The Krembil

September 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.

Stories in this month's issue:

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

News

A New Vision, a New Institute

(L-R) Dr. Valerie Wallace, Head of Vision Sciences at UHN; Donald K. Johnson; Anna McCowan-Johnson; Dr. Robert Devenyi, Ophthalmologist-in-Chief at UHN (Photo credit: John Loper Photography).

The creation of a new clinical and vision research institute—named the Donald K. Johnson Eye Institute—was announced at a special UHN celebration on the evening of September 20, 2016. The new institute is a result of merging UHN's Ophthalmology Department (previously known as the Donald K. Johnson Eye Centre) with the Division of Vision Sciences. Its research activities will continue to operate under the direction of the Krembil Research Institute.

By bringing together a clinical centre with a comprehensive research program, it will be guided by dual clinical/research leadership through co-directors Dr. Robert Devenyi, Director of Retinal Services, and Dr. Valerie Wallace, Head of Vision Sciences. This integrated approach will promote new collaborations and strengthen existing partnerships between clinicians and researchers, with the aim of developing innovative approaches to treating patients at UHN and worldwide.

"The greatest research advances often stem from simple conversations between clinicians and researchers, which spark new ideas," says Dr. Wallace. "The organizational structure of the Donald K. Johnson Eye Institute will ensure that more of these conversations happen."

The new institute could not have been formed without the continued leadership and generosity of philanthropists Donald K. Johnson and his wife, Anna McCowan-Johnson. The name of the institute reflects the long-standing support that they have provided to clinical efforts and basic research at UHN—support that totals more than $15 million.

It is the vision of Dr. Peter Pisters, UHN President and CEO, to establish similar clinical-research sub-institutes across all UHN programs; he commented on the benefits of this approach during his address, saying, "This transformation will facilitate improved collaboration between clinicians, researchers and educators, with the ultimate goal of improving patient care."

Krembil Summer Students Shine

(L-R) Summer Student Research Day was hosted by Krembil Senior Scientists Drs. Frances Skinner and Joan Wither, and featured opening and closing remarks from Dr. Donald Weaver.

The Krembil Summer Student Research Day took place on August 23 at the Toronto Western Hospital. The event was co-organized by the Krembil Research Institute's Trainee Affairs Committee and its administration team.

After opening remarks from Dr. Donald Weaver, Director of the Krembil Research Institute, 25 summer students from 15 different research labs presented their results. Through 5-minute 'rapid fire' talks, Krembil-led advances were highlighted in the fields of neuroscience, arthritis and health outcomes research. Examples included three talks—by Emilie Matip, Brian Wu and Mitchell Greniqueca—from the lab of Krembil Senior Scientist Dr. Mohit Kapoor; the students described their research on the role of various proteins and microRNAs in arthritis and inflammatory processes.

Dr. Frances Skinner, Chair of the Trainee Affairs Committee, commented, "Performing quality research is challenging, but being able to communicate the results of the research is just as big of a challenge. Without learning the skills required to describe our findings in a way that is clear and understandable, the potential impact of our research would be lost. Thank you to the Krembil Research Institute for supporting this event,

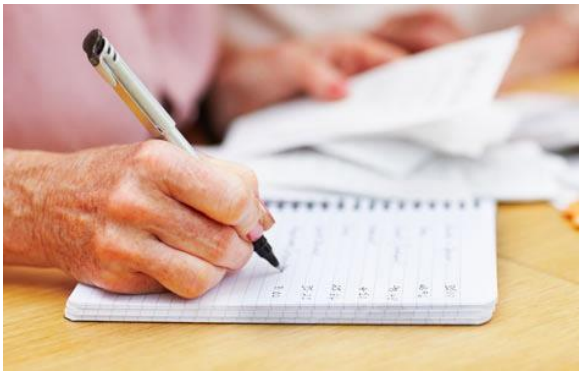
which serves as an important venue for young scientists to share their results and to develop vital communication and knowledge translation skills."

Dr. Weaver closed the event by congratulating the students on their research achievements and their engaging presentations.

For more information or to provide feedback about the Summer Student Research Day, please contact the Krembil Administration office.

Research

Treating Hand Tremors



Around one in ten individuals who are 65 years or older experience 'essential tremor'—uncontrollable shaking that intensifies when attempting a movement (such as writing).

The most common movement disorder—known as 'essential tremor'—causes uncontrollable shaking in the hands, arms and sometimes the head and vocal cords. While it is often mild, it worsens with age and can lead to difficulty completing daily tasks.

When medications fail to improve the tremors, a surgical treatment is performed: a small region of the brain, known as the ventral intermediate nucleus (VIM), is targeted and shut down.

