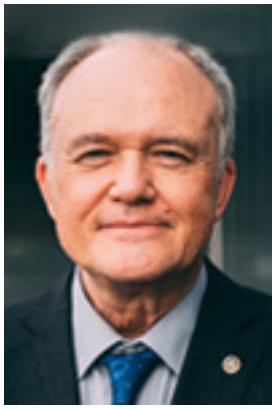
The Krembil

March 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:

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

News

2020 Krembil Annual Report is Here

Read the latest annual report to learn how Krembil is making progress from promise.

The cover of this year's report features photographs of patients and their family members who have contributed to and benefited from research in the fields of neuroscience, vision science and arthritis.

Krembil is pushing forward.

The year 2020 witnessed tremendous global challenges. The COVID-19 pandemic changed lives around the world and transformed the way we work, learn and interact. Daily activities came to an abrupt halt for many. Science was thrust into the spotlight.

While research was forced to change dramatically, Krembil scientists continued to work with utmost dedication to pursue treatments for diseases of the brain, eyes, bones and joints. We have many exciting stories of progress to share.

This year's Krembil Annual Report highlights a selection of our greatest achievements over the past year, including:

- identifying a marker of brain degeneration following repeated concussions
- revealing how a protein contributes to the development of brain networks

● discovering how immune cells in the joints differ between healthy individuals and those with arthritis
● advancing our understanding of COVID-19 and developing strategies and therapies to beat the disease

Click here to read the report.

Alzheimer’s Gairdner Symposium

Krembil to host Gairdner Symposium on Alzheimer’s disease for scientists and the public.

The Krembil Brain Institute is hosting a live virtual Gairdner Symposium on Alzheimer’s Disease research on March 30-31, 2021.

The event is free to attend and open to the public.

Click here to register for the event. Graduate students, postdoctoral fellows and other learners are also invited to attend daily academic breakout sessions to interact with symposium presenters. To register for a breakout session, email krembil@uhnresearch.ca with your first and last name, position, current institution and top 3 speaker selections.

More than 700,000 Canadians live with dementia, including Alzheimer’s disease, the most common type of dementia. In the absence of new innovations to treat or prevent dementia, this number is projected to reach nearly one million by 2030. Scientists have made significant strides in understanding Alzheimer’s and identifying risk factors for developing the disease. Despite this, many questions remain unanswered.

This virtual Gairdner Symposium, which is being presented in partnership with Johns Hopkins University, will address some of these questions and make Alzheimer’s research accessible to the public. The event will bring together internationally renowned leaders in Alzheimer’s research and will be moderated by Jay Ingram, Canadian science communicator and author of ‘The End of Memory’.

The symposium will feature presentations from eight Alzheimer's research experts: four from Canada and four from the United States. Speakers will discuss topics ranging from risk factors for Alzheimer's to the importance of diversity and inclusion in clinical studies of the disease. The symposium will also include daily panels during which presenters will answer questions submitted live by attendees.

