The Krembil

January 2017

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
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News

A Letter from the Director

Dr. Weaver (pictured) envisions a world without chronic, debilitating disorders. In 2017, he and the other Krembil researchers will continue their relentless pursuit of making this vision a reality.

As we enter 2017, I wish to reflect on the many accomplishments achieved by the Krembil Research Institute's faculty, students and staff in the past year.

In 2016 we held the one-year anniversary celebration of our rebranding as "the Krembil". We also unveiled the first of three program integrations, with the creation of the Donald K. Johnson Eye Institute. This new institute was born from the merging of UHN's Ophthalmology Department (previously known as the Donald K. Johnson Eye Centre) and the Division of Vision Sciences. At the unveiling, Dr. Peter Pisters, UHN President and CEO, summarized the benefits of this merger: "This transformation will facilitate improved collaboration between clinicians, researchers and educators, with the ultimate goal of improving patient care."

A highlight of the past year was also our continued research excellence. These accomplishments include the following discoveries: a new therapeutic strategy to reduce brain inflammation after stroke (story link); two biological markers that can distinguish between early- and late-stage osteoarthritis (story link); and new insight into how transplanted stem cells behave after they are injected into the retina with the aim to restore vision loss (story link).

These research advancements are no small feat; they require collaboration within and across research centres and the hard work and dedication of our administrative staff and many trainees. Going forward, the Krembil will continue to enrich our research community and promote trainee engagement through our Annual Research Day, Trainee Affairs Committee events and internal trainee funding competitions. We will also continue our small equipment competition and will endeavour to secure larger infrastructure and project grants that will benefit the entire Institute.

Most importantly, we will continue our relentless pursuit of new diagnostics, therapeutics and management strategies for chronic debilitating disorders of the brain and spine, bone and joints, and eye. Because if we're not here to find cures, then why the hell are we here?

Yours,
Don Weaver

Building Computational Biology Power

The development of cutting-edge computing technology has revolutionized life sciences research. For example, it has streamlined drug discovery by enabling researchers to rapidly screen databases of compounds and identify new drugs.

Computational biology is a field of study in which researchers use mathematics and computer technology to analyze large datasets and explain complex biological processes. There is a growing demand for computational biologists because of the increase in the number of large datasets generated by neuroimaging and other advanced methods. In response to this demand, the Krembil Research Institute (the "Krembil") has been expanding its expertise in the field, particularly in computational neuroscience—applying computational power and mathematics to answer questions about the brain.

Last year, recent recruit and Krembil Scientist Dr. Jérémie Lefebvre published a study in the prestigious *Journal of Neuroscience*. In that study, he used computational techniques to shed light on how a brief series of treatments with electrical stimulation can cause lasting behavioural improvements in people with neuropsychiatric disorders such as major depression and Parkinson disease (story link). Also in 2016, Krembil Senior Scientist Dr. Frances Skinner and colleagues published in the journal *eNeuro*. In that study, they developed computer models that simulated the electrical characteristics of cells in the hippocampus—a brain region involved in memory (PMID: 27679813). Using their models, they were able to make predictions about how these cells work.

Another highlight in 2016 was the first-ever Toronto Computational Neuroscience Workshop, which was co-organized by Drs. Lefebvre, Skinner and Taufik Valiante. This event raised awareness of current trends and facilitated new collaborations among basic, clinical and computational researchers.

To enhance the Institute's computational biology capacity, the Krembil Foundation has donated a generous gift to develop dedicated lab space on the fourth floor of the Krembil Discovery Tower (4KD489). The new space will feature Principal Investigator offices, workstations and collaborative space, facilitating the Institute's continued expansion in this area.

As computational biology principles and methods can be applied to any discipline, this enhanced expertise will support the Krembil's mission to become a world leader in neuroscience, arthritis and vision research.

Research

When Surgery is Superior

Common symptoms associated with brain arteriovenous malformations include sudden and severe headaches, seizures and bruit (an abnormal swishing or ringing sound in the ear).

An arteriovenous malformation (AVM) is an abnormal bundle of arteries and veins that can occur anywhere in the body, including the brain. People with a brain AVM are at greater risk for bleeding into the brain (ie, hemorrhaging) and subsequent brain damage.

