The Krembil

May 2018

The Krembil is the official newsletter of the Krembil Research Institute (formerly the Toronto Western Research Institute). It 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.

Stories in this month's issue:

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

News

Bridging the Gap

New facility established to help move research discoveries from laboratory to benefit patients.

The path of translating a research discovery into a product that benefits patients is frequently referred to by researchers as 'crossing the valley of death'.

Every year, Krembil researchers make discoveries that provide new insight into the mechanisms that underpin arthritis, as well as diseases of the brain and eyes. Converting these discoveries into novel therapeutics and diagnostics—through a process known as knowledge translation—is a daunting and challenging task.

To support researchers in this pursuit, the Krembil Research Institute has established a new facility: the Centre for Medicinal Chemistry and Drug Discovery (CMCDD). This facility is led by Dr. Mark A. Reed, a medicinal chemist with extensive experience in drug discovery and development in industry.

Once the facility is fully operational, Dr. Reed envisions that it will offer a variety of services to promote knowledge translation. It will work closely with researchers to assess the 'translatability' of their research and provide them with a roadmap of experiments that need to be completed to pique the interest of potential investors. The

facility will employ medicinal chemists who will build compounds needed to validate new drug targets—an essential step in the drug discovery process. It will also assist researchers in securing funds to support preclinical and clinical studies.

Since his recruitment in August 2017, Dr. Reed has made significant progress in building CMCDD and nurturing relationships with researchers—its primary clientele. He has been advising several researchers and helping them prepare translational research grants, including some submitted to LAB150, a new initiative created by MaRS Innovation and the company Evotec to accelerate drug development. Two of the grants were selected to progress to the final stage of the competition.

The CMCDD is located on the 5th floor of the Krembil Discovery Tower, where it has access to all of the equipment and resources needed for the Centre's medicinal chemistry activities. Within the next two years, Dr. Reed plans to populate this space with up to five medicinal chemists to support drug discovery efforts.

"By providing key capabilities that facilitate knowledge translation, CMCDD will help UHN bridge the gap between scientific discovery and improved patient outcomes," said Dr. Reed.

Dr. Mark Reed, Krembil Staff Scientist, Centre for Medicinal Chemistry and Drug Discovery (CMCDD)

Advocating for Science

Krembil's large presence at the Toronto March for Science shows strong support for research.

Amy Ma, Planning Manager, Krembil (left); and Dr. Don Weaver, Institute Director, Krembil (right)

Krembil is passionate about science. Nowhere was this more evident than at the second annual Toronto March for Science. Held on April 14 at Nathan Phillips Square, the event was one of approximately 230 satellite marches to the official March for Science in Washington, D.C. Krembil joined hundreds of thousands of people in this global event to empower science supporters and advocate for equitable and effective science-based policy.

Despite the inclement weather, Krembil researchers, staff and trainees came out in droves to display their unwavering enthusiasm and creative signs to celebrate science and its vital role in our everyday lives. Of the Research Institutes at UHN, Krembil had the largest presence at the event. The March was also attended by clinicians from Toronto Western Hospital, including Dr. Jennifer Stanga who won a $50 gift certificate for her creative poster on the back of a pizza box (see photo below).

The event concluded with a series of speeches given by representatives from the Federation for the Humanities and Social Sciences, Ryerson University, hEr VOLUTION and others, all of whom advocated for evidence-based decision-making and protecting the integrity of the scientific process.

Dr. Jennifer Stanga, Clinical Neuropsychologist, Toronto Western Hospital

Dr. Cathy Barr, Senior Scientist, Krembil (left); and Kathryn Tzimika, Administrative Coordinator, Krembil (right)

Dr. David Jaffray, EVP, Technology and Innovation, UHN (left); Dr. Carmela Tartaglia, Clinician Investigator, Krembil (centre); and Dr. Antonio Strafella, Senior Scientist, Krembil (right), with his family

Research

Being in the Right State of Mind

Krembil study helps to explain why mental state influences effect of therapy on brain cells.

The brain displays distinct patterns of activity which are disturbed in some mental illnesses, including depression, obsessive compulsive disorder, schizophrenia and post-traumatic stress disorder.

A new study led by Krembil Scientist Dr. Jérémie Lefebvre could help make repetitive transcranial magnetic stimulation (rTMS) and other forms of non-invasive brain stimulation more effective for the treatment of depression and other psychiatric illnesses.

rTMS therapy is most commonly used to treat depression that has not improved with medications or psychotherapy. It involves applying a series of short pulses from a strong electromagnet to a particular area of the brain. The pulses gradually cause long-term changes in brain activity, correcting the abnormal patterns of activity that occur in depression.