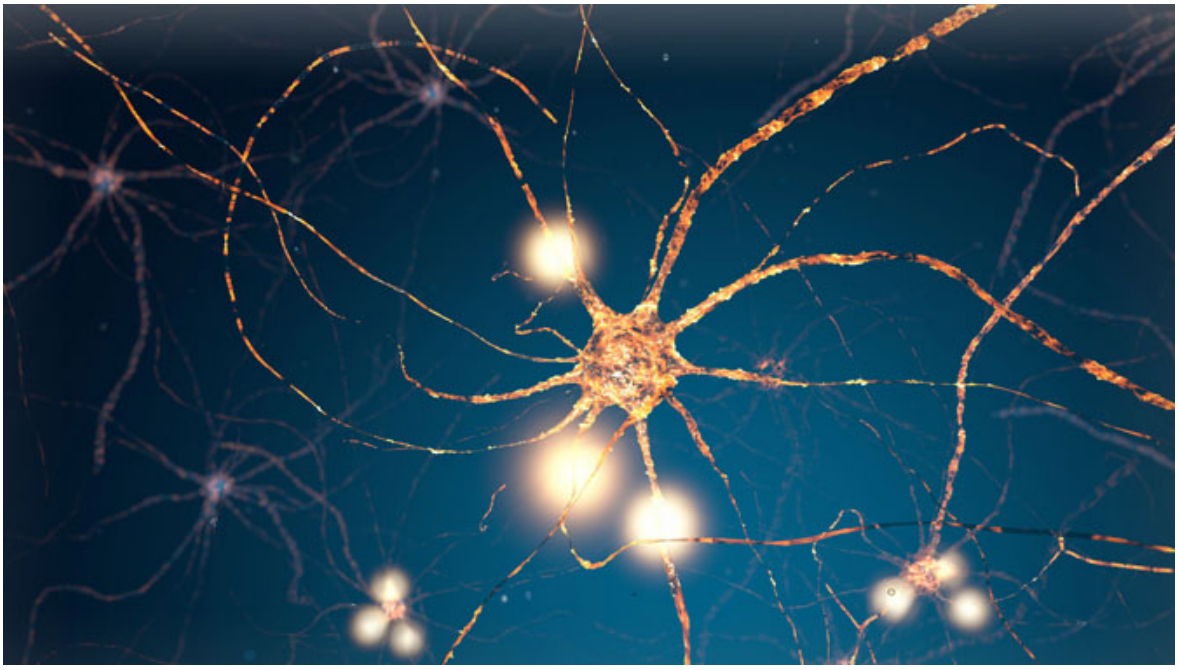
"We are very excited to host this event," says Dr. Weaver, symposium Co-Chair and Co-Director of the Krembil Brain Institute. "This is an excellent opportunity to showcase Canadian research to international leaders in the field of Alzheimer's disease and share research advances with the public."

For more information about this event, contact Carley McPherson at carley.mcpherson@uhnresearch.ca.

Research

Cholesterol & Nervous System

Drugs used to lower cholesterol levels can help nerve fibres regenerate following injury.



Neurons are specialized cells in the nervous system that have long extensions, known as axons that transmit electrical signals to other cells. When axons are damaged, cells cannot communicate properly with each other.

Medications known as statins are often used to reduce cholesterol as a way to prevent stroke or heart disease in high-risk individuals. However, their benefits may also extend to other health conditions.

New findings from the Donald K. Johnson Eye Institute show that these drugs may play a favourable role in treating injuries to nerve cells, called neurons, in the central nervous system.

“Injured neurons contain cholesterol-rich regions on their surface. These regions bind to proteins that prevent damaged nerve fibres, known as axons, from regrowing and can also trigger neuron death,” explains Dr. Philippe Monnier, Senior Scientist and corresponding author of the study.

The researchers studied the effects of reducing cholesterol—using statins and other cholesterol reducing drugs—on the regrowth of damaged axons and neuron survival. They first studied the effects of statins following injury to the optic nerve, which is the nerve that carries visuals signals from the eye to the brain. They found that reducing cholesterol prevented proteins that are known to restrict axon growth from accumulating on the cell surface. This change promoted axon growth and neuron survival following injury to the optic nerve.

They next studied the effects in an experimental model of retinitis pigmentosa—an eye disease involving the death of cells that enable vision, known as photoreceptors. In this case, reducing cholesterol promoted the survival of these specialized cells.

“While more work is needed to understand the therapeutic potential of statins in the nervous system, our findings suggest that these drugs could improve the survival of injured neurons. If true, drugs that lower cholesterol could offer therapeutic benefits for a variety of nervous system conditions, such as traumatic brain injury,” says Dr. Monnier.

This work was supported by Heart & Stroke, the Glaucoma Research Society of Canada, the Canadian Institutes for Health Research and the Toronto General & Western Hospital Foundation.

Shabanzadeh AP, Charish J, Tassew NG, Farhani N, Feng J, Qin X, Sugita S, Mothe AJ, Wälchli T, Koeberle PD, Monnier PP. Cholesterol synthesis inhibition promotes axonal regeneration in the injured central nervous system. Neurobiol Dis. 2021 Mar. doi: 10.1016/j.nbd.2021.105259.

Dr. Philippe Monnier, Senior Scientist at the Donald K. Johnson Eye Institute.

Predicting Lupus Flare-Ups

Scientists identify a new way to predict the severity of systemic lupus erythematosus symptoms.

Like the ups and downs of a rollercoaster, many individuals with lupus experience alternating periods of remission, characterized by mild symptoms, followed by flare-ups with intensified and sometimes severe symptoms.

Researchers at the Schroeder Arthritis Institute have identified a blood-based biomarker that can predict future disease severity in patients with systemic lupus erythematosus (SLE).