The best way to treat brain AVMs remains controversial. One perspective is that microsurgery—complete removal of the AVM without damaging adjacent brain tissue—offers the benefit of an immediate cure and eliminates the risk of future complications. On the other hand, a recent clinical trial (known as the ARUBA trial) suggested that medical observation alone resulted in fewer strokes or deaths than more invasive interventions. However, because the ARUBA trial combined three different interventions (microsurgery, embolization and

radiosurgery) into a single category, the result may obscure whether one of these offer benefits to certain patients.

To help ensure that all patients receive the most appropriate treatment for brain AVMs, Krembil Senior Scientist Dr. Michael Tymianski explored whether patients with low risk for surgical complications benefit more from microsurgery than observation alone. The research team studied the clinical records of 155 patients who received AVM microsurgery and found that, in patients with low risk for complications, the procedure was consistently successful: complete obliteration of the AVM occurred 99.2% of the time. Furthermore, these patients experienced fewer negative symptoms after surgery than results from the ARUBA trial would suggest.

“Our study demonstrates the safety and efficacy of surgery in a carefully selected subset of people with predominantly low-grade AVMs, challenging the conclusion that medical management is superior to all other interventions,” says Dr. Tymianski. “Thus, eliminating microsurgery as a potential treatment option could unnecessarily deprive certain AVM patients of a beneficial therapy.”

This work was supported by the Aneurysm Research Fund, Neurovascular Therapeutics Program, University Health Network; and the Toronto General & Western Hospital Foundation. M Tymianski holds a Tier 1 Canada Research Chair in Translational Stroke Research.

Wong J, Slomovic A, Ibrahim G, Radovanovic I, Tymianski M. Microsurgery for ARUBA trial (a randomized trial of unruptured brain arteriovenous malformation)-eligible unruptured brain arteriovenous malformations. Stroke. 2016 Nov 17 doi: 10.1161/STROKEAHA.116.014660.

Signalling the End of Cancer

Dr. Wallace (pictured), Krembil Senior Scientist and Co-Director of the Donald K. Johnson Eye Institute, and collaborators published these findings in the journal eLife.

Medulloblastoma is the most common type of brain tumour that can develop in children. The disease develops when normal cells undergo progressive genetic changes that enable them to multiply uncontrollably.

Much of the research on cancer progression focuses on defining these genetic changes; however, another key to understanding how cancer forms is the role of surrounding tissues– the ‘tumour microenvironment’—in preventing or supporting tumour growth.

Krembil Senior Scientist Dr. Valerie Wallace, along with collaborators at the Ottawa Health Research Institute and the Hospital for Sick Children, published a study where they explored how the tumour microenvironment controls medulloblastoma development.

Using an experimental model, Dr. Wallace’s team discovered that certain proteins found in the surrounding tissues that control the Norrin/Frizzled4 signalling pathway—a coordinated set of molecular signals that govern tissue structure and blood vessel development—can stop cancer progression early on. Blocking the Norrin/Frizzled4 signal enabled pre-cancerous growths to form and accelerated tumour initiation. The results suggest that, when functioning normally, the Norrin/Frizzled4 pathway may help prevent cancer progression.

“By identifying a potential role for these proteins in medulloblastoma development, our research reveals new observations that down the road might change what happens in the clinic,” says Dr. Wallace. “Our next step will be to investigate what it is exactly about dysfunctional Norrin/Frizzled4 signalling that makes cells more likely to become cancerous, so we can devise strategies to prevent tumour growth.”

This work was supported by the Canadian Cancer Society, the Cancer Research Society and the Toronto General & Western Hospital Foundation.

Bassett EA, Tokarew N, Allemano EA, Mazerolle C, Morin K, Mears AJ, McNeill B, Ringuette R, Campbell C, Smiley S, Pokrajac NT, Dubuc AM, Ramaswamy V, Northcott PA, Remke M, Monnier PP, Potter D, Paes K, Kirkpatrick LL, Coker KJ, Rice DS,Perez-Iratxeta C, Taylor MD, Wallace VA. Norrin/Frizzled4 signalling in the preneoplastic niche blocks medulloblastoma initiation. Elife. 2016 Nov 8. PMID: 27823583.

Identifying Hidden Inflammation

Lupus is a leading cause of premature kidney disease. It is difficult to diagnose because symptoms vary—no two cases are exactly alike.