Targeting the VIM is challenging; it is a small region of the brain that is only a few millimeters in length. Furthermore, current imaging techniques are limited and clinicians must rely on indirect methods to approximate the location of the target.

To address this issue, Krembil Scientist and Techna Affiliated Faculty Dr. Mojgan Hodaie and her team developed a new approach to more accurately identify the location of the VIM. Her strategy involved direct visualization of the white matter fibers coursing through VIM using a technique called diffusion tensor imaging (DTI). To overcome the difficulty in targeting the region, Dr. Hodaie's team employed novel methods to improve the accuracy of targeting, and compared the location of the DTI tracts with the location of the target found during surgery.

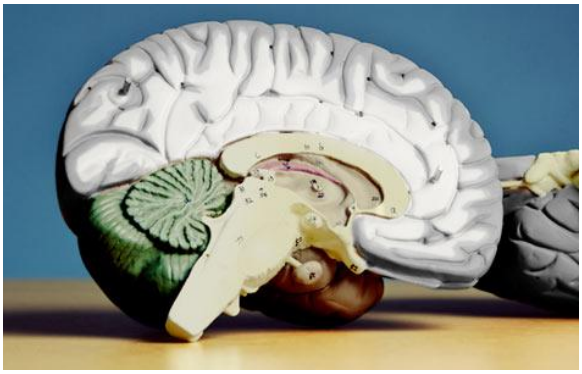
The results showed that this method of targeting is accurate and, because it is not time-consuming, represents a clinically feasible strategy to precisely locate the VIM nucleus in each patient.

Future studies will determine whether DTI targeting translates into better outcomes for those suffering from medication-resistant tremors. The results of these studies are particularly far-reaching because targeting the VIM is also used to treat the severe tremors experienced by individuals suffering from medication-resistant Parkinson disease.

This work was supported by the Toronto General & Western Hospital Foundation. AM Lozano holds a Tier 1 Canada Research Chair in Neuroscience .To learn more about Dr. Hodaie's research, visit the Hodaie Lab Website.

Sammartino F, Krishna V, Kon Kam King N, Lozano AM, Schwartz ML, Huang Y, Hodaie M. Tractography-based ventral intermediate nucleus targeting: novel methodology and intraoperative validation. Movement Disorders*. 2016 May 23. doi: 10.1002/mds.26633.*[Pubmed abstract]

Reading Brain Signals



White matter (shown above in white) is located within the central area of the brain; it is involved in learning and facilitates communication between different brain regions.

Magnetic resonance imaging (MRI) provides a detailed view of the soft tissues of the body. When used to visualize the brain, MRI has revealed a phenomenon where high intensity 'bright signals' appear in the brain's white matter. Researchers also call these bright signals leukoaraiosis or white matter hyperintensities (WMHs).

Because they are observed more often in the elderly, WMHs were initially thought to represent structural brain changes that occur as part of normal aging. However, findings have recently linked them to a number of neurological disorders, such as dementia and age-related intellectual decline.

Now, WMHs are the focus of intense study, and it has been proposed that they represent localized 'mini-strokes'—small brain regions that are damaged as a result of limited blood flow. Despite these hypotheses, much is still unknown about how WMHs form and how to prevent them.

Krembil Senior Scientist Dr. David Mikulis led a study focused on how WMHs form. Using MRI, his team obtained detailed brain images from 45 patients (aged between 50 and 91 years old) at the start of the study and one year into the study.

The researchers found that WMHs formed in brain regions with specific readouts that can be measured with MRI. Specifically, these 'at risk' brain regions displayed the following characteristics [MRI readout in brackets]:

- decreased blood flow reserve [cerebrovascular reactivity]
- reduced 'connectivity'—e.g. reduced ability of the white matter to connect different parts of the brain [fractional anisotropy]
- increases in water distribution [transverse relaxation time]
- increased rates of liquid movement through the tissue, suggestive of tissue injury [mean diffusivity]

Dr. Mikulis comments, "Cerebrovascular reactivity represents a novel marker that can be used to predict brain tissue, which has an increased risk for future brain injury. The specific type of injury that can be predicted, known as ischemic demyelination, has been related to cognitive decline. Thus, early detection will enable researchers to monitor the effects of new preventative therapies to stop brain damage before it occurs."

This work was supported by the Canadian Stroke Network, the Ontario Research Fund, the Academic Health Science Centre Alternative Funding Plan and the Toronto General & Western Hospital Foundation.