SLE is the most common form of lupus—a chronic autoimmune disease in which the immune system attacks healthy tissues in the body. SLE can affect the joints, skin and organs.

There is no cure for SLE, but medications can reduce the frequency and severity of flare-ups. Currently, it is very challenging to predict when a patient is likely to experience periods of worsened symptoms and how severe they will be. This makes it difficult to administer therapies proactively.

To address this issue, a research team led by Dr. Joan Wither, a Senior Scientist at the Schroeder Arthritis Institute, set out to identify a biomarker that could predict the risk of flare-ups.

“Predicting the prognosis of SLE is extremely difficult,” explains Dr. Wither. “Being able to anticipate flare-ups would transform how we treat this disease.”

The researchers explored whether levels of type 1 interferons (IFNs)—a class of proteins involved in boosting the body's immune response—could predict SLE severity. They studied type 1 IFNs because SLE symptoms have been linked to persistent immune system activation by these proteins.

IFNs function in the body by activating certain genes—known as IFN-responsive genes—within cells of the immune system. Because of this, the research team chose to look at the levels of these genes in individuals with SLE. The researchers tested the levels of five IFN-responsive genes in whole blood samples from 137 SLE patients and monitored these patients over five years. Each patient was assigned a score—called an IFN5 score—based on the levels of the five genes detected in their blood.

The team found that the IFN5 score was linked to disease severity over the five-year study period. Patients with high IFN5 scores were more likely to experience recurrent flare-ups and require increased or additional medications to treat their symptoms, compared to patients with low IFN5 scores.

"This finding is exciting because it means that a simple blood test could help determine how serious a patient's symptoms will be over the next five years," says Dr. Wither. "Patients with high IFN5 scores are likely to have more severe disease and flare-ups, so these patients might benefit from close monitoring and more aggressive treatments."

This work was supported by the Canadian Institutes of Health Research and the Toronto General & Western Hospital Foundation. PR Fortin holds a Tier 1 Canada Research Chair in Systemic Autoimmune Rheumatic Diseases at Université Laval.

Mai L, Asaduzzaman A, Noamani B, Fortin PR, Gladman DD, Touma Z, Urowitz MB, Wither J. The baseline interferon signature predicts disease severity over the subsequent 5 years in systemic lupus erythematosus. Arthritis Res Ther. 2021 Jan 16. doi: 10.1186/s13075-021-02414-0.

The senior author of the study, Dr. Joan Wither, is a Senior Scientist at the Schroeder Arthritis Institute, University Health Network.

Wired Differently

Brain circuitry features may explain why men and women experience chronic pain differently.

Several chronic pain conditions are more common among women than men. These differences may be influenced, in part, by sex-based differences in brain connectivity.

Chronic pain does not affect women and men equally. Women are more likely to experience chronic pain than men, and many chronic pain conditions are more common in women. How the brain responds and adapts to prolonged pain also differs between women and men.

Dr. Karen Davis, a Senior Scientist at the Krembil Brain Institute, and her research team have recently discovered connections within the brains of women with chronic pain that could help explain differences in how men and women experience chronic pain.

“Understanding sex differences in brain circuitry is key to knowing how to best treat chronic pain in both men and women,” says Dr. Davis. “These distinct brain connections could become targets for therapy.”

The distinct connections that the researchers discovered center on a particular region of the brain called the subgenual anterior cingulate cortex (sgACC). This region plays an important role in how the brain responds to pain. For example, the sgACC has been linked to the mind’s ability to spontaneously wander away from thinking about pain.

The research study, which was led by Dr. Davis and her doctoral student Natalie Osborne and involved Schroeder Arthritis Institute Co-Director and Senior Scientist Dr. Robert Inman, analyzed functional magnetic resonance imaging (fMRI) scans of the brains of men and women with and without chronic pain. The research team focussed on one form of chronic pain caused by a type of arthritis in the lower back called ankylosing spondylitis.

By inspecting brain activity in the fMRI scans, the researchers identified sex differences in the functional connectivity between various brain regions implicated in acute and chronic pain. Functional connectivity measures how similar the activity patterns are between two different brain areas and provides insight into how these regions communicate with one another.

When the team compared functional connectivity of the sgACC in women with and without chronic pain, they found that women with chronic pain have greater connectivity with regions involved in self-awareness and monitoring the body's internal state, and less connectivity with regions associated with controlling pain perception and emotional responses to pain.