Systemic lupus erythematosus (lupus) is a disorder in which the body's immune system attacks healthy tissue. This attack results in a range of symptoms including painful joints, rashes and fatigue. Lupus patients sometimes experience kidney inflammation (nephritis), which is one of the major causes of distress and death in people suffering from lupus.

Nephritis can be treated using powerful drugs that suppress the immune system. But these drugs have serious side effects, such as increasing patients' risk of developing brittle bones and cardiovascular disease. Therefore, knowing exactly who needs treatment is critical.

Diagnosing kidney inflammation currently requires an invasive procedure, where a piece of the patient's kidney is removed for laboratory analysis. Thus, having an easier way to diagnose nephritis would help clinicians better manage the disorder.

To find a non-invasive marker of nephritis, Krembil Senior Scientist Dr. Joan Wither and her team performed a comprehensive survey of 128 proteins found in the urine, and compared the levels of these proteins in lupus patients with and without active nephritis. The team found 44 proteins that were significantly increased in the urine of lupus patients with kidney inflammation. Ten of these proteins in particular (adiponectin, PAI-1, IL-16, wVF, IP-10, TIMP-1, eotaxin, sgp130, HGF, and PDGF-BB) were elevated in patients whose biopsies indicated that they required more aggressive treatment for kidney inflammation.

"We have identified a novel cluster of proteins that discriminate between lupus patients with and without nephritis. Many of these proteins return to normal levels when patients are in remission," says Dr. Wither. "Therefore, measuring these urinary proteins has potential clinical utility for identifying which patients require therapy and monitoring treatment response—without requiring a renal biopsy."

This work was supported by the Canadian Institutes of Health Research, the Alliance for Lupus Research, the Arthritis and Autoimmunity Research Centre of the University Health Network, The Arthritis Society, the Arthritis Centre of Excellence, University of Toronto and the Toronto General & Western Hospital Foundation. PR Fortin is a Tier 1 Canada Research Chair in Systemic Autoimmune Rheumatic Diseases.

Landolt-Marticorena C, Prokopec SD, Morrison S, Noamani B, Bonilla D, Reich H, Scholey J, Avila-Casado C, Fortin PR, Boutros PC, Wither J. A discrete cluster of urinary biomarkers discriminates between active systemic lupus erythematosus patients with and without glomerulonephritis. Arthritis Res Ther. 2016 Oct 4. doi: 10.1186/s13075-016-1120-0.

A Changing Brain is Good for Pain

People respond differently to pain and pain treatment; finding out why may be the key to unlocking better, more personalized treatment strategies.

Brain activity is highly variable and fluctuates with each passing moment. This is because each person's brain is inherently unique and these fluctuations vary depending on the individual and their experience.

It has been hypothesized that inherent brain signal variability can influence how people respond to and process a diverse range of stimuli and also how well people can perform a challenging task. A new study by Krembil Senior Scientist Dr. Karen Davis, her graduate student Anton Rogachov and other members of her research team demonstrates that this variability may also contribute to how individuals sense and cope with pain.

The team used an advanced technique called "resting state" functional magnetic resonance imaging (fMRI) to visualize brain activity variability and relate it to each person's pain sensitivity and their ability to do a cognitive task when in pain. After analyzing the activity signals in specific brain regions that are associated with pain

perception, the team found that those with highly variable signals were less sensitive to the additive effects of repeated exposure to painful stimuli. Moreover, while experiencing pain, these individuals outperformed those with less brain signal variability in a set of cognitive tasks, which included tests that measure how quickly subjects respond to numerical problems.

“Our study is the first to demonstrate that variable activity in specific brain regions reflects a mechanism to process nociceptive signals and cope with pain,” says Dr. Davis. “It also reveals the potential to use fMRI as a predictive tool for pain tolerance and coping with everyday activities while in pain. This could help clinicians identify those that are likely to be vulnerable to chronic pain—the most common cause of long-term disability—and to intervene earlier with personalized therapeutic strategies for pain management.”

This work was supported by the Canadian Institutes of Health Research, an Ontario Graduate Scholarship, the University of Toronto and the Toronto General & Western Hospital Foundation.

Rogachov A, Cheng JC, Erpelding N, Hemington KS, Crawley AP, Davis KD. Regional brain signal variability: a novel indicator of pain sensitivity and coping. Pain. 2016 Nov. doi: 10.1097/j.pain.0000000000000665.