Sam K, Crawley AP, Conklin J, Poublanc J, Sobczyk O, Mandell DM, Venkatraghavan L, Duffin J, Fisher JA, Black SE, Mikulis DJ. Development of White Matter Hyperintensity Is Preceded by Reduced Cerebrovascular Reactivity. Annals of Neurology*. doi: 10.1002/ana.24712. 2016 Aug.* [Pubmed abstract]

Asking the Right Questions

Although myasthenia gravis can lead to weakening of any voluntary muscle, the muscles that control the eye, eyelid, facial expressions and swallowing (pictured) are frequently affected.

Myasthenia gravis (MG) is a disease caused by the gradual breakdown of communication between nerves and muscles. This breakdown leads to varying degrees of weakness in the body's muscles, which worsens during periods of activity and improves after periods of rest.

An interesting aspect of MG is that treatments—ranging from medication to surgery—vary depending on the severity of symptoms. However, measuring disease severity remains a challenge because some symptoms are only triggered by activities that are not easily observed in the clinic.

In order to improve disease tracking, University of Toronto Assistant Professor Dr. Carolina Barnett Tapia, working with Krembil Senior Scientist Dr. Aileen Davis, set out to develop a questionnaire that could be used by clinicians to more reliably assess disease stage. The original draft of the questionnaire was assembled using common examination questions taken from the MG literature and provided by various MG experts. Then, the study team asked 18 MG patients and 72 MG experts for their input on what questions should be changed, removed or added in order to improve comprehension and diagnostic accuracy.

The team tested the revised questionnaire on 200 individuals with MG. The results revealed that the questionnaire excelled in two important ways: reliability and accuracy. Specifically, they found that the questionnaire yielded similar scores when administered to the same patient on separate occasions (known as the "test–retest reliability"). They also found that the questionnaire was a good indicator of actual disease state (known as "construct validity").

"Overall, the main advantages of our questionnaire are that it is easy to use, does not take long to complete and, at the same time, provides a comprehensive assessment of the myasthenic state in patients." says Dr. Davis.

This work was supported by the American Academy of Neurology, the American Brain Foundation and the Toronto General & Western Hospital Foundation.

Development and validation of the Myasthenia Gravis Impairment Index. Barnett C, Bril V, Kapral M, Kulkarni A, Davis AM. Neurology*. PMID: 27402891. 2016 Jul 8.* [Pubmed abstract]

Decrypting Stroke Causes

The effects of a stroke—such as paralysis, memory loss and changes in behaviour—depend on several factors, including the location of the obstruction.

Atherosclerosis is a process in which plaque (comprising cholesterol and other substances) accumulates within—and can lead to narrowing of—the blood vessel wall. When a fragment of the plaque breaks off of the wall, it can be carried through the blood towards the brain. This fragment can cause a blockage—depriving the brain of oxygen and causing an ischemic stroke.

To assess whether atherosclerosis is the cause of a stroke, doctors use an imaging technique called CT angiography to visualize blood vessels in the head and neck. The traditional thinking has been that only those plaques that significantly narrow the blood vessels cause strokes.

However, one in four people who have suffered an ischemic stroke have neither significant narrowing of blood vessels nor evidence of other causes. These strokes are classified as 'cryptogenic', meaning that there is no identifiable reason for the stroke. Without this information, it is difficult for stroke survivors to know which treatment options are best to prevent recurrence.

Krembil Clinician Investigator Dr. Daniel Mandell initiated a study to address this gap in knowledge. His research team used CT angiography to examine the vessels of those with cryptogenic stroke; however, instead of looking for vessel narrowing as is routinely done, they looked directly at the vessel wall to identify plaques in the absence of narrowing.

They found a striking number of large plaques in the blood vessels supplying the brain of those with cryptogenic stroke. This suggests that plaque accumulation may be a causative factor in cryptogenic strokes, despite the fact that these plaques were not causing significant narrowing and not considered clinically relevant, until now.

“CT angiography is a widely available imaging technique. Doctors interpreting these images usually look for blood vessel narrowing but don’t attempt to directly visualize plaques,” says Dr. Mandell. “Our study suggests that it is possible to measure the plaque itself. Interpreting images in this way may improve our ability to identify the cause of strokes.”

This work was supported by The Netherlands Organisation for Scientific Research, the Dutch Thrombosis Society, the Remmert Adriaan Laan Foundation, the Association of University Radiologists and the Toronto General & Western Hospital Foundation.

Nonstenotic carotid plaque on CT angiography in patients with cryptogenic stroke. Coutinho JM, Derkatch S, Potvin AR, Tomlinson G, Kiehl TR, Silver FL, Mandell DM. Neurology. *doi 10.1212/WNL.0000000000002978. 2016 Jul 13.* [Pubmed abstract]

Answers in the Blood

As psoriatic arthritis progresses, patients develop painful joint deformities that prevent them from being able to perform activities requiring manual dexterity, such as sewing or playing the piano.