In contrast, these differences in functional connectivity were not seen when comparing men with and without chronic pain.

The results pose interesting questions about whether the unique brain circuitry seen in women with chronic pain is a cause or consequence of the condition and whether this circuitry relates to disease severity. They also come alongside other work from Dr. Davis' team showing sex differences in brain organization associated with chronic pain (Pain 2020) and sex differences in brain communication related to acute pain sensitivity (Human Brain Mapping 2021).

Future work will continue to investigate the mechanisms underlying chronic pain, with the aim of developing effective treatments for chronic pain that account for the differences between men and women.

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

Osborne NR, Cheng JC, Rogachov A, Kim JA, Hemington KS, Bosma RL, Inman RD, Davis KD. Abnormal subgenual anterior cingulate circuitry is unique to women but not men with chronic pain. Pain. 2021 Jan. doi: 10.1097/j.pain.0000000000002016.

Dr. Karen Davis, Senior Scientist at the Krembil Brain Institute.

Jump-Staring Memory

Scientists learn how deep brain stimulation causes memory recall in patients with dementia.

Alzheimer disease is the most common cause of dementia. Researchers are exploring how deep brain stimulation might be used to improve memory in individuals with the disease.

Deep brain stimulation (DBS) is being explored as a treatment for individuals with Alzheimer disease. Researchers have previously shown that stimulation applied to the fornix—a memory-related structure located deep in the brain—can cause vivid flashbacks of old memories and events in some, but not all, individuals with Alzheimer disease. The occurrence of flashbacks suggests that the stimulation is activating brain circuits involved in memory recall.

“It is a mystery why only certain individuals experience these flashbacks—especially considering that the fornix is stimulated in everyone who undergoes the procedure,” says Krembil Senior Scientist Dr. Andres Lozano, who led a recent study that has shed new light on how DBS causes flashbacks.

DBS involves the use of surgically implanted electrodes to stimulate specific regions of the brain. DBS has been successfully used to reduce the symptoms of certain neurological conditions, including tremors in Parkinson disease. In this study of DBS for Alzheimer disease, DBS electrodes are implanted to stimulate the fornix.

Although the fornix is the main target in this type of DBS, other brain structures are likely activated at the same time due to the placement of the electrodes. Lozano's team suspected that this effect, which would vary between patients, may be the key to why only certain patients experience flashbacks.

The researchers examined scans from 39 individuals with mild Alzheimer disease who previously participated in a clinical trial of fornix DBS to reduce memory impairment. Using computer modeling of the connections between different brain regions, the team identified three structures involved in flashbacks. They found that flashbacks were associated with stimulation of the fornix, the anterior commissure (a collection of nerve fibres that connects the two halves of the brain), and the bed nucleus of the stria terminalis (a part of the brain's emotion and memory circuits).

Patients were more likely to experience flashbacks when electrodes were placed in such a way that they stimulated these three regions. This finding provides further evidence that these deep brain structures make up an important memory-related circuit.

"Our findings reveal the areas of the brain where electrical stimulation produces DBS-induced memory recall, in approximately half the patients," says Dr. Lozano. "By demonstrating the importance of stimulating different, yet connected brain regions with DBS, these results improve our understanding of the brain circuits involved in memory. This information will help us to refine the DBS procedure so it has the greatest therapeutic impact for people with Alzheimer disease, and perhaps other forms of dementia."

This work was supported by the Canadian Institutes of Health Research, the German Research Foundation and the Toronto General & Western Hospital Foundation. A Lozano is the RR Tasker Chair in Functional Neurosurgery.

Germann J, Elias GJB, Boutet A, Narang K, Neudorfer C, Horn A, Loh A, Deeb W, Salvato B, Almeida L, Foote KD, Rosenberg PB, Tang-Wai DF, Wolk DA, Burke AD, Salloway S, Sabbagh MN, Chakravarty MM, Smith GS, Lyketsos CG, Okun MS, Lozano AM. Brain structures and networks responsible for stimulation-induced memory flashbacks during forniceal deep brain stimulation for Alzheimer's disease. Alzheimers Dement. 2021 Jan 21. doi: 10.1002/alz.12238.

The lead author of the study, Dr. Andres Lozano, is a Senior Scientist at the Krembil Brain Institute.