Taking a Trip Down Memory Lane

The hippocampus is a region of the human brain that is intimately involved in learning and memory as well as navigation.

Our memories are what shape us. When we retrieve the memory for an event in our past, called an autobiographical memory, there can be a lot of perceptual detail—such as sights, sounds, smells and tastes—making them more vivid and life-like. And it is believed that this perceptual “richness” can help us to recall memories. How our brains create, store and retrieve these complex memories remains unknown.

Researchers have gained some insight into the process by studying patients affected by medial temporal lobe (MTL) epilepsy, a neurological condition that damages the MTL region of the brain. This damage impairs the recollection of autobiographical memories and diminishes their perceptual richness, suggesting that the MTL contributes to the retrieval of perceptually rich memories.

Recently, a team led by Krembil Postdoctoral Fellow Dr. Marie St-Laurent used functional magnetic resonance imaging (fMRI), an imaging technique that can be used to measure regional brain activity during certain tasks, to examine the link between brain function and the perceptual richness of memories. This work was performed under the supervision of Krembil Senior Scientist Dr. Mary Pat McAndrews.

Healthy participants and people with MTL epilepsy were asked to recall perceptually rich memories (ie, audio-visual film clips or autobiographical memories) and memories lacking perceptual content (ie, written narratives), while undergoing an fMRI scan. In the group of healthy adults, several brain regions, including the right hippocampus within the MTL, were more active when they retrieved perceptually rich memories. And this right hippocampal activation corresponded with their ability to retrieve perceptual details. In contrast, patients with MTL epilepsy and right hippocampus damage experienced less activation in these brain regions and were impaired at remembering perceptual details.

These findings suggest that the hippocampus plays an important role in determining how vividly we relive past life events.

This work was supported by the James S. McDonnell Foundation, the Canadian Institutes of Health Research, the Savoy Epilepsy Foundation, the Natural Sciences and Engineering Research Council of Canada and the Toronto General & Western Hospital Foundation.

St-Laurent M, Moscovitch M, McAndrews MP. The retrieval of perceptual memory details depends on right hippocampal integrity and activation. Cortex. 2016 Nov. doi:10.1016/j.cortex.2016.08.010.

Lasers Lessen Damaging Eye Lesions

The exact cause of age-related macular degeneration is unknown; however, exercising and maintaining a healthy diet can reduce your risk of developing the disease.

Age-related macular degeneration (AMD) is a disease where the retina, the light-sensitive coating at the back of the eye, deteriorates. It can lead to irreversible blindness and affects nearly 50 million people worldwide.

There are two types of AMD: wet and dry. The dry type affects 80-90% of AMD patients. Although it is unclear what role they play in the disease, it is characterized by the presence of yellowish deposits known as drusen. There is currently no approved treatment for dry AMD.

Krembil Clinician Investigator Dr. Robert Devenyi and Dr. Graham Merry from Photospectra Health Sciences recently investigated the use of an emerging laser-based therapy to remove drusen. The approach, which is called photobiomodulation (PBM), was used in 24 people with dry AMD. Before and after treatment, the research team measured visual function, including visual acuity (patients' ability to see fine details) and contrast sensitivity (ability to detect low contrast images).

The team found that PBM significantly improved visual acuity and contrast sensitivity immediately after treatment. This improvement was sustained, with benefits lasting for up to three months after treatment. The team also shed light on the role of drusen in dry AMD, as the benefits varied with the change in drusen size: greater decreases in drusen size were associated with greater improvements in vision.

"Our results suggest that PBM treatment can simultaneously reduce drusen volume and improve vision," says Dr. Devenyi. "We are now conducting a large-scale clinical trial to further elucidate the safety and efficacy of PBM, with the hopes of establishing it as a novel treatment for dry AMD."

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

Merry GF, Munk MR, Dotson RS, Walker MG, Devenyi RG. Photobiomodulation reduces drusen volume and improves visual acuity and contrast sensitivity in dry age-related macular degeneration. Acta Ophthalmol. 2016 Dec 18. doi: 10.1111/aos.13354.

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If you have any feedback about the newsletter, please contact Nick Dery: **ndery@uhnresearch.ca**

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