The Krembil

January 2021

The Krembil is the official newsletter of the Krembil 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:

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

News

Inspiring the Future of STEM

Krembil to host livestream for the International Day of Women and Girls in Science.

On February 11, 2021, will be hosting a one-hour livestream in honour of the sixth annual International Day of Women and Girls in Science. The event is being held in partnership with the Durham District School Board, and it will be streamed to students during curriculum time with the aim of sparking curiosity and inspiring the next generation of scientists.

Around the world, women continue to be underrepresented in the fields of science, technology, engineering and mathematics, also known as STEM. To help address this, in 2015 the United Nations made a commitment to achieve gender equality in education and STEM careers. This marked the first International Day of Women and Girls in Science, which gave rise to hundreds of events dedicated to discussing global issues and sustainable solutions.

Krembil's event will be moderated by Dr. Gelareh Zadeh, Co-Director of Krembil Brain Institute and Senior Scientist at the Princess Margaret Cancer Centre at UHN. In 2020, Dr. Zadeh became the first female Chair of Neurosurgery in Canada.

Krembil Scientists Drs. Mojgan Hodaie, Valerie Wallace and Sowmya Viswanathan will share their journeys in STEM through TED talk-style presentations and answer questions submitted by students across the region.

“The number one reason women give for not choosing neurosurgery is a lack of role models and mentorship opportunities,” says Dr. Zadeh. “At UHN, we have countless strong, visible role models to show girls that there is a place here for them.”

Click here watch the event, which will be streamed live at 10am on February 11, 2021.

The event recording will be available for teachers wishing to show their classroom the presentations at a later date. For more information, contact Carley McPherson at carley.mcpherson@uhnresearch.ca.

Envisioning a Brighter Future

Krembil launches the Vision Magazine, a look inside the Donald K. Johnson Eye Institute.

More than 5.5 million Canadians are living with eye diseases such as cataracts and glaucoma—a group of disorders that damage the optic nerve. Individuals with eye conditions experience higher rates of depression and falls, which can impact their quality of life.

However, more than 75% of vision loss is preventable or treatable. At the Donald K. Johnson Eye Institute at University Health Network, researchers, clinicians and therapists are working together to find innovative treatments and cures for vision-related illnesses and advance discoveries from the lab to a clinical setting faster.

The 2020 Vision Magazine provides a look inside one of North America's leading vision institutes, featuring stories of innovation, collaboration and hope for a brighter future. Examples of these stories are listed below:

• **Vision testing in the comfort of home**: at home eye examinations developed using virtual reality headsets are improving access to glaucoma screening in remote areas

• **Stopping glaucoma in its tracks**: a molecule called lipoxin has been discovered that can protect the optic nerve from damage and is a target for new therapies to prevent or reverse glaucoma

• **New solutions for the window of the eye**: UHN scientists have helped develop a cutting-edge synthetic cornea, which will make corneal transplants easier and reduce the reliance on donors

• **Protein with potential**: researchers discovered a therapeutic target to prevent vision loss and blindness due to degeneration of the retina

Click here to read the 2020 issue of the Vision Magazine.

Research

A Window to Spinal Cord Recovery

Researchers identify the critical window for surgical decompression after spinal cord injury.

An adult's spine has four sections: cervical, thoracic, lumbar and sacral. Because each section protects nerves that control a different part of the body, the type of spinal cord injury depends on which section is injured.

The nerves that run through the spinal cord exchange messages between the brain and the rest of the body. Traumatic injuries to the spinal cord can damage these nerves and cause paralysis, numbness or loss of bladder or bowel control.

A treatment called surgical decompression alleviates compressed nerves in the spinal cord and can help patients regain some sensory and motor function. Krembil Senior Scientist Dr. Michael Fehlings and a team of neurosurgeons including Dr. Jetan Badhiwala sought to find out the optimal time to perform this surgery.

"We've identified a critical window within which surgical decompression should take place." Dr. Fehlings explains, "Patients who had surgical decompression within 24 hours of their injury had the greatest neurological recovery after one year. Furthermore, we discovered that motor recovery plateaus with surgeries performed after 36 hours."

