The Krembil

July 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.

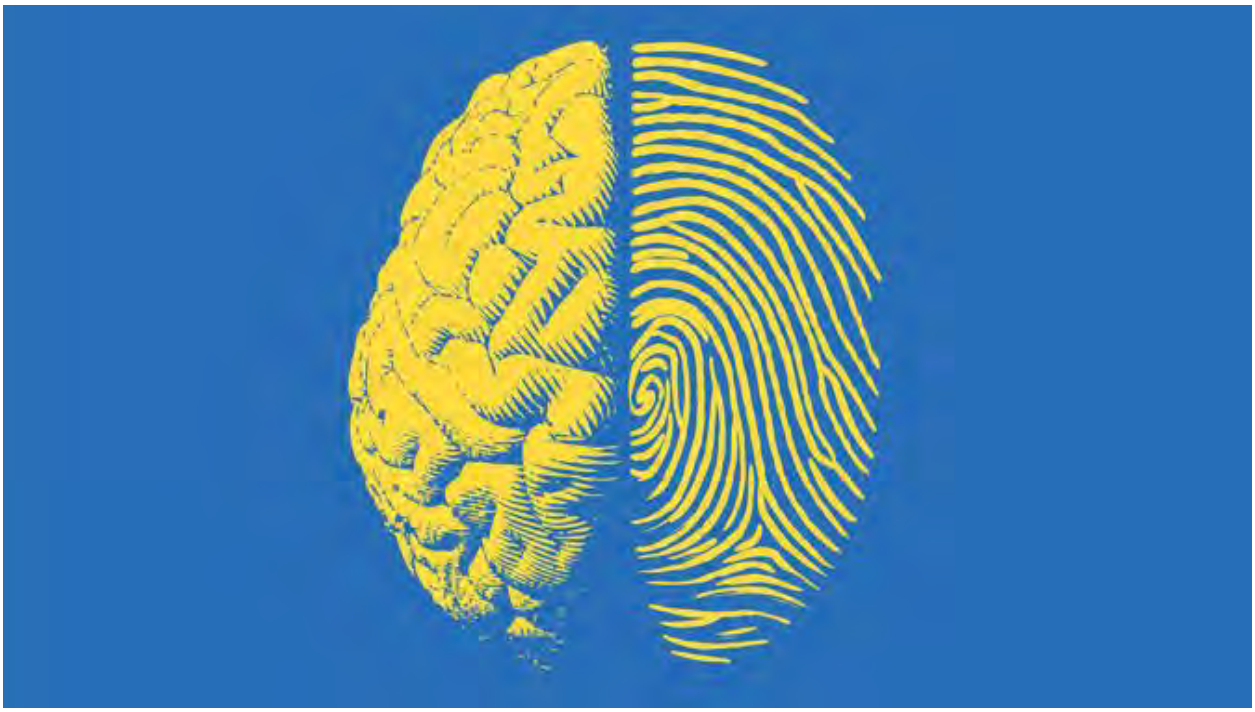
Stories in this month's issue:

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

News

UHN Launches Krembil Brain Institute

New institute will harmonize and integrate clinical and research programs in neuroscience.



Your brain is what makes you…you! Its billions of brain cells underpin our behaviours and thoughts. And when these cells malfunction or are damaged, it can lead to neurological disorders and impairments.

On June 20, UHN established the Krembil Brain Institute to formally create an academic health sciences entity that harmonizes the institution's clinical and research priorities in the neurosciences.

The new Institute will help clinicians and researchers at Toronto Western Hospital and across UHN work together to seek better treatments and cures for diseases of the brain, spine and nerves.

Dr. Gelareh Zadeh, neurosurgeon, Scientist and Program Medical Director, Krembil Neuroscience Centre at UHN, and Dr. Donald Weaver, dementia neurologist, medicinal chemist and Director of the Krembil Research Institute, will act as co-directors of the Krembil Brain Institute.

"Aligning the clinical and research priorities at Krembil is crucial to making a bigger impact in our field and the community we serve, and for improving outcomes and wellness of the aging brain," said Dr. Zadeh.

"It is important that we devise strategies that accelerate and focus our research discoveries, education and training towards improving clinical outcomes and standards of care in order to advance early detection, prevention and treatment of brain conditions," she said.

The Krembil Neuroscience Centre and the Krembil Research Institute will remain as operational entities within UHN alongside the Krembil Brain Institute; however, UHN will move towards the use of a single Krembil Brain Institute brand for neuroscience activities.

It is estimated that one in three Canadians will be affected by a brain disease, disorder or injury in their lifetime and that 3.6 million Canadians are currently affected by a neurological condition.

Giving UHN a competitive advantage

"In this coming century, the diagnosis and treatment of brain diseases will emerge as one of the pre-eminent pursuits of modern medicine," said Dr. Weaver.

