The Krembil

May 2022

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

Recognizing Community Leadership

Dr. Nigil Haroon receives the Pravasi Ratna Award for his community outreach in Kerala, India.

The National Federation of Malayalee Associations in Canada is an umbrella organization of groups that represent Keralites in Canada.

Congratulations to Krembil Senior Scientist Dr. Nigil Haroon, for receiving the Pravasi Ratna Award from the National Federation of Malayalee Associations in Canada.

Dr. Haroon received the award in recognition of his outstanding contributions to society, as well as being an internationally recognized leader in his field.

Outside his lab, Dr. Haroon contributes to multiple health-related outreach initiatives around the world. For example, in 2018, multiple floods occurred in Kerala, India, where Dr. Haroon grew up and completed his medical education. Floods frequently cause major outbreaks of water-borne diseases due to disruptions in clean water supplies. To help to reduce these outbreaks, Dr. Haroon worked with the humanitarian aid organization GlobalMedic and the local government administration to provide water

filtration kits. These kits supplied clean drinking water to nearly 40,000 people in three different towns that were most affected.

Dr. Haroon continued this volunteerism during the COVID-19 pandemic, which quickly overwhelmed India's hospital capacity. Dr. Haroon spearheaded a multi-institutional effort to collect and deliver $4.5 million-worth of medical supplies, including masks. He also partnered with the Indian Medical Association (IMA) to develop a local home-care program in Kerala to reduce hospital burden.

"Many patients with COVID-19 can be effectively managed at home, but they worry about what will happen to them if they worsen outside a hospital," explains Dr. Haroon. "We set up a system in which each person being treated at home gets connected with a local healthcare worker who they can call if they have issues. By enabling patients to be safely cared for in their homes, we freed up ICU beds for patients who require advanced care."

To facilitate at-home patient monitoring, Dr. Haroon also worked with the IMA and the Association of Kerala Medical Graduates to increase the availability of pulse oximeters. The team set up a centralized system for identifying and loaning pulse oximeters to nearby patients in need. Dr. Haroon also oversaw the collection and delivery of over 2000 pulse oximeters to launch the program.

Many of Dr. Haroon's colleagues from across UHN have generously donated to each of these activities, delivering on UHN's vision of A Healthier World. "Each of these projects was a massive team effort," he explains. "Their success has been due to the many driven individuals, from all walks of life, who have come together with a shared goal of helping others."

Donation to Support Research

UHN receives an anonymous donation of $11 million to support neurofibromatosis research.

(L-R) Drs. Gelareh Zadeh and Vera Bril are co-Directors of the Neurofibromatosis Program at UHN.

On World Neurofibromatosis Day, May 17, UHN celebrated an anonymous donation of $11 million to support neurofibromatosis research and patient care at the Krembil Brain Institute.

Neurofibromatoses are a group of genetic disorders that cause tumours to form in the nervous system. These disorders can cause numerous complications such as vision and hearing loss, skeletal problems, increased risk of cancer and various neurological disorders.

In 2015, UHN established the Elisabeth Raab Neurofibromatosis Clinic—the first-in-Canada multidisciplinary clinic for adults with neurofibromatoses—with sites at Toronto Western Hospital and Toronto General Hospital.

A portion of this generous donation will go towards establishing the Elisabeth Raab Early Career Research Chair in Neurofibromatosis, which will enable the recruitment of a neurosurgeon-scientist specialized in neurofibromatosis research and patient care.

“Currently there is a shortage of medical and scientific experts in the neurofibromatosis field,” says Dr. Gelareh Zadeh, Medical Director of the Krembil Brain Institute and co-Director of UHN’s Neurofibromatosis Program. “This gift will help to promote research and development excellence in neurofibromatosis care. Most importantly, it will strengthen our collaborative work with other leading neurofibromatosis-related programs globally.”

This gift will also support basic research that will spur the development of improved approaches for managing neurofibromatoses. For example, this investment will boost ongoing research into how benign tumours become cancerous.

“Current treatment options are limited, so this research is essential to help identify more targets for therapeutic intervention,” says Dr. Vera Bril, co-Director of the Neurofibromatosis Program and a Clinician Investigator at the Toronto General Hospital Research Institute.