The team analyzed data from four multicentre studies for 1,548 patients. The patients were split into two groups based on the time from injury to surgery: individuals who received surgery within 24 hours, and those who received surgery at or after 24 hours. At one year after surgery, those who received surgery within 24 hours showed greater improvement in all motor scores tested. Moreover, even within 24 hours, the earlier patients received surgery, the better their recovery.

Using the data, the team also discovered that at 36 hours after the injury there was a plateau in recovery. This suggests that at this point the nerves and tissue become irreversibly damaged and surgery is no longer beneficial.

“This study demonstrates that ‘time is spine’—timely surgical decompression, specifically within 24 hours, can provide patients the greatest chance for recovery,” says Dr. Fehlings.

In a separate clinical trial, Dr. Fehlings and his team, including Dr. Badhiwala, assessed whether the drug riluzole could help enhance sensorimotor recovery if taken prior to surgical decompression. While the drug did not improve motor recovery, researchers found evidence that it might reduce neck pain after decompression in patients with degenerative cervical myelopathy, or compression of the spinal cord.

Dr. Fehlings comments, “We hope that our findings help inform existing clinical guidelines for the treatment of spinal cord injuries, and put in motion more research into therapeutic strategies that can be rapidly deployed after injury to help improve the recovery of patients with spinal cord injuries.”

Badhiwala JH, Wilson JR, Witiw CD, Harrop JS, Vaccaro AR, Aarabi B, Grossman RG, Geisler FH, Fehlings MG. The influence of timing of surgical decompression for acute spinal cord injury: a pooled analysis of individual patient data. Lancet Neurol. 2020 Dec 21. doi: 10.1016/S1474-4422(20)30406-3.

Supported by the Canadian Institutes of Health Research, and the Toronto General & Western Hospital Foundation.

Fehlings MG, Badhiwala JH, Ahn H, Farhadi HF, Shaffrey CI, Nassr A, Mummaneni P, Arnold PM, Jacobs WB, Riew KD, Kelly M, Brodke DS, Vaccaro AR, Hilibrand AS, Wilson J, Harrop JS, Yoon ST, Kim KD, Fourney DR, Santaguida C, Massicotte EM, Kopjar B. Safety and efficacy of riluzole in patients undergoing decompressive surgery for degenerative cervical myelopathy (CSM-Protect): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial. Lancet Neurol. 2020 Dec 22. doi: 10.1016/S1474-4422(20)30407-5.