The Krembil Brain Institute will give UHN a competitive advantage over other organizations by establishing a single identity and offering integrated, multidisciplinary, comprehensive neuroscience health care that is second to none in Canada and among the best in the world.

The new Institute is also expected to help UHN recruit leaders in the neuroscience field, attract high-quality students and build on pre-existing partnerships with the Toronto Rehabilitation Institute, The Centre for Addiction and Mental Health (CAMH) and other organizations provincially, nationally and internationally.

"We have the expertise, the people power and the ambition to take neurosciences to the next phase, which is to understand where we can make the biggest impact on outcomes," said Dr. Zadeh.

"Establishing the Krembil Brain Institute allows us to position ourselves to be the predominant leader in brain medicine now and in the years to come," added Dr. Weaver.

This is an adaptation of a story originally published by UHN News on www.uhn.ca.

The Krembil Brain Institute will be led by co-directors Drs. Gelareh Zadeh and Donald Weaver (Photo: UHN).

Spreading the Word

Trainees showcase their research and hard work at Krembil Research Day 2018.

(L-R) Winners of the presentation competitions; Dr. Donald Weaver, Director of the Krembil Research Institute; and Dr. Mary Pat McAndrews, Chair of the Trainee Affairs Committee.

Krembil's annual Research Day was held on May 23 and was attended by approximately 200 researchers, trainees and staff, as well as Dr. Bradly Wouters, UHN's EVP of Science and Research.

Since the event's creation in 2000, Research Day has been and continues to be devoted to showcasing the hard work of Krembil graduate students and postdoctoral fellows. The 2018 edition gave 78 trainees the opportunity to share their research with their colleagues through a variety of formats including oral presentations, posters and three-minute elevator pitches. At the end of the day, those who did the best job presenting their work were rewarded with an honorary certificate and a cash prize.

Krembil trainees were also instrumental in making Research Day happen: they played a leading role in organizing the day, designing the front cover of the Research Day booklet and hosting the keynote speaker.

This year's invited speaker was Dr. Samer Hattar, Chief and Senior Investigator of the Section on Light and Circardian Rhythms (SLCR) at the National Institute of Mental Health. Dr. Hattar is most well-known for his research characterizing a light-sensing cell in the eye known as the intrinsically photosensitive retinal ganglion cell (ipRGC). His

keynote address at Krembil Research Day focused on his latest work showing how light can influence mood and learning through ipRGCs and specific brain regions.

Dr. Donald Weaver thanks all of the individuals who made this year's Research Day a success, including the Trainee Affairs Committee and its Chair, Dr. Mary Pat McAndrews; the Krembil Administration team; the presentation judges; and the Nadler Family, whose generous donation funded the presentation prizes.

Congratulations to everyone who presented their work!

A complete list of presentation awardees can be viewed here.

View a video of the Krembil Research Day here.

Trainees, staff and researchers at Krembil Research Day. Courtesy of Travis Boyco.

Dr. Samer Hattar, Chief and Senior Investigator at the National Institute of Mental Health, presenting his research findings during his keynote address.

Research

Traffic Control in the Brain

Study shows that brain's machinery for chemical messaging is important for learning.

The junction between brain cells, known as a synapse, can be thought of as a one-way highway for sending chemical messages to neighbouring cells.

Our thoughts and actions—no matter how simple—are underpinned by a complex network of chemical traffic in our brain. This traffic consists of chemical messages that are exchanged between brain cells, a process that enables thousands of cells in the brain to communicate and share information with each other.

Although this 'chemical communication' is crucial for brain function, we know relatively little about the machinery responsible for sending and receiving these messages.

Recently, Dr. Shuzo Sugita, a Senior Scientist at the Krembil Research Institute, found that the protein syntaxin 4 is important for the exchange of chemical messages in the hippocampus, a part of the brain that helps us store long-term memories and keep track of the location of objects in space.

Using a variety of experimental models, Dr. Sugita and his team showed that the loss of syntaxin 4 disrupted the communication between brain cells within the hippocampus. This in turn impaired learning—a process that involves storing and retrieving memories.

Upon closer examination, the researchers discovered why syntaxin 4 is important for communication and learning: the protein helps to add sensors that receive chemical messages to the surface of brain cells. Moreover, when a lot of information needs to be communicated from one cell to another, syntaxin 4 recruits more chemical sensors to the surface of the receiving cell to help it capture the extra incoming messages.

