also commonly prescribed to patients at risk of developing heart disease. This suggests that patients with LN may have the dual benefits of improved kidney and heart function following ACE inhibitor treatment.

To determine if this is the case, Krembil Scientist Dr. Murray Urowitz and his team led a five-year study to measure cardiac events in patients with LN who were either treated or not treated with ACE inhibitors. He found that patients who were treated with the inhibitors were just as likely to experience the type of heart-related problems that occur due to narrowed or clogged arteries, such as a heart attack or stroke.

“There are many possible explanations for these results, including the fact that the efficacy of ACE inhibitors was mostly evaluated in individuals without lupus,” explains Dr. Urowitz. “We need to confirm our findings in a large scale multicentre study to get a more definite answer as to why patients with lupus respond differently to ACE inhibitors.”

This work was supported by the Toronto General & Western Hospital Foundation.

Does renin-angiotensin system blockade protect lupus nephritis patients from atherosclerotic cardiovascular events? A case-control study. Tselios K, Gladman DD, Su J, Urowitz MB. Arthritis Care Research (Hoboken). 2016 Feb 11. doi: 10.1002/acr.22857. [Pubmed Abstract]

Vision Loss: Early Detection

Diabetic retinopathy is the leading cause of vision loss in Canada and the most common cause of blindness in individuals with diabetes under the age of 65. It occurs when blood vessels in the eye become damaged causing abnormal bleeding and is associated with chronically high levels of sugar in the blood in those with diabetes.

With proper treatment and monitoring of the eye, vision loss could be slowed in a majority of cases; however, once vision loss occurs it is irreversible. Researchers have therefore been searching for new methods to improve the early detection and management of diabetic retinopathy.

Krembil Senior Scientist Dr. Christopher Hudson and his research team, which included Drs. Faryan Tayyari, Lee-Anne Khuu and other collaborators, recently conducted a study to address this problem. As part of the study, his team measured retinal blood flow in patients with mild to moderate diabetic retinopathy. As an indirect measure of retinal blood vessel health, they quantified the rate at which oxygen from the blood was being taken up by retinal cells.

The researchers found that, compared to healthy study participants, individuals with mild diabetic retinopathy had significantly lower retinal blood flow and reduced rates of oxygen consumption.

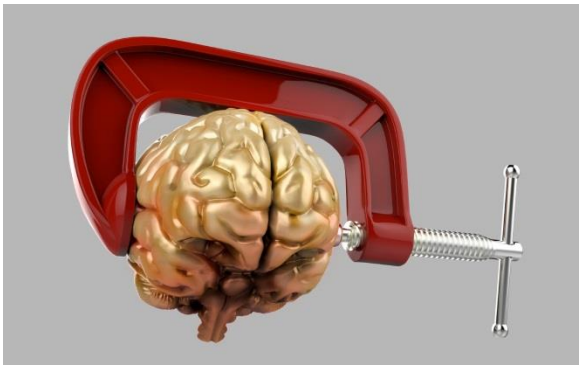
“To the best of our knowledge, this is the first study to non-invasively investigate the relationship between retinal blood flow, retinal oxygen levels and diabetic retinopathy in humans,” explains Dr. Hudson. “The findings suggest that we could

use changes in retinal blood flow and oxygen consumption to detect the disease earlier and initiate treatments to slow down disease progression."

This work was supported by Ontario Research Fund for Research Excellence, The University of Toronto/University Health Network Vision Science Research Program Scholarship to Dr. L Khuu, Optina Inc. and the Toronto General & Western Hospital Foundation.

Retinal blood flow and retinal blood oxygen saturation in mild to moderate diabetic retinopathy. Tayyari F, Khuu LA, Flanagan JG, Singer S, Brent MH, Hudson C. Investigative Ophthalmology & Visual Science. 2015 Oct. doi:10.1167/iovs.15-17481. [Pubmed Abstract]

Chronic Pain: Rewiring the Brain



The brain is organized into specialized regions that are highly connected with each other. These connected regions are called networks. Research insights have linked a wide range of disorders—including autism and Alzheimer disease—to changes in how different brain networks communicate with each other.