Approximately 2-3% of Canadians have a condition known as psoriasis, which causes red patchy skin that can be itchy and sore. Up to a third of these patients will develop psoriatic arthritis, a debilitating condition that causes joint pain, stiffness and swelling.

Psoriatic arthritis is often misdiagnosed because of a lack of disease awareness. Moreover, there are no reliable screening tools for determining which patients with psoriasis will progress to psoriatic arthritis. This is problematic because patients with psoriatic arthritis are more likely to develop serious conditions such as heart disease.

In order to identify a screening method for psoriatic arthritis, Krembil Senior Scientist Dr. Dafna Gladman and her team conducted a comprehensive eight-year-long study in patients with psoriasis who did not have arthritis when they first presented at the clinic. Having previously identified increased expression of the CXCL10 gene among patients with psoriatic arthritis, they decided to measure the levels of CXCL10 protein in blood and joint fluid samples taken during the study. They collected clinical data and blood samples from patients with psoriasis (before and after the development of psoriatic arthritis) and joint fluid from patients with psoriatic arthritis.

The researchers found higher blood levels of CXCL10 in patients with psoriasis who later developed psoriatic arthritis than in those who did not. However, once the psoriatic arthritis developed there was no difference in blood levels of CXCL10 across patient groups. This suggests that blood levels of CXCL10 may predict which patients are more likely to develop psoriatic arthritis, even before any clinical symptoms develop, such as joint swelling or stiffness. The study team also found that patients with psoriatic arthritis had much higher levels of CXCL10 in their joint fluid compared to controls, suggesting that CXCL10 plays a role in joint inflammation.

Explains Dr. Gladman, “It is increasingly important for us to look beyond clinical features to improve how psoriatic arthritis is diagnosed. Our results suggest that CXCL10 might be a useful screening tool in this regard, either alone or in combination with other clinical information, allowing us to prevent more serious complications of the disease.”

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

C-X-C motif chemokine 10 is a possible biomarker for the development of psoriatic arthritis among patients with psoriasis. Abji F, Pollock RA, Liang K, Chandran V, Gladman DD. Arthritis & Rheumatology. *doi: 10.1002/art.39800. 2016 Jul 7.* [Pubmed abstract]

Making a Mark on Back Pain

Cartilage—the smooth, protective tissue that protects the ends of bones where they meet at a joint—breaks down and wears away in people with osteoarthritis, causing pain, swelling and loss of motion.

Osteoarthritis (OA) affects about three million Canadians and leads to the breakdown of the protective cartilage found in the body's spine, hand, knee and hip joints. The identification of biological markers ("biomarkers") could be used to develop new preventative therapies; however, there were no known biomarkers of spine OA, until now.

A team led by Krembil Senior Scientist Dr. Mohit Kapoor, comprising Dr. Akihiro Nakamura (a postdoctoral fellow in Dr. Kapoor's lab) and Krembil Clinician Investigator Dr. Y. Raja Rampersaud, recently analyzed tissue biopsies from 55 patients with spine OA. They screened 2,100 biological molecules known as microRNAs and found that two of these—microRNA-181a-5p and microRNA-4454—may be able to help clinicians determine the severity of spine OA. The study also revealed that elevated levels of these biomarkers may actually cause inflammation, cartilage destruction and collagen depletion.

"The most critical aspect of this discovery is that we have found that these two molecules are actively involved in increasing inflammation and destroying cartilage. This suggests that they could be used in targeted therapies—new strategies that are developed to block their activity may actually prevent damage," says Dr. Kapoor.

Next, the team will investigate whether these new biomarkers can be detected in the blood and their utility as an early detection test: if they are present in the blood when early or mild symptoms arise, then clinicians will know to prescribe treatments that can help prevent significant damage before it begins. The researchers will also test if blocking these biomarkers can halt spine degeneration.

This work was supported by the University Health Network Arthritis Program, the Krembil Foundation and the Toronto General & Western Hospital Foundation. I Jurisica is a Tier 1 Canada Research Chair in Integrative Cancer Informatics.

Identification of microRNA-181a-5p and microRNA-4454 as mediators of facet cartilage degeneration. Nakamura A, Rampersaud YR, Sharma A, Lewis SJ, Wu B, Datta P, Sundararajan K, Endisha H, Rossomacha E, Rockel JS, Jurisica I, Kapoor M. Journal of Clinical Investigation Insight. *doi:10.1172/jci.insight.86820.I.* [Pubmed abstract]

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UHN Toronto Western Hospital

krembil@uhnresearch.ca

@KrembilRI

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

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