Although patients with depression have been benefitting from rTMS therapy for over 15 years, some important questions remain in the field. For example, why is rTMS more

likely to influence brain activity when it is administered while the brain is performing a mental task—like performing a simple memory test—than when the brain is at rest?

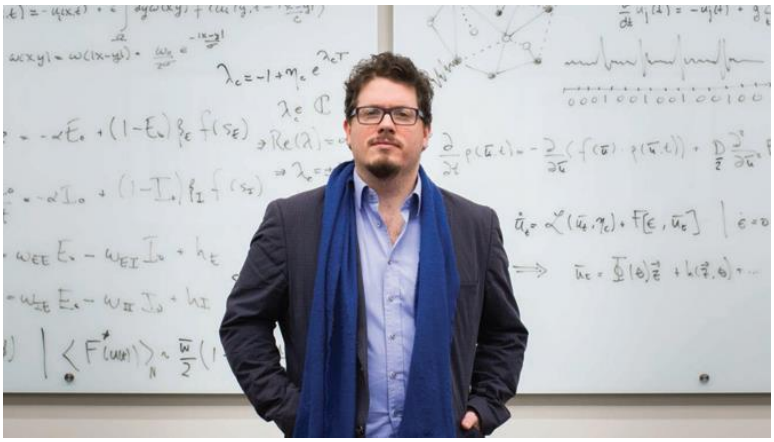
To gain new insight into the mechanisms of rTMS and to answer this question, Dr. Lefebvre is combining mathematics with computational models of the brain.

He applied simulated transcranial alternating current stimulation (tACS), a modified version of rTMS involving fluctuating waves of electrical currents instead of series of pulses, in different conditions of brain activity: one at rest and the other engaged in a task. He found that when the brain is at rest, cell activity is highly synchronized and resistant to the effect of tACS. In contrast, when the brain is engaged in a mental task, cell activity is much more asynchronous and more easily influenced by tACS.

“Our findings suggest that a patient’s brain is most responsive to tACS and rTMS therapy when it is engaged in a mental task. Implementing these findings in the clinic could make the therapy more effective at restoring healthy brain patterns in patients affected by not only depression, but also other psychiatric disorders,” explains Dr. Lefebvre.

This work was supported by the Natural Sciences and Engineering Research Council of Canada, the National Institute of Mental Health and the Toronto General & Western Hospital Foundation.

Lefebvre J, Hutt A, Frohlich F. Stochastic resonance mediates the state-dependent effect of periodic stimulation on cortical alpha oscillations. Elife. 2017 Dec 27;6. pii: e32054. doi: 10.7554/eLife.32054



Dr. Jérémie Lefebvre, Krembil Scientist. Photo courtesy of the Globe and Mail

Bringing Objectivity into Sight

New way to objectively measure visual discomfort could unlock new avenues in vision research.

The current study links blue light to visual discomfort. Some studies suggest that use of blue light-blocking glasses (pictured) may provide relief for light-induced discomfort.

A team of researchers in Toronto have developed a new way to measure visual discomfort—also known as photophobia—that could help advance our understanding of debilitating light sensitivities.

“We all experience visual discomfort at some point in our lives, for example when coming out of a cinema during daytime. However, for those with certain health conditions, such as a migraine headache, cataracts or damage to the eye, even normal light levels can be difficult to tolerate,” explains Dr. Agnes Wong, a Senior Scientist at the Krembil Research Institute.

Dr. Wong developed a new test to provide clinicians and researchers with a more rigorous way to measure visual discomfort in patients. Current approaches typically involve questionnaires or polls, which are hard to interpret and can vary according to patients' mood, health or cultural background.

The researchers designed the test to take advantage of new research suggesting that visual discomfort may be influenced by a relatively unstudied cell in the retina known as an intrinsically photosensitive retinal ganglion cell (ipRGC).

“ipRGCs are a rare type of cell located in the back of the eye and are believed to provide the brain with a general readout of ambient light levels. Although several lines of evidence have implicated ipRGCs in photobias, to date there is limited clinical data to support this,” says Marija Zivcevska, the lead author and a Master’s student under Dr. Wong.

The test that they developed uses a commercially available ‘flash stimulator’—a device that is normally used to test for vision disorders—and which was programmed to deliver tightly controlled flashes of light of varying colours. This device was linked to two push buttons, through which patients could indicate when they experienced visual discomfort.

