The Krembil

November 2015

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

Toronto Western Research Institute Becomes the Krembil

Krembil
Relentless.

The Toronto Western Research Institute was rebranded as the Krembil Research Institute (Krembil) during an event held on November 13, 2015. Her Royal Highness, The Princess Edward, Countess of Wessex, the patron of the Toronto Western and General Hospitals, was on hand to make the announcement. Other speakers at the event included UHN President and CEO Dr. Peter Pisters; Director of the Krembil Research Institute Dr. Donald Weaver; and philanthropist, visionary and UHN trustee Robert Krembil.

The Krembil takes its new name in recognition of a family that understands the value of supporting world-class medical research. “Our family has been involved with the Toronto Western Hospital for

more than 18 years," said Robert Krembil. "During this time, we have gained a deep appreciation for the research excellence of the scientists who are working to find cures for some of the most debilitating health issues of our day."

Dr. Weaver sees the Krembil family's ongoing investment as vital to the Institute's lasting success. "One of the important things to recognize is that brilliant science needs support to make it come to life," said Dr. Weaver. The Director of the newly-branded Krembil looks to a world without chronic, debilitating disorders. He sees the chronic diseases that affect the brain, spine, bones, joints and eyes being cured—easing an enormous burden on patients, their families and the healthcare system. "We're not here simply to research these diseases... we're here to stop them in their tracks."

Krembil Research Institute's New Clinician Investigator Appointment

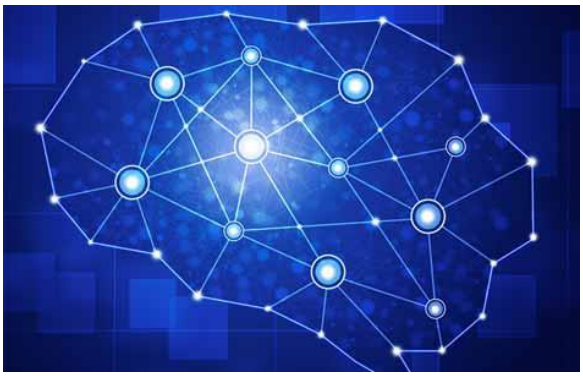
A new "Clinician Investigator" appointment has been created at the Krembil Research Institute to facilitate and advance clinical research at the Toronto Western Hospital. The appointment is open to physicians, nurses and allied health professionals who meet UHN's policy for Principal Investigator eligibility.

Clinician Investigators spend a majority of their time dedicated to clinical service, but they also lead clinical research projects; they hold a primary appointment outside of the Krembil Research Institute. Accordingly, Clinician Investigators will not receive salary, space or research start-up funds from the Krembil Research Institute. However, they will be eligible to apply for Krembil Research Institute funding opportunities that are dedicated to clinical research. Clinician Investigator grant applications will be approved by Dr. Donald Weaver, Director of Krembil Research Institute, and supported by other resources based on availability.

Interested applicants must be actively performing clinical research and meet the criteria of research excellence established for this class of appointment, which will be evaluated based on the following: research funding; publication record; invited lectureships; engagement in teaching and mentorship roles; and participation on committees. Interested applicants should submit a letter of interest and a current CV to the Krembil Research Institute's Interim Business Officer Dr. Amy Ma (amy.ma@uhnresearch.ca; 416-603-5873).

Research

Neuroscience: Connectivity Curbs Compulsiveness



Obsessive compulsive disorder (OCD) is a devastating illness characterized by intrusive and persistent thoughts (obsessions) as well as disruptive and repetitive behaviours (compulsions). People afflicted with OCD are unable to control their obsessions or compulsions and close to 60% of them do not respond to traditional drug therapy.

Communication errors between certain brain regions (known as abnormal connectivity) is thought to underlie OCD. Thus, therapies aimed at restoring normal brain connectivity offer a novel approach to OCD treatment. Preliminary trials using surgically based therapies, such as deep brain stimulation, have shown promise but there is a need for more accessible and non-invasive alternatives.

Krembil Scientist Dr. Jonathan Downar and collaborators devised a new approach to treat OCD. First, they used repeated transcranial magnetic stimulation (rTMS) to restore normal connectivity between affected brain regions. The application of rTMS is a painless and non-invasive approach that involves placing a magnetic field on patients'' scalps to influence electrical activity in the brain. Second, they used an imaging technique to confirm the regions of OCD patients'' brains that displayed abnormal connectivity before treatment and how that connectivity changed after treatment.

Dr. Downar comments, "Of those treated, half responded favourably to rTMS—a remarkable finding considering that all of these patients were non-responsive to traditional therapy. The next step will be to refine our brain imaging method to better customize the rTMS treatment for each individual patient, with the aim of further improving treatment response."