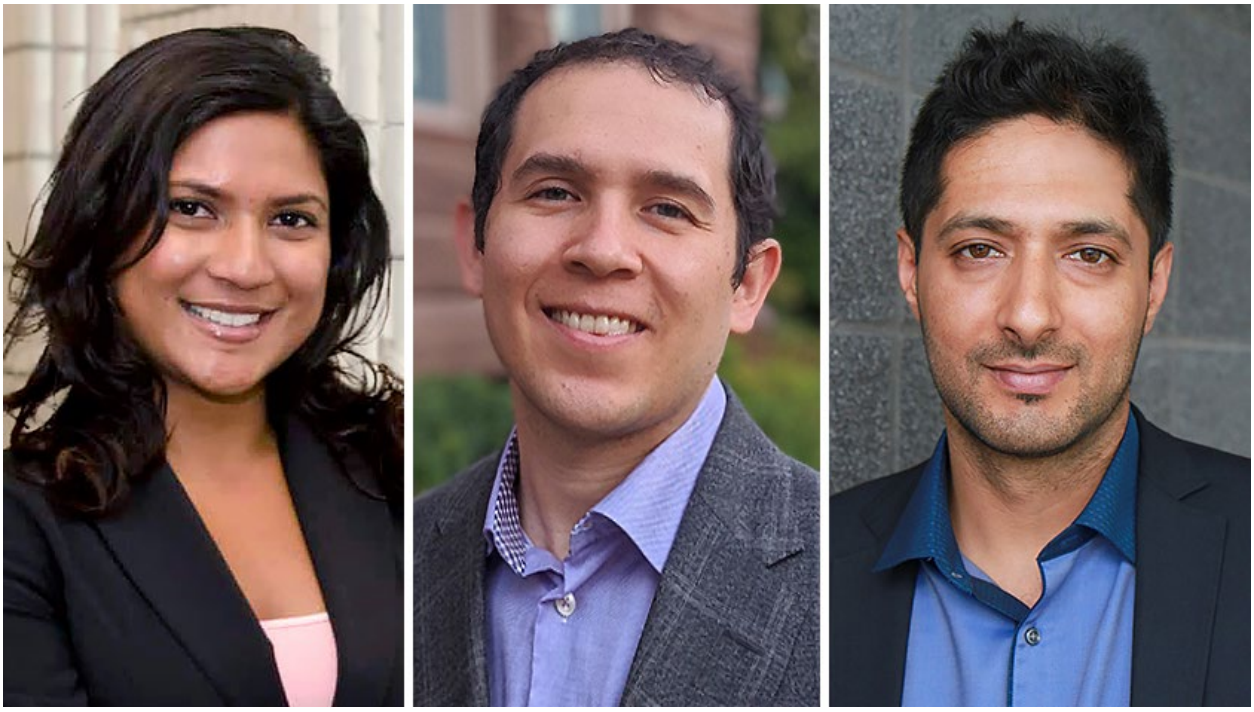
“Our team is so grateful for this gift, one of the largest ever in support of neurofibromatosis research,” says Dr. Zadeh.

Click here to read the full story.

Research

Predicting Disease Progression

Blood-based molecules may predict how quickly knee osteoarthritis will become more severe.



(L-R) Dr. Shabana Amanda Ali, Osvaldo Espin-Garcia and Mohit Kapoor.

Researchers at the Schroeder Arthritis Institute have identified circulating molecules that can differentiate between patients with fast-progressing, slow-progressing and stable knee osteoarthritis.

Osteoarthritis is a degenerative joint disease that affects 50% of individuals over the age of 65. Joint deterioration can progress quickly or slowly, but clinicians have no way of knowing in which individuals the disease will rapidly worsen.

“We previously identified circulating microRNAs—small molecules that alter gene expression—that contribute to joint damage in osteoarthritis,” says Dr. Mohit Kapoor, Co-Director and Senior Scientist at the Schroeder Arthritis Institute and senior author of the study. “These molecules have great promise as predictive markers of disease progression because they can be easily detected in a patient’s blood before the onset of advanced joint damage.”

Dr. Kapoor's team examined the expression of microRNAs in blood samples from over 100 patients in the Osteoarthritis Initiative—a large cohort of patients with knee osteoarthritis for which scientists have collected biospecimens and clinical data over at least 10 years of disease progression.

The researchers analyzed blood samples that were collected at baseline, when patients had mild osteoarthritis, and four years later. They categorized the patients into three groups based on how quickly their disease progressed: fast progressors, who exhibited moderate to severe osteoarthritis by the four-year follow-up; slow progressors, who experienced worsening disease by the eight-year follow-up; and non-progressors, who did not experience worsening symptoms over the study period.

Using this approach, the team identified several circulating microRNAs that are associated with fast-progressing disease. "We found that patients with fast-progressing disease had higher levels of 48 different microRNAs at baseline compared to patients with slow- and non-progressing disease," explains Dr. Osvaldo Espin-Garcia, a principal biostatistician at the Schroeder Arthritis Institute and co-first author of the study. "Among these were members of the microRNA-320 family, which target genes that contribute to inflammation and joint damage."

This finding suggests that elevated levels of these microRNAs in a patient's blood may signal rapid osteoarthritis progression. Next steps for this research include characterizing how these microRNAs contribute to the disease and determining if they can serve as targets for new therapies.

"Our study has revealed that molecular markers can predict whether a patient will experience fast- or slow-progressing knee osteoarthritis," says Dr. Shabana Amanda Ali, a former postdoctoral fellow in Dr. Kapoor's lab and co-first author of the study. "Clinicians could eventually screen patients for these markers to identify those at the greatest risk of disease progression. This would open a new treatment window during which patients could be prescribed preventative interventions or be enrolled into clinical trials for promising experimental therapies."

This work was supported by the Canadian Institutes of Health Research, the Natural Sciences Research Council of Canada, the Canada Foundation for Innovation, the Government of Ontario, the Arthritis Society, the IBM and Ian Lawson van Toch Fund, the Krembil Foundation and the UHN Foundation. Dr. Mohit Kapoor is Co-Director and Senior Scientist at the Schroeder Arthritis Institute and a Professor in the Departments of Laboratory Medicine and Pathobiology, and Surgery at the University of Toronto. He holds a Tier I Canada Research Chair in the Mechanisms of Joint Degeneration.

Ali SA, Espin-Garcia O, Wong AK, Potla P, Pastrello C, McIntyre M, Lively S, Jurisica I, Gandhi R, Kapoor M. Circulating microRNAs differentiate fast-progressing from slow-progressing and non-progressing knee osteoarthritis in the Osteoarthritis Initiative cohort. Ther Adv Musculoskelet Dis. 2022 Mar 18. doi: 10.1177/1759720X221082917.

Osteoarthritis can range from mild to severe and the rate of disease progression varies between people. Molecules called microRNAs may help to predict how quickly a patient's disease will progress.

Brain Aging in Fast Forward

Study reveals how trigeminal neuralgia and other chronic pain conditions speed up brain aging.

(L-R) Dr. Peter Shih-Ping Hung, first author; and Dr. Mojgan Hodaie, senior author of the study.

Researchers at the Krembil Brain Institute have used artificial intelligence (AI) approaches to create a brain age calculator to explore the effects of chronic pain conditions on brain aging.

The findings, published recently in the journal *PAIN*, show that the effects of chronic pain on brain aging vary according to the underlying condition. They also found that women living with chronic pain are most at risk for accelerated brain aging.

The team's approach relied on recent technological advancements that have revolutionized how researchers study brain aging. "We used AI to analyze magnetic resonance imaging (MRI) scans of the brains of 959 individuals. Using this approach, we developed an algorithm that can calculate an individual's brain age from their brain structure with very good accuracy," says Dr. Mojgan Hodaie, Krembil Senior Scientist and senior author of the study.

Traumatic brain injury and diseases such as HIV and Down syndrome have been linked to accelerated brain aging; however, previous research studying accelerated brain

aging in chronic pain has turned up conflicting results, as they mainly used mixed populations who had different types of chronic pain.

“In this study, we aimed to overcome the limitations of previous studies, which have not factored in patients’ specific pain conditions. Importantly, previous studies have also not accounted for sex—an important factor in pain research because chronic pain is more common and severe in women than men,” adds Dr. Hodaie.

The research team looked at three chronic pain disorders: trigeminal neuralgia—a debilitating condition that causes extreme pain in one side of the face; osteoarthritis and chronic low-back pain.

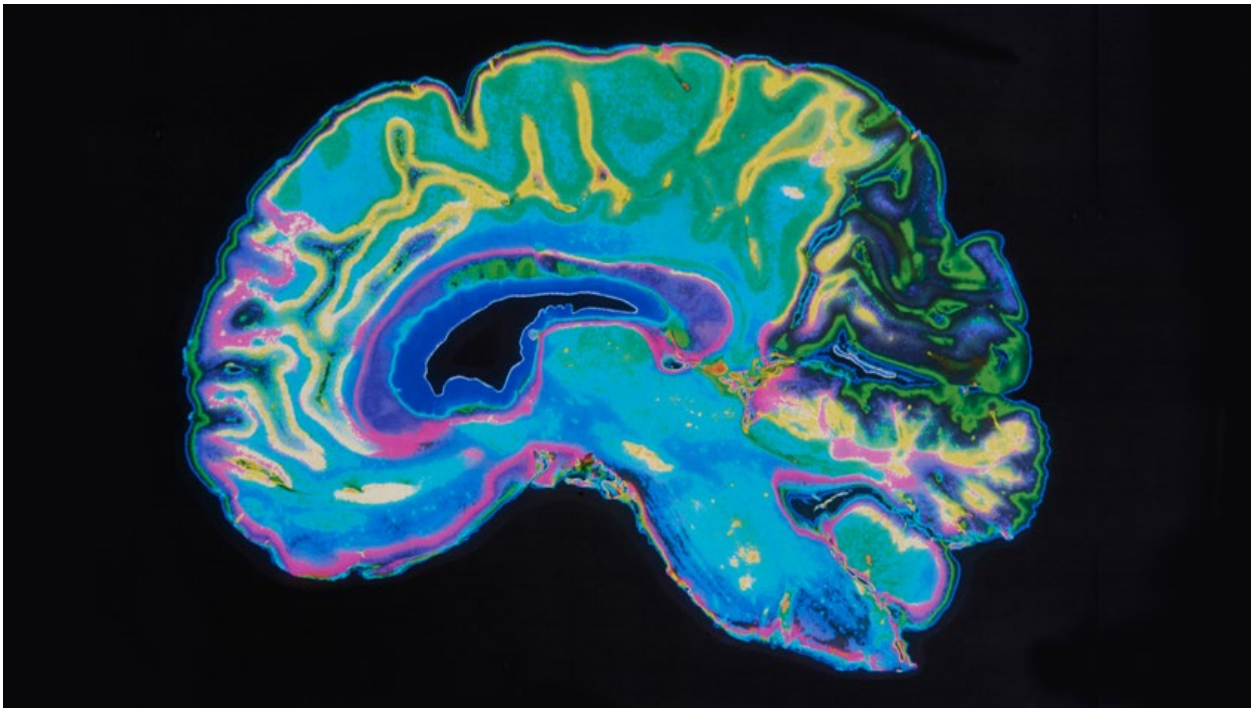
The team discovered that trigeminal neuralgia patients have significantly accelerated brain aging—on average over 10 years older than healthy controls. With respect to sex, females experienced accelerated brain aging in response to all chronic pain conditions tested, whereas men only experienced accelerated brain aging with the diagnosis of osteoarthritis. Brains also aged differently, with trigeminal neuralgia and osteoarthritis being linked to more rapid aging than chronic low-back pain.

A surprising finding in this study is that trigeminal neuralgia patients who had “older brains” were more likely to benefit from Gamma Knife radiosurgery. Based on this observation, pre-treatment brain age can serve to separate future responders from non-responders to surgical treatment. Based on this observation, pre-treatment brain age can serve to separate future responders from non-responders to surgical treatment.

Dr. Hodaie concludes, “Our findings reveal a more nuanced view of the relationship between chronic pain, existing therapies, sex and brain changes. Defining brain age in individuals living with chronic pain could hold the key to unlocking better, more targeted treatment approaches—and help ensure that those who will benefit get the treatment they need.”

This study was supported by the Canadian Institutes of Health Research and the UHN Foundation. Dr. Mojgan Hodaie is a Professor in the Department of Surgery at the University of Toronto, and Surgical co-Director of the Joey and Toby Tanenbaum Family Gamma Knife