The Krembil

November 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

Krembil's New Communications Team

Meet the two new communications specialists who will help our researchers share their work.

Krembil's new Public Affairs team (pictured, L-R): Heather Sherman and Travis Boyco.

We are pleased to announce that two new talented individuals have joined our communications team: Heather Sherman and Travis Boyco. Together, they bring a wealth of experience, knowledge and social media savvy to help promote our discoveries and success stories.

Meet Heather Sherman

Heather is a seasoned and award-winning storyteller.

Before joining Krembil, she spent six years as a producer/director at Discovery Canada's Daily Planet, where she generated over 200 short documentaries about groundbreaking technology, scientific discoveries and world-changing inventions. In recognition of her exceptional coverage, she received two awards at the Houston Film Festival and was nominated for the Walter Sullivan Award for Excellence in Science Journalism. Heather has also worked for the Marilyn Denis Show, Canada AM and City

TV's City Pulse News.

At Krembil, Heather works closely with the media to promote high-profile research and technological innovations. She also provides strategic advice and media & science communication training to the Institute's doctors and scientists.

"My goal is to raise the Institute's profile by sharing its incredible stories with the world," says Heather.

Meet Travis Boyco

Travis is a broadly trained communications specialist with an artistic flare.

He completed a Master's degree in Professional Communication, for which he examined the strategic use of social media during public health and health care crises. He also holds a degree in human geography and political science, as well as a diploma in multimedia design and production.

"I've been interested in health care for as long as I can remember. Whether health and fitness or science and medicine, I always knew I wanted to work at the interface of these fields and to encourage a positive change. My new role at Krembil enables me to do both of these," says Travis.

In his new role, he performs a wide range of tasks—such as shooting videos and taking photos, liaising with the media, writing news stories, managing social media channels and creating branded materials.

Heather and Travis encourage researchers to reach out to them through the contact information listed below to introduce themselves and their work to the new pair.

Welcome Heather and Travis to Krembil!

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Sharing our Stories

Two newly released publications showcase Krembil's research and achievements.

Publication covers (L-R): the 2018 Krembil Annual Report and the Krembil Brain Institute Magazine.

Two new publications were launched in October to promote Krembil's relentless pursuit of new diagnostics and therapies for chronic debilitating diseases: the Krembil Annual Report and the Krembil Brain Institute Magazine. Both include a collection of stories describing our research and achievements, interesting facts and figures and eye-catching visuals.

Krembil Annual Report

The Krembil Annual Report highlights a selection of the Institute's greatest achievements in the past year—in research, knowledge mobilization and translation, funding and recruitment. Research stories include:

- discovering a cancer gene that contributes to stroke;
- repairing damaged nerves using a microscopic 'message in a bottle';
- identifying a therapeutic target that could help patients affected by a wide range of arthritic diseases; and
- revealing how genetic tests could improve epilepsy diagnosis and treatment.

Click here to read the report.

Krembil Brain Institute Magazine

In partnership with the Globe and Mail, Krembil published a magazine insert showcasing the groundbreaking science and world-class innovation happening at our Institute. This year the magazine focused on the struggles and successes of the Krembil Brain Institute's researchers who are striving to develop new treatments for stroke, epilepsy, Alzheimer's, Parkinson's, pain and concussion. Over 60,000 printed copies of the magazine were distributed across Canada.

Click here to read the magazine.

Printed copies of both publications are available at the Krembil Directorate Office (room 4KD478, Krembil Discovery Tower).

Research

Giving Old Drugs a New Life

Researchers show that two drugs for fungal infections could help treat brain cancer.

The drugs examined in this study treat infections caused by a primitive organism known as a fungus. Mushrooms, mold and yeast are all members of the fungus family.

Ever used a jam jar as a coin bank? Or a worn-out boot as a planter? Giving old household items a new purpose is an easy and cost-effective way to solve a problem.

In rare cases, a drug developed to treat one disease is also found to be effective against another disease. However, when it comes to repurposing drugs, the stakes are often a matter of life and death, and hundreds of millions of dollars can be saved in the drug discovery process.

Dr. Gelareh Zadeh, Medical Director of the Krembil Brain Institute, Scientist and Neurosurgeon in the MacFeeters-Hamilton Neuro-oncology Program, recently discovered that two antifungal drugs hold great promise for treating glioblastoma multiforme (GBM)—the most aggressive and common form of brain cancer. This work was recently published in the journal *Clinical Cancer Research*.

“GBM unfortunately and sadly remains an incurable cancer and survival time from diagnosis is typically 18 to 20 months. Currently the treatment is surgery followed by chemo- and radiation therapy,” explains Dr. Zadeh. “There are very few drugs for GBM outside of traditional chemotherapies. Being able to identify drugs that effectively reach the tumour, prevent its progression and prolong patient survival is really quite critical.”