Recently, it has been shown that two networks in particular—known as the salience network (SN) and the default mode network (DMN)—play a role in how we experience pain. However, how these two brain networks coordinate their activities in the context of chronic pain is not understood. Under normal conditions, the SN is active during attentive or focused thinking, while the DMN is deactivated.

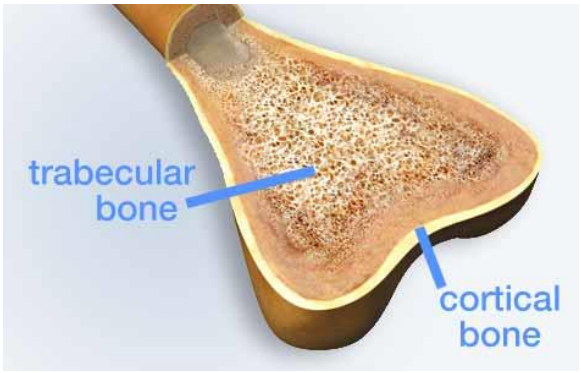
To look at whether these two networks behave differently in chronic pain, Krembil Senior Scientists Drs. Karen Davis and Robert Inman, and doctoral student Kasey Hemington measured brain network activity in individuals with a form of arthritis called ankylosing spondylitis. The results showed that, compared to healthy controls, activity in the SN and DMN brain regions in those experiencing chronic pain were less coordinated—when one region was on, the other did not turn off as expected. Importantly, the greater the level of cross-network dysfunction, the greater the individuals' perceived level of pain.

"Our study implicates altered communication between brain networks as a key feature underlying chronic pain," says Dr. Davis. "While further study is needed to determine the exact interaction between pain, and SN and DMN activity, these findings lay the groundwork for new therapeutic approaches that could help relieve chronic pain."

This work was supported by the Canadian Institutes of Health Research and the Toronto General & Western Hospital Foundation. K Davis was supported by the Canada Research Chairs program.

Abnormal cross-network functional connectivity in chronic pain and its association with clinical symptoms. Hemington KS, Wu Q, Kucyi A, Inman RD, Davis KD. Brain Structure & Function*. 2015 Dec 15.* [Pubmed Abstract]

Arthritis and Bone Health: the Anatomy of Disease



Ankylosing spondylitis is a debilitating form of arthritis that mainly affects the spine. As the disease progresses, complex changes in bone architecture occur. At early stages, the density of the minerals in the spine (bone mineral density) is reduced, while at later stages the outer parts of the vertebrae thicken and fuse together.

To study disease progression, much of the existing research has relied on the use of X-ray images (radiographs) to measure changes in bone. However, because radiographs are two-dimensional, they are unable to show the differences between the harder outer bone and the spongy inner bone.

A recent study, led by TGRI Senior Scientist Dr. Angela Cheung along with Krembil Senior Scientist Dr. Robert Inman, Krembil Scientist Dr. Nigil Haroon and TGRI Scientist Dr. Janet Raboud, used newer, high-resolution imaging to analyse the changes to bone architecture in three dimensions. Their findings revealed that in those with ankylosing spondylitis, the

harder outer bone in certain skeletal regions had reduced thickness and reduced bone mineral density when measured in three dimensions. These regions were also found to be more porous. Surprisingly, no changes were found in the spongy inner bone.

"While previous findings have suggested that ankylosing spondylitis is associated with weakening of the inner, spongy trabecular bone, our results suggest that an important feature of the disease is that the compact, outer cortical bone becomes compromised. Because cortical bone is weight bearing, these results may explain why those with the disease are at increased risk of vertebral fractures," explains Dr. Cheung.

These findings provide much needed insight into changes that occur in the bones of those with ankylosing spondylitis that will inform the development of new ways of diagnosing and treating the disease.

This work was supported by Amgen Canada and the Canadian Institutes of Health Research. AM Cheung holds a Tier 1 Canada Research Chair in Musculoskeletal and Postmenopausal Health.