This work was supported by the Canadian Institutes of Health Research, the National Institutes of Health, the Klarman Family Foundation, the Buchan Family Foundation and the Toronto General & Western Hospital Foundation.

Reductions in cortico-striatal hyperconnectivity accompany successful treatment of obsessive-compulsive disorder with dorsomedial prefrontal rTMS. Dunlop K, Woodside B, Olmsted M, Colton P, Giacobbe P, Downar J. Neuropsychopharmacology*. 2015 Oct 6.* [Pubmed Abstract]

Arthritis: Risk Factors for Cardiovascular Disease

People with psoriatic arthritis (PsA) experience the symptoms of psoriasis and arthritis, including itchy and scaly skin accompanied by joint inflammation, pain and discomfort. Studies have shown that cardiovascular events—such as heart attacks and strokes—occur more frequently in PsA patients than in the general population. Recently, Krembil Senior Scientist Dr. Dafna D Gladman, Dr. Lihi Eder (University of Toronto postdoctoral fellow) and collaborators analysed results from a large-scale study over 35 years to identify factors that put PsA patients at greater risk of cardiovascular disease.

For the study, the researchers enrolled 1,091 PsA patients who were examined every 6 to 12 months. The researchers tracked demographic information, lifestyle habits, medical history, medication use, laboratory test results and measures of PsA disease for each of the study participants. The study revealed that PsA patients with high blood pressure and diabetes were at a higher risk of cardiovascular disease. In addition to these traditional cardiovascular risk factors, the researchers showed that as the number of swollen fingers and toes increased, so did the patient's likelihood of having a cardiovascular event.

"We found that patients with PsA are much more likely to develop cardiovascular disease at some point in their lives as well as the characteristics of PsA that contribute to poor cardiovascular health," says Dr. Gladman. "These results highlight the importance of screening and controlling PsA symptoms in preventing cardiovascular disease."

This work was supported by the Krembil Foundation, the Canadian Institutes of Health Research (CIHR), the Arthritis Society and the Toronto General & Western Hospital Foundation. R Cook holds a Tier 1 Canada Research Chair in Statistical Methods for Health Research.

Incidence and predictors for cardiovascular events in patients with psoriatic arthritis. Eder L, Wu Y, Chandran V, Cook R, Gladman DD. Annals of the Rheumatic Diseases. *2015 Oct 22.* [Pubmed abstract]

Vision Disorders: Connecting the Dots

When human eyes look at their environment they collect pictures that are sent to the brain. Together these pictures form a visual representation of our world. The eyes transmit visual images to the brain through a cable that is composed of nerve fibres called retinal axons. The retinal axons connect the eye to visual areas of the brain, including the optic tectum (OT).

Unfortunately, retinal axons can degenerate in conditions like glaucoma, eventually leading to irreversible blindness. Currently, it is unknown how developing retinal axons connect with the brain, which has limited the creation of new therapies.

Recent findings from Krembil Senior Scientist Dr. Philippe Monnier have addressed this problem by shedding light on how retinal axons are guided during development. The researchers found that a group of peptides, known as Repulsive Guidance Molecule a (RGMa) subtypes, work in combination to help retinal axons target the OT. One of the subtypes, C-RGMa, inhibits deep projections in the optic tectum, while the other, N-RGMa, promotes deeper projections in the OT. A balance of both peptides ensures that retinal axons connect with the appropriate area of the OT.

Remarks Dr. Monnier, "Our work has uncovered the peptides responsible for ensuring that retinal axons integrate into the correct layer of the OT. These insights may help developing therapies aimed at restoring vision in patients with retinal axon damage."

This work was supported by the Canadian Institutes of Health Research, the Vision Science Research Program of the University of Toronto and the Toronto General & Western Hospital Foundation.

Y-secretase and LARG mediate distinct RGMa activities to control appropriate layer targeting within the optic tectum. Banerjee P, Harada H, Tassew NG, Charish J, Goldschneider D, Wallace VA, Sugita S, Mehlen P, Monnier PP . Cell Death and Differentiation*. 2015 Aug 21.* [Pubmed Abstract]

Neurological Disorders: Seizing Brain Activity

Neurological disorders, including Rett syndrome (RTT), neonatal encephalopathy, X-linked mental retardation and autism have something in common: patients with these disorders are more likely to experience recurrent seizures. Seizures are sudden rushes of electrical activity in the brain that can physically manifest as changes in how a person behaves—from a momentary lapse in attention to full-blown convulsions. These disorders are associated with reduced function of a gene known as Methyl-CpG-binding protein 2 (MeCP2). Recent evidence suggests that MeCP2 deficiency and seizures are associated, but the underlying reason for this link remains unknown.