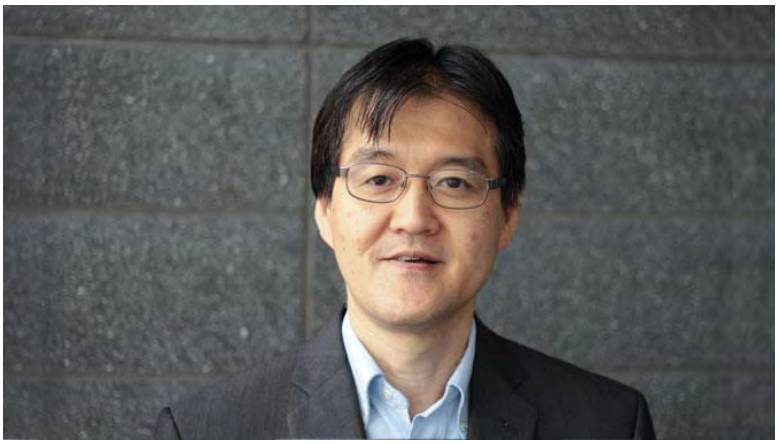
“It’s like adding more lanes to the road during rush-hour traffic,” explains Dr. Na-Ryum Bin, who led the study with Dr. Sugita.

These findings show that syntaxin 4 is important for learning because it is involved in the receipt of chemical messages in brain cells within the hippocampus.

Of his work, Dr. Sugita says, “It takes us one step closer to understanding what happens in the hippocampus when we learn and remember. The eventual goal is to design personalized medicine to help restore these functions when they are lost.”

This work was supported by the Natural Sciences and Engineering Research Council of Canada, the Heart and Stroke Foundation of Ontario, the Canadian Institutes of Health Research and the Toronto General & Western Hospital Foundation.

Bin N-R, Ma K, Harada H, Tien C-W, Bergin F, Sugita K, Luyben TT, Narimatsu M, Jia Z, Wrana JL, Monnier PP, Zhang L, Okamoto K, Sugita S. Crucial role of postsynaptic syntaxin 4 in mediating basal neurotransmission and synaptic plasticity in hippocampal CA1 Neurons. Cell Rep. 2018 June 5. doi: doi.org/10.1016/j.celrep.2018.05.026.



Dr. Shuzo Sugita, Senior Scientist, Krembil Research Institute

Gut Reactions to Arthritis

Researchers discover new link between ankylosing spondylitis and gut inflammation.

Inflammation is a sign that the body is actively protecting itself. However, in some diseases—like ankylosing spondylitis—inflammation can do more harm than good.

Imagine superheroes who can destroy their enemies by engulfing them whole, acquire new powers to ward off unfamiliar threats and enlist the help of others when the going gets tough.

To find such superheroes, you'd have to look no further than your own body. Monocytes—the largest cells circulating in the blood—have all of these capabilities and more. They patrol the blood for disease-causing bacteria and viruses and use their 'special powers' to eliminate them.

Dr. Nigil Haroon, a Scientist at Krembil Research Institute, has recently shown that instead of fighting disease, some monocytes contribute to it. He and his team have found evidence suggesting that some monocytes worsen the symptoms of ankylosing spondylitis (AS)—a form of spinal arthritis.

AS is characterized by inflammation, stiffness of the spine and chronic back pain. Unusually, over half of those with the condition also have gut inflammation. Researchers have been trying to understand the mechanisms behind this puzzling connection.

By analyzing spinal tissues of AS patients who have gut inflammation, Dr. Haroon's team made a startling discovery: while patrolling for threats in the gut, some monocytes pick up information that causes them to travel to the spine where they promote inflammation.

"It's as if these monocytes were tricked into overreacting, thus exacerbating the symptoms of AS," explains Dr. Francesco Ciccia, who led the study with Dr. Haroon.

"Our results suggest that monocytes from the gut could play an important role in AS pathogenesis. Moreover, they're providing new insight into the complex relationship between AS and gut inflammation, one factor at a time," comments Dr. Haroon. "Our goal is to eventually develop specific drugs to help alleviate the symptoms in these patients."

This work was supported by the Italian Ministero dell'Istruzione, dell'Università e della ricerca Scientifica and the Toronto General & Western Hospital Foundation.

Ciccia F, Guggino G, Zeng M, Thomas R, Ranganathan V, Rahman A, Alessandro R, Rizzo A, Saieva L, Macaluso F, Peralta S, Di Liberto D, Dieli F, Cipriani P, Giacomelli R, Baeten D, Haroon N. Pro-inflammatory CX3CR1+ CD59+ TL1A+ IL-23+ monocytes are expanded in patients with Ankylosing Spondylitis and modulate ILC3 immune functions. Arthritis Rheumatol. 2018 June 5. doi: 10.1002/art.40582.

Dr. Nigil Haroon, Scientist, Krembil Research Institute. Photo courtesy of the Globe and Mail.

The Waxing and Waning of Pain

Krembil study reveals how brain networks communicate during chronic pain.

Ankylosing spondylitis is a form of arthritis that causes chronic swelling, stiffness and pain in the joints of the spine.