When the test was used on a small group of adults with no history of visual disorders, the results supported the idea that ipRGCs are involved in visual discomfort. For example, they revealed that blue light is more likely to induce visual discomfort than red light—which agrees with previous findings that ipRGCs are activated when exposed to blue light.

The test—the first of its kind—provides an objective way to assess the light conditions that cause discomfort. This work represents an important first step towards improving our understanding of photobia and developing new therapies to treat this condition.

Supported by the Canada Foundation for Innovation, the John and Melinda Thompson Endowment Fund for Vision Neuroscience, the Department of Ophthalmology and Vision Sciences at The Hospital for Sick Children and the Toronto General & Western Hospital Foundation.

Zivcevska M, Lei S, Blakeman A, Goltz HC, Wong AMF. A Novel Visual Psychometric Test for Light-Induced Discomfort Using Red and Blue Light Stimuli Under Binocular and Monocular Viewing Conditions. Invest Ophthalmol Vis Sci. 2018 Mar 1. doi: 10.1167/iovs.17-23526.

Dr. Agnes Wong, Krembil Senior Scientist (left); and Marija Zivcevska (right), lead author of the current study and a Master’s student in Dr. Wong’s laboratory

Confirming TOR-BSST© is the Best

Screening tool is the most sensitive way to detect swallowing problems in stroke patients.

Stroke patients with dysphagia, a condition characterized by difficulties swallowing, are three times more likely to develop pneumonia than stroke patients without the condition.

Difficulty swallowing, or dysphagia, affects over half of all stroke patients. Dysphagia in turn can cause patients to inhale food or drink into their lungs when trying to swallow, leading to pneumonia and increased risks of disability and death.

Identifying patients with dysphagia early allows the care team to bring in the services of a Speech Language Pathologist (SLP), who can recommend and implement strategies to reduce the risk of developing pneumonia.

How clinicians identify those patients is an area for improvement.

Screening tools, such as the Toronto Bedside Swallowing Screening Test (TOR-BSST©) developed by Krembil Affiliate Scientist Dr. Rosemary Martino's team can identify patients at risk of dysphagia with a high degree of sensitivity. The TOR-BSST helps guide clinicians through a quick but systematic screening of the patient, including how they swallow water, to ensure any warning signs are caught and patients at risk are referred to a SLP.

However, more than half of acute stroke care institutions in Canada and the US do not use a formal screening tool. Instead, they detect swallowing problems by performing an

informal assessment, in which a clinician makes a judgement as to whether a patient is at risk without evaluating all the possible symptoms.

In a recent study, Dr. Martino along with her students and colleagues used clinical data from before and after the implementation of the TOR-BSST at Toronto Western Hospital to compare the accuracy of dysphagia detection using the tool to that of the informal assessments. They found that the screening tool identified over 95% of patients at risk for dysphagia, whereas informal screens missed a high number of patients at risk: just 45% were identified and referred for specialized assessment and care.

“In an ideal health care system with unlimited resources, every patient would be seen by an SLP for a comprehensive swallowing assessment. However, in the real world properly validated screening tools are critical for directing the rarer and more expensive resources, such as an SLP, only toward those patients at risk for dysphagia,” Dr. Martino concludes.