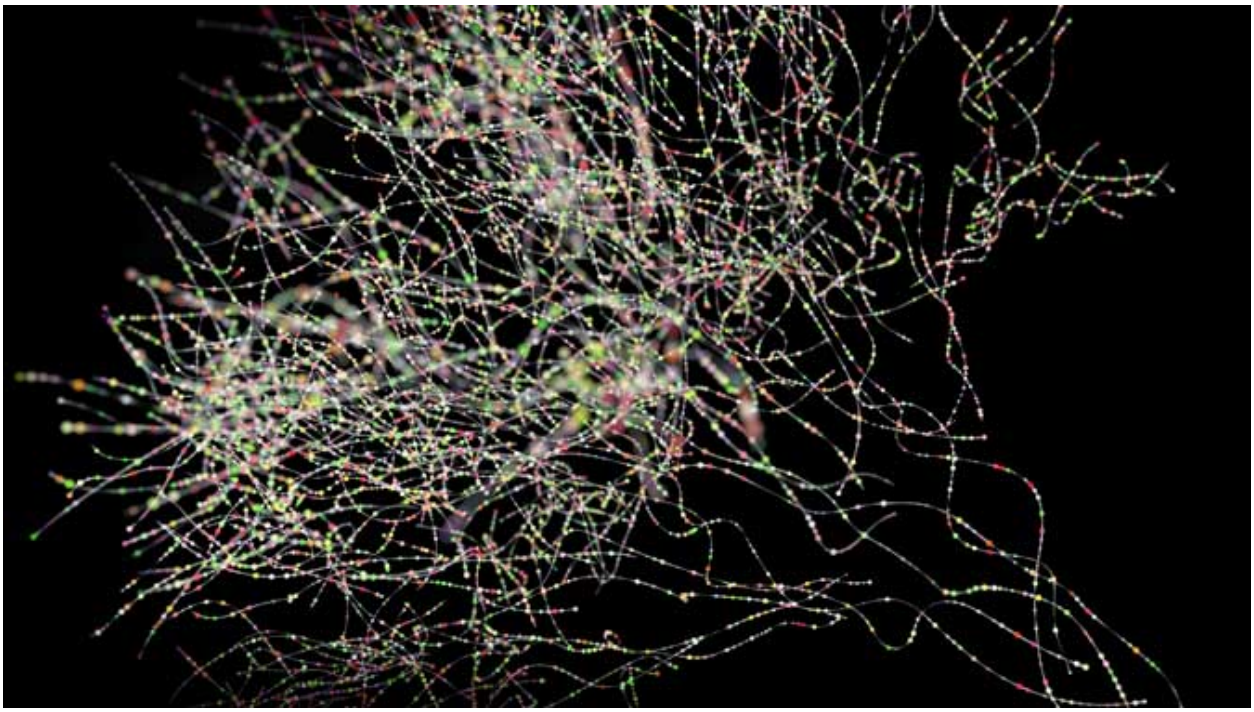
Sponsored by AOSpine North America, and the Toronto General & Western Hospital Foundation.

This surgical decompression research also benefits from the support of the DeGasperis Family Foundation. Dr. Fehlings holds the Gerald and Tootsie Halbert Chair in Neural repair and Regeneration.

(L-R) Senior author of both studies Dr. Michael Fehlings and author Dr. Jetan Badhiwala.

Visionary Computational Model

Study describes new molecular model of the brain connections involved in visual processing.



Neurons are cells of the brain and spinal cord that interconnect to form complex networks. The human brain has 1015 connections—close to the same number of neurons as there are stars in the Milky Way.

Krembil researchers, led by Senior Scientist Dr. Michael Reber, have constructed the first computational model that describes the molecular and cellular mechanisms of visual connectivity organization in the brain.

The model simulates and predicts the organization of visual connectivity in the brain and how different networks of neurons interact with one another, which is very important for our daily functioning—in particular, for our ability to visualize and comprehend our surroundings.

The model is based a 'three-step' map alignment algorithm. The algorithm serves as a set of programming and mathematical instructions for constructing a visual map. The benefit of the three-step approach is that it closely mimics the three steps taken by the brain to process visual information.

The three steps defined in the algorithm and taken in the brain are 1) the formation of a visual map from information sent from the eye to a region of the brain known as the superior colliculus; 2) the incorporation of complementary information from the visual cortex, which is the main area in the brain the processes visual information, and 3) the 'alignment' of the visual information so that it makes sense to the brain.

Findings from the computational model were compared to those from real-life biological models. The results revealed that errors that arise in certain neurological conditions can be faithfully recreated in the computational model.

Commenting on the new model, Dr. Reber says, “This work is essential for recreating and ultimately predicting what can go wrong in the connections between the eye and brain. Our model has the power to ‘connect the dots’ between how biological parameters—such as the concentration or the function of a particular molecule, or the number of cells—affect visual perception. In the future, our model could reveal what happens to neural connections in diseases such as age-related macular degeneration, glaucoma or diabetic retinopathy—ultimately shedding light on new therapeutic approaches to improve vision.”

This work was supported by The University of Strasbourg Institute for Advanced Study, The French National Centre for Scientific Research (CNRS), the Donald K. Johnson Eye Institute, the Krembil Research Institute, and the Toronto General & Western Hospital Foundation.

Savier EL, Dunbar J, Cheung K, Reber M. New insights on the modeling of the molecular mechanisms underlying neural maps alignment in the midbrain. Elife. 2020 Sep 30;9:e59754. doi: 10.7554/eLife.59754.