Dr. Zadeh and her team screened thousands of existing drugs for their potential to control the growth of tumour cells in the brain, before identifying the two drugs: ketoconazole and posaconazole. These drugs possess a key characteristic required to treat GBM: they can enter the brain from circulating blood through the blood-brain barrier, a highly selective filter between the brain and the rest of the body.

The two drugs are effective against fungal infections because they prevent the fungus from making a key molecule that helps maintain its shape. Dr. Zadeh’s team showed that the drugs also hinder the growth and progression of GBM, but through a different mechanism: they interfere with the metabolism of tumour cells.

“Based on these results, we have started using a rather unexplored clinical trial design for GBMs where we first give the drug to the patient before we take the patient into surgery. Once the tumour is removed, we then test whether the drug made it to the tumour, had the desired penetrance into the tumour and had the desired impact on tumour growth,” adds Dr. Zadeh.

“If we can show that giving the drug before surgery leads to better outcomes, this will really transform how we manage GBMs. The hope is to be able to control the tumour without the need for surgery.”

This work was supported by the Canadian Institutes of Health Research and The Princess Margaret Cancer Foundation.

Agnihotri S, Mansouri S, Burrell K, Li M, Mamatjan Y, Liu JC, Nejad R, Kumar S, Jalali S, Singh S, Vartanian A, Chen EX, Karimi S, Singh O, Bunda S, Mansouri A, Aldape K, Zadeh G. Ketoconazole and Posaconazole Selectively Target HK2 Expressing Glioblastoma Cells. Clin Cancer Res. 2018 Oct 15. doi: 10.1158/1078-0432.CCR-18-1854.

Dr. Gelareh Zadeh, Medical Director of the Krembil Brain Institute.

A Harbinger of Severe Disease

Back X-rays could help rheumatologists identify patients with severe psoriatic arthritis.

Although back X-rays can reveal inflammation in back joints, which is a sign of potentially severe psoriatic arthritis (PsA), they are not routinely performed on PsA patients.

A new study from researchers at University Health Network recommends that all patients with psoriatic arthritis (PsA) be screened for inflammation in their back joints, regardless of whether or not they have back pain.

PsA typically occurs in people with a skin condition known as psoriasis. PsA is characterized by inflammation and pain primarily in the joints of the hands, feet, knees, ankles, wrists, elbows or hips. If left untreated, the disease can lead to irreversible joint damage and disability.

In some patients, PsA can also cause inflammation and pain in the joints of the back, which is referred to as axial arthritis. When axial arthritis occurs in patients, it can signal the presence of more severe forms of PsA—forms that could benefit from treatment with more potent medications.

“Despite its importance, accurately detecting axial arthritis in patients with psoriatic arthritis is difficult,” says Dr. Vinod Chandran, an Affiliate Scientist at the Krembil Research Institute.

“There is no widely accepted definition or test for axial disease in psoriatic arthritis. Instead, when chronic back pain is identified, a rheumatologist will rely on his or her

professional judgement to predict whether it is caused by axial arthritis or by other factors, such age, excess weight or osteoarthritis."

In the new study, Dr. Chandran evaluated the accuracy of rheumatologists' prediction in diagnosing axial arthritis in PsA patients.

He enrolled 171 PsA patients with or without back pain into his study. A rheumatologist judged whether or not a patient's back pain was caused by PsA after considering the patient's history and physical examination. Additionally, each patient received a back X-ray to detect inflammation in their back joints.

By comparing results of the X-rays to the predictions made by rheumatologists, Dr. Chandran found that rheumatologists are not very good at detecting axial arthritis in PsA patients. Moreover, he showed that over 30% of PsA patients with axial arthritis detected by the X-ray images experienced no back pain at all.

"Our findings suggest that rheumatologists should consider conducting back X-rays or MRI in all patients with PsA regardless of the presence or the nature of their back pain. To date, imaging appears to be the best way to detect axial involvement. This approach would also enable rheumatologists to better identify patients with potentially severe PsA early so that their treatments could be better optimized to slow joint damage."

This study was supported by the Krembil Foundation and the Toronto General & Western Hospital Foundation.

Yap KS, Ye JY, Li S, Gladman DD, Chandran V. Back pain in psoriatic arthritis: defining prevalence, characteristics and performance of inflammatory back pain criteria in psoriatic arthritis. Ann Rheum Dis. 2018 Aug 4. pii: annrheumdis-2018-213334. doi: 10.1136/annrheumdis-2018-213334.

Dr. Vinod Chandran, Affiliate Scientist, Krembil Research Institute.

Breathing a Sigh of Relief

Distinct group of nerve cells promote breathing after spinal cord injury.

A spinal cord injury can lead to loss of movement and loss of sensation in different parts of the body, as well as difficulty breathing and coughing.

A team of researchers from University Health Network has developed an innovative strategy that could help to restore breathing following spinal cord injury (SCI).