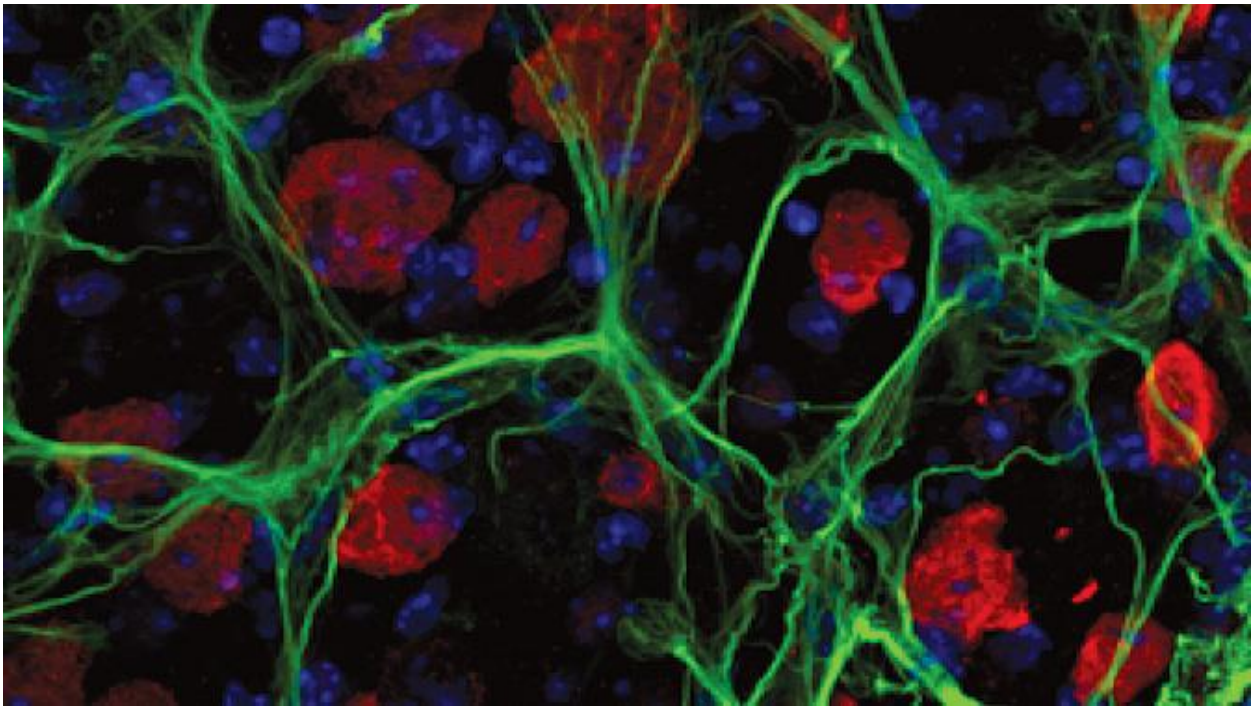
This work was supported by the Canadian Stroke Network Summer Student Program, the Heart and Stroke Foundation, the University of Toronto and the Toronto General & Western Hospital Foundation. Dr. R. Martino holds a Tier 2 Canada Research Chair in Swallowing Disorders.

Sherman V, Flowers H, Kapral MK, Nicholson G, Silver F, Martino R. Screening for Dysphagia in Adult Patients with Stroke: Assessing the Accuracy of Informal Detection. Dysphagia. 2018 Mar 1. doi: 10.1007/s00455-018-9885-8

Dr. Rosemary Martino, Krembil Affiliate Scientist

Eyeing Better Protection

Scientists discover a signalling pathway that could help prevent eye damage.



Retinal astrocytes (shown here in green) are star-shaped helper cells that surround the neurons (red) in the retina. Photo courtesy of Alessandra Tuccitto.

Imagine that you've been diagnosed with a debilitating eye disease. Your vision suddenly decreases, and you can no longer clearly see your loved ones or the things that matter most to you. It can be a frightening experience. This irreversible loss of vision, which is a symptom of eye diseases such as glaucoma, occurs when the neurons (nerve cells) that control our sight are destroyed.

While researchers still do not know the exact mechanism by which this occurs, there is evidence to suggest that the accumulation of toxic reactive oxygen species is involved. These toxic compounds damage light-sensitive neurons through a process called oxidative stress. Luckily, the body has specialized cells (astrocytes) that help produce a powerful antioxidant known as glutathione (GSH) that neutralizes the damaging effects of the reactive oxygen species.

Krembil Research Institute Senior Scientist Dr. Jeremy Sivak has been searching for ways to promote the production of GSH in order to halt, prevent or reverse vision loss in patients with eye disease.

His team recently discovered that a protein called adenosine monophosphate-activated kinase (AMPK) increases the production of GSH in astrocytes by activating another key protein known as PGC-1 alpha.

The researchers also demonstrated—using an experimental model of eye disease—that therapeutic compounds that mimic AMPK, increase GSH levels while reducing the death of neurons in the eye.

“Activating PGC-1 alpha represents a novel strategy for enhancing protective astrocyte activity in the eye,” explains Dr. Sivak. “It is an exciting discovery that could not only be applied to eye diseases such as glaucoma, but also other degenerative diseases—such as Alzheimer disease—where neurons are damaged by oxidative stress.”

This work was supported by the Canadian Institutes of Health Research, the Glaucoma Research Society of Canada, the Natural Sciences and Engineering Research Council of Canada and the Toronto General and Western Hospital Foundation. J. Sivak is the Toronto General and Western Hospital Foundation Glaucoma Research Chair.

Guo X, Jiang Q, Tuccitto A, Chan D, Alqawlaq S, Won GJ, Sivak JM. The AMPK-PGC-1α signaling axis regulates the astrocyte glutathione system to protect against oxidative and metabolic injury. Neurobiol Dis. 2018 May;113:59-69. doi: 10.1016/j.nbd.2018.02.004.

Dr. Jeremy Sivak, Krembil Senior Scientist. Photo courtesy of the Globe and Mail