Krembil Senior Scientist Dr. James Eubanks and Krembil Affiliate Scientist Dr. Liang Zhang co-led a study to determine how lower levels of MeCP2 could lead to seizures in an experimental model. The study focused on GABA, a chemical messenger responsible for moderating electrical activity across brain cells. When MeCP2 levels were reduced, they found that the actions of another protein known as GAT-1, which serves to decrease GABA's effects, were lost. Without GAT-1, the brain was exposed to higher GABA levels; this potentially increased the likelihood of spontaneous electrical firing, which could contribute to the manifestation of seizures.

"Imbalances in electrical brain activity may be a key determinate of neurological disorders, including RTT," remarks Dr. Eubanks. "These results bring us one step closer to understanding how altered MeCP2 function modifies brain activity—knowledge that could be used by researchers to develop broad-range therapies to reverse the symptoms found in RTT and related disorders."

This work was supported by the Canadian Institutes of Health Research, the International Rett Syndrome Foundation and the Toronto General & Western Hospital Foundation.

A role for diminished GABA transporter activity in the cortical discharge phenotype of Mecp2-deficient mice. Zhang L, Wither RG, Lang M, Wu C, Sidorova-Darmos E, Netchev H, Matolcsy CB, Snead III OC, Eubanks JH. Neuropsychopharmacology*. 2015 Oct 26.* [Pubmed abstract]

Arthritis: Sex Differences Explained

Ankylosing spondylitis (AS) is a form of chronic arthritis that causes pain and stiffness in spine and other joints. Both men and women are affected by AS, although important sex differences exist: men are three times more likely to develop the disease, while women have slower disease progression, but increased spinal pain. The reason for these apparent sex differences has remained a mystery until now.

A team of investigators led by Krembil Senior Scientist Dr. Robert Inman collected blood samples from male and female AS patients and then screened their blood for factors associated with the body's immune response. A key feature of AS is activation of the immune system and consequent inflammation. Eric Gracey, an Immunology graduate student in Dr. Inman's lab, found that levels of IL-17A proteins and Th17 cells, two factors that promote inflammation, were elevated in male AS patients.

Dr. Inman's finding may lead to a paradigm shift in the development of treatment options for AS. "We have identified a clear difference in how the immune system is activated in male and female AS patients. It is vital that we use this new knowledge to specifically design precision treatment options for each sex," explains Dr. Inman.

This work was supported by the Canadian Institutes of Health Research (CIHR), the Arthritis Research Center and the Toronto General & Western Hospital Foundation.

Sexual dimorphism in the Th17 signature of ankylosing spondylitis. Gracey E, Yao Y, Green B, Qaiyum Z, Baglaenko Y, Lin A, Anton A, Ayearst R, Yip P, Inman RD. Arthritis & Rheumatology*. 2015 Oct 16.* [Pubmed abstract]

Brain Injury: Sad, Sleepless Nights

In Ontario, almost half a million people live with a brain injury. Of these, many have experienced a mild traumatic brain injury (mTBI)—also known as a concussion—that can lead to persistent symptoms, such as anxiety, headaches, depression and fatigue.

Although the symptoms associated with mTBI are known to be worsened by poor sleep, few studies have explored the connection between mTBI and insomnia. To address this, Dr. Tatyana Mollayeva and TRI Senior Scientist Dr. Angela Colantonio, along with Krembil Senior Scientists Dr. Colin Shapiro and Dr. J David Cassidy, led a study to identify whether insomnia occurs more often in those with mTBI.

The study enrolled 94 people who experienced mTBI at work and had symptoms that persisted longer than normal. The findings revealed that as many as 69% of those in the study group experienced insomnia—a value that was higher than previously thought.

Furthermore, the research team analyzed whether medical, social, behavioural and demographic factors were involved. Dr. Mollayeva explains, "While we found that many factors influence insomnia in these patients, depression was most closely linked to insomnia. Our results strongly suggest that sleep assessment should be incorporated into rehabilitation care after mild brain injury. Finding ways to improve sleep in those with mild traumatic brain injury may speed recovery and reduce the chance of depression."

This work was supported by the Canadian Institutes of Health Research, the Toronto Rehab Foundation and the Toronto General & Western Hospital Foundation. A Colantonio is the Saunderson Family Chair in Acquired Brain Injury Research. T Mollayeva was supported by a CIHR Frederick Banting and Charles Best Graduate Scholarship Award.

Insomnia in workers with delayed recovery from mild traumatic brain injury. Mollayeva T, Mollayeva S, Shapiro CM, Cassidy JD, Colantonio A. Sleep Medicine*. 2015 Jul 10.* [Pubmed Abstract]

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Contact us