Dysfunctional breathing is a major cause of death or disease after SCI. To help them breathe, many SCI patients require an assistive ventilation device or a tracheotomy, a surgical procedure that creates a hole through the front of the neck and into the windpipe. Moreover, 80% of deaths among SCI patients are caused by respiratory complications.

To better understand the mechanisms underpinning breathing difficulties in SCI, the researchers examined a variety of experimental models of the condition. Their findings identified a distinct population of cells in the spinal cord that—when stimulated—promoted recovery of breathing following injury. The research team also showed that these cells are not essential for normal breathing and that their activity appears to be recruited in SCI.

“The biggest implication of this work is that one day we may be able to flip a switch and improve the breathing of people living with these injuries,” says the leader of the team, Dr. Michael Fehlings, a Senior Scientist at the Krembil Research Institute.

Next, the team plans to leverage advances in regenerative medicine to translate their discovery into a therapy for SCI patients. Such a therapy could also potentially benefit individuals with other neurological diseases that cause breathing problems, including those with amyotrophic lateral sclerosis (ALS).

This work was supported by the Krembil Foundation, the Toronto General & Western Hospital Foundation, the Canadian Institutes of Health Research, the Paralyzed Veterans of America, AOSpine North America, the Onassis Foundation and the Dezwirek Foundation.

Satkunendrarajah K, Karadimas SK, Laliberte AM, Montandon G, Fehlings MG. Cervical excitatory neurons sustain breathing after spinal cord injury. Nature. 2018 Oct 10. doi: 10.1038/s41586-018-0595-z.

Dr. Michael Fehlings, Senior Scientist, Krembil Research Institute

Intercepting the Messenger

Potential new treatment for osteoarthritis could stop knee and spine joint destruction.

The new drug intercepts and blocks microRNA-181a-5p molecules, just as a defensive team is meant to intercept the ball from an opposing team.

Researchers at the Krembil Research Institute have developed a novel therapeutic treatment that has the potential to stop knee and spine osteoarthritis in its tracks.

The team led by Dr. Mohit Kapoor, Arthritis Research Director at the University Health Network and Krembil Senior Scientist published the results in the Annals of the Rheumatic Diseases, a leading journal for arthritis research.

Osteoarthritis is the most common form of arthritis. It affects about five million Canadians and is characterized by a breakdown of the protective cartilage found in the body's spine, hand, knee and hip joints.

"Current treatments for osteoarthritis address symptoms, such as pain, but are unable to stop the progression of the disease," explains Dr. Kapoor.

Dr. Kapoor and his team used a variety of experimental models to identify a molecule, called microRNA-181a-5p, which is believed to cause the inflammation, cartilage destruction and collagen depletion associated with the disease. They then developed a drug to selectively prevent microRNA-181a-5p from doing its job.

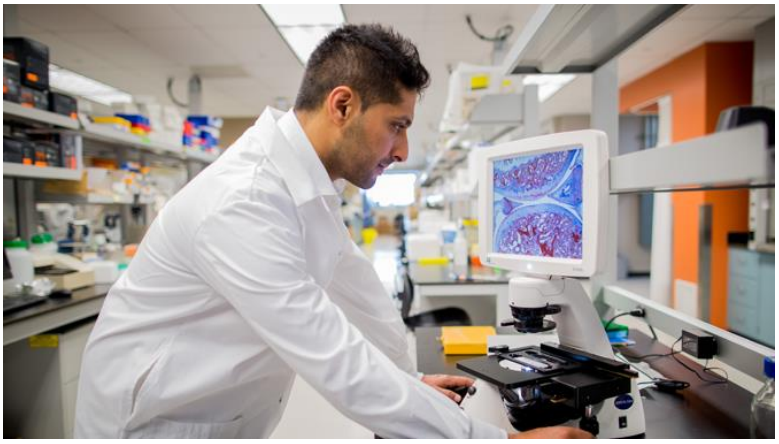
“When you inject this synthetic drug into the joints, it blocks the destructive activity caused by microRNA-181-5p and stops cartilage degeneration,” says Dr. Akihiro Nakamura, first author of the paper and a postdoctoral research fellow in the Kapoor lab.

The drug also prevented the breakdown of cartilage tissues taken from Toronto Western Hospital patients with knee and/or spine osteoarthritis.

Next steps for the research team include commencement of human safety studies that will determine the proper dosage and method for delivering the new drug to inflamed joints.

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

Nakamura A, Rampersaud YR, Nakamura S, Sharma A, Zeng F, Rossomacha E, Ali SA, Krawetz R, Haroon N, Perruccio AV, Mahomed NN, Gandhi R, Rockel JS, Kapoor M. microRNA-181a-5p antisense oligonucleotides attenuate osteoarthritis in facet and knee joints. Ann Rheum Dis. 2018 Oct 4. pii: annrheumdis-2018-213629. doi: 10.1136/annrheumdis-2018-213629.



Dr. Mohit Kapoor, Senior Scientist, Krembil Research Institute. Photo courtesy of the Globe and Mail.