The senior author of the study, Dr. Michael Reber (pictured) is a Senior Scientist at the Krembil Research Institute.

Tackling Brain Inflammation

Study identifies a common diuretic as a stepping stone for new therapies for Alzheimer disease.

Alzheimer disease is a neurodegenerative condition characterized by cognitive, memory and behavioural changes. Brain inflammation is a hallmark of the disease and a target for disease-modifying drugs.

A team of researchers led by Krembil Director and Senior Scientist Dr. Donald Weaver has shown that the diuretic medication furosemide can reduce inflammation in brain cells. This finding reveals that furosemide could serve as a new starting point for the design of innovative treatments for Alzheimer disease.

Alzheimer disease is the most common cause of dementia. Currently over 700,000 Canadians experience dementia—a number that is expected to double in the next decade. While current medications can slow the development of symptoms such as memory impairment, no treatment exists that can stop or reverse the progression of the disease.

“For patients battling Alzheimer disease and families watching their loved ones disappear, existing symptomatic treatments are not enough,” says Dr. Weaver.

To address the need for new treatments, Dr. Weaver’s research team is searching for ways to prevent or stop the brain changes that are known to cause disease symptoms.

In Alzheimer disease, one key change that occurs in the brain is the accumulation of a protein known as amyloid beta. The accumulated protein activates a type of immune cell known as microglia. Once activated, microglia release molecules that cause inflammation, which further damages brain cells.

Using an experimental model of inflammation, the team found that furosemide reduces the production of inflammation-causing molecules. They also found that the drug improves the ability of microglia to clear toxic debris.

Dr. Weaver adds, "Because furosemide is unable to cross the blood-brain barrier and get into the brain, our next focus will be to develop variants of the drug that can overcome this limitation. Furosemide has been proven to be safe and it represents an exceptional starting point for the development of exciting therapies for this devastating disease."

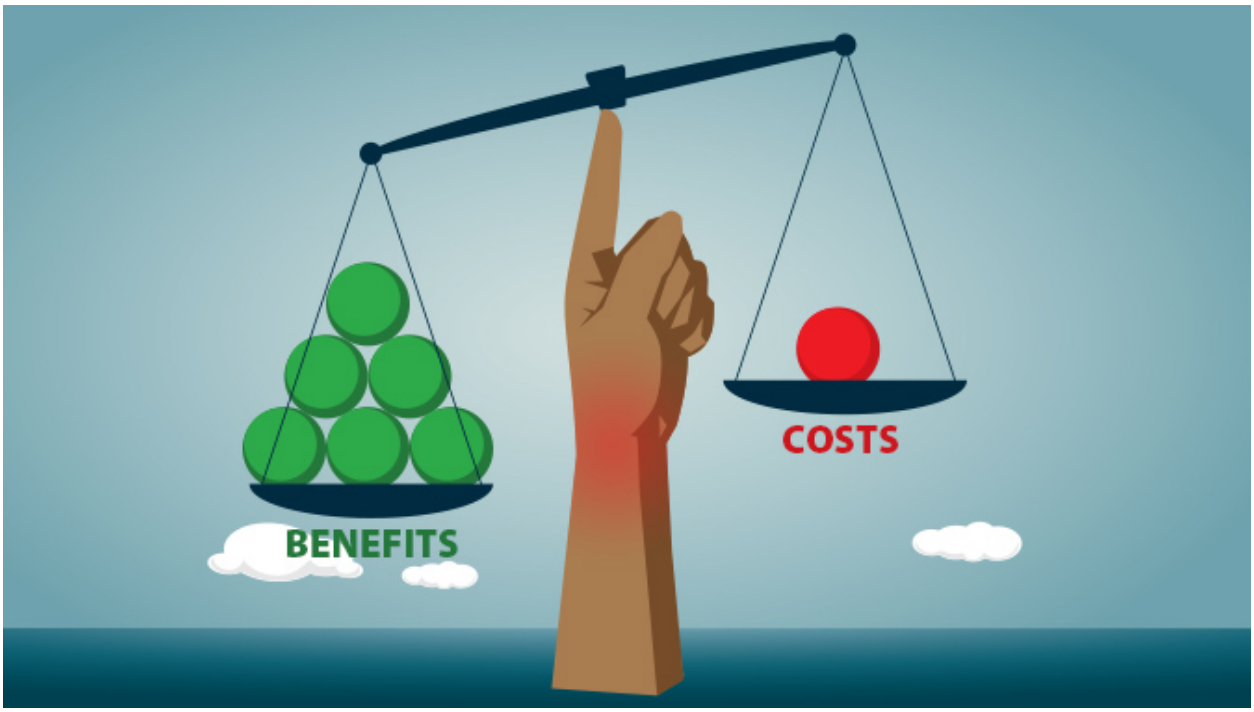
This work was supported by the Toronto General & Western Hospital Foundation. Dr. Weaver holds a Tier 1 Canada Research Chair in Drug Design for Protein Misfolding Disorders.