Alterations of bone mineral density, bone microarchitecture and strength in patients with ankylosing spondylitis: a cross-sectional study using high-resolution peripheral quantitative computerized tomography and finite element analysis. Haroon N, Szabo E, Raboud JM, Mcdonald-Blumer H, Fung L, Josse RG, Inman RD, Cheung AM. Arthritis Research & Therapy. *2015 Dec 24.* [Pubmed Abstract]

Spinal Injury: Improving Surgical Outcome

Cervical spondolytic myelopathy (CSM) is the leading cause of spinal cord injury in individuals over the age of 55. It occurs when the spinal cord becomes compressed due to chronic and progressive deterioration of the spine.

Surgery can alleviate some of the symptoms associated with CSM and improve the quality of life for patients with the disease. However, the procedure has a high risk of failure and can damage the spine and lead to a decrease in brain function.

By using an experimental model of CSM, Krembil Senior Scientist Dr. Michael Fehlings and his team have been able to determine why decompression surgeries can sometimes lead to neurological decline.

They found that CSM post-surgery complications are partly caused by a rapid increase in blood flow, which occurs when the pressure on the spinal cord is removed. Administering riluzole—a drug that has been shown to protect the health of neurons—can protect the spine from injury after surgery and reduce the risk of any additional neurological decline.

“Our report identifies a silent and thus far unrecognized factor that may account for the rate of post-surgical complications in patients with CSM,” explains Dr. Fehlings. “Based on these findings, we have launched a large-scale North American clinical trial to determine whether riluzole can improve outcomes for patients with CSM following decompression surgery.”

This work was supported by the Cervical Spine Research Society, the Canadian Institutes of Health Research, the Gerry and Tootsie Halbert Regeneration Chair, AOSpine North America and the Toronto General & Western Hospital Foundation.

Riluzole blocks perioperative ischemia-reperfusion injury and enhances postdecompression outcomes in cervical spondylotic myelopathy. Karadimas SK, Laliberte AM, Tetreault L, Chung YS, Arnold P, Foltz WD, Fehlings MG. Sci Transl Med. *2015 Dec 2;7(316):316ra194. doi: 10.1126/scitranslmed.aac6524.* [Pubmed Abstract]

Parkinson Disease: Targeted Therapy

Brain plasticity—the ability of the brain to strengthen or weaken neural connections—allows the brain to adapt to experiences. In advanced Parkinson disease, researchers have found that plasticity is impaired in certain regions of the brain.

Two emerging therapies, which have been shown to improve brain plasticity and reduce symptoms in those with advanced Parkinson disease, are currently under development. These therapies, known as deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS), are typically used independently. However, a recent study led by Krembil Senior Scientist Dr. Robert Chen explored the effect of combining DBS and TMS on inducing brain plasticity in those with Parkinson disease.

Dr. Chen comments, “DBS and TMS have different targeting capabilities: DBS can stimulate deep brain structures, while TMS can alter the electrical activity of the outer regions of the brain. By taking advantage of these different capabilities, we were able to enhance communication between two regions of the brain that are dysfunctional in Parkinson disease.”

“While only 10 patients were involved in this preliminary study, the results are very promising—this is the first study to combine these two therapies and demonstrate that they can promote plasticity in the specific neural pathways that are involved in disease,” says Dr. Chen.

Future studies will explore whether this combined therapy has therapeutic effects beyond improving plasticity in those with Parkinson disease.

This work was supported by the Canadian Institutes of Health Research and the Toronto General & Western Hospital Foundation. AM Lozano is a Tier 1 Canada Research Chair in Neuroscience. R Chen holds the Catherine Manson Chair in Movement Disorders.

Cortical plasticity induction by pairing subthalamic nucleus deep-brain stimulation and primary motor cortical transcranial magnetic stimulation in Parkinson's disease. Udupa K, Bahl N, Ni Z, Gunraj C, Mazzella F, Moro E, Hodaie M, Lozano AM, Lang AE, Chen R. The Journal of Neuroscience*. 2016 Jan 13.* [Pubmed Abstract]

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For inquiries related to The Krembil newsletter, please contact us: ndery@uhnresearch.ca.