It's easy to describe how much pain you're in when you stub your toe. However, describing chronic pain—persistent pain that lasts longer than three months—is much more complex. Not only does the intensity of chronic pain fluctuate from day to day, but the features of pain may also change over time.

To better understand what happens in the brain during chronic pain, clinicians and researchers are using functional magnetic resonance imaging (fMRI), a sophisticated technology that enables them to visualize the communication within or among brain networks. fMRI can be used to measure communication as a single snapshot or as a flexible dynamic interaction over a longer period of time.

However, it is not well understood how these measurements relate to chronic pain or whether they better reflect a person's current state of pain or the overall intensity of their chronic pain over time.

To address this gap in knowledge, Krembil Senior Scientist Dr. Karen Davis and her PhD student Joshua Cheng initiated a study in research participants with or without ankylosing spondylitis, a form of arthritis that causes chronic back pain.

Dr. Davis's research team collected fMRI measurements of brain network communication that reflect a static snapshot and a dynamic interaction over time, and also asked participants to rate their current pain and their average monthly pain using a questionnaire. Computer-based machine learning was then used to create two chronic pain brain models based on the fMRI measurements and pain scores—one to represent current 'state' pain and another to represent average 'trait' pain over a period of time.

The team found that three specific brain networks displayed abnormal communication in people with ankylosing spondylitis, all of whom experience chronic pain. They also found that different patterns of communication between these networks were related to current or monthly trait pain ratings. In general, the dynamic fMRI measurements taken over time were more informative than the static snapshots in relating communication to chronic pain.

"Our study is the first to reveal how changes in the communication patterns of brain networks relate to fundamental features and timing of chronic pain," explains Dr. Davis. "These findings shed new light on the complexities of chronic pain and will contribute to the development of new solutions for those with this long-term and disabling condition."

This work was supported by the Canadian Institutes of Health Research, the Canadian Chronic Pain Network, The Mayday Fund and the Toronto General & Western Hospital Foundation.

Cheng JC, Rogachov A, Hemington KS, Kucyi A, Bosma RL, Lindquist MA, Inman RD, Davis KD. Multivariate machine learning distinguishes cross-network dynamic functional connectivity patterns in state and trait neuropathic pain. Pain. 2018 Apr 26. doi: 10.1097/j.pain.0000000000001264.

Dr. Karen Davis, Senior Scientist, Krembil Research Institute

The Fight against Forgetfulness

Diabetes medications could help to protect mental function in Alzheimer disease.

High blood sugar—a hallmark of diabetes—can damage many different tissues and organs throughout the body including the brain and its blood vessels.

Type 2 diabetes (T2D) and Alzheimer disease are linked.

People with T2D, a chronic condition characterized by high blood sugar levels, are at a higher risk of developing Alzheimer disease than those who don't have it. Moreover, high blood sugar levels have been implicated in brain dysfunction—such as deficits in attention, memory and information processing—which are hallmarks of Alzheimer disease and other forms of dementia.

Several clinical studies suggest that some anti-diabetic medications, which lower blood sugar levels, might improve brain function in Alzheimer disease and slow its progression. However, it's unclear which of the approximately 20 anti-diabetic medications currently available would be most effective.

To begin to narrow down this list, a team led by Krembil Clinician Investigator Dr. Roger McIntyre performed a study that examined relevant clinical trials completed within the past 13 years. Dr. McIntyre was named one of 'the world's most influential scientific minds' by Clarivate Analytics/Thomson Reuters in 2014, 2015, 2016 and 2017.

The researchers identified 19 clinical trials that evaluated the effect of six different diabetes medications in patients with either Alzheimer disease or mild forms of dementia.

By performing a comprehensive analysis of the studies' findings, the researchers found that all six diabetic medications produced significant improvements in the mental function of participants. The two drugs that produced the most improvement—pioglitazone and rosiglitazone—lower blood sugar through the same mechanism: by stimulating cells to absorb more sugar and use it as a source of energy.

"Our study provides compelling evidence that anti-diabetic drugs, especially piglitazone, help protect brain function in Alzheimer disease. However, before these findings can be applied in the clinic, they need to be replicated and confirmed in large-scale clinical trials," says Dr. McIntyre.

This work was supported by the China Scholarship Council and the Toronto General & Western Hospital Foundation.

Cao B, Rosenblat JD, Brietzke E, Park C, Lee Y, Musial N, Pan Z, Mansur RB, McIntyre RS. Comparative efficacy and acceptability of antidiabetic agents for Alzheimer's disease and mild cognitive impairment: A systematic review and network meta-analysis. Diabetes Obes Metab. 2018 May 23. doi: 10.1111/dom.13373.

Dr. Roger McIntyre, Clinician Investigator, Krembil Research Institute