Wang Z, Vilekar P, Huang J, Weaver DF. Furosemide as a Probe Molecule for the Treatment of Neuroinflammation in Alzheimer's Disease. *ACS Chem Neurosci. 2020 Dec 16. doi: 10.1021/acschemneuro.0c00445.*

The senior author of the study, Dr. Donald Weaver, is the Director of the Krembil Research Institute and a Senior Scientist specializing in medicinal chemistry.

Getting the Upper Hand

Study reveals which surgical option is the most cost-effective for wrist osteoarthritis.



Detailed studies to weigh the benefits and costs of new treatments and technologies on patient health and the economic sustainability are vital for making informed decisions in health care.

A research team led by Dr. Heather Baltzer has published a new study that evaluated surgical options for two forms of osteoarthritis of the wrist. Their findings will help settle the debate over which option should be preferred.

Dr. Baltzer is a hand surgeon and a Clinician Investigator at the Schroeder Arthritis Institute and the Krembil Research Institute.

Osteoarthritis is the most common form of arthritis. It involves a progressive breakdown of the protective layer of cartilage in the joints, which can lead to debilitating chronic pain and reduced motion.

“Because multiple surgical procedures to relieve pain and restore motion exist, deciding which option is the best can be a challenge,” says Dr. Baltzer. “Our work will help surgeons and health care systems to better understand the costs and benefits of these treatments.”

Defining what is best can also be difficult. For example, a procedure may be expensive up front and complicated but may have lower costs and provide substantial health benefits in the long-term.

To make sense of the various costs and benefits, Dr. Baltzer's research team, which included fellow UHN investigators Drs. Herbert von Schroeder and Beate Sander, built a model that could simulate patients progressing through different stages of health. By feeding real-world data and statistics into the model, such as complication rates and the costs to hospitals, the team was able to directly compare the surgical options.

One procedure emerged as the winner: proximal row carpectomy. The model showed that this surgery, which removes three of the nine bones in the wrist to stop the remaining bones from rubbing, was the most cost-effective over the long term.

Cost-effectiveness is a measure that balances the value of improvements to patient health against the financial costs to the health care system. Proximal row carpectomy was found to provide lower costs and better health outcomes in comparison to the other options.

Dr. Baltzer's results will help inform policy makers and clinicians working within Canada's universal health care system. By providing the costs and benefits over the entire patient journey, these findings will help maximize benefits to the health care system and to patients.

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

Retrouvey H, Sander B, von Schroeder HP, Binhammer P, Baltzer HL. Cost-Effectiveness Analysis of Motion-Preserving Operations for Wrist Arthritis. Plast Reconstr Surg. 2020 Nov. doi: 10.1097/PRS.0000000000007260.

Dr. Heather Baltzer is a Clinician Investigator at the Schroeder Arthritis Institute and the Krembil Research Institute, and the Director of the Hand Program at Toronto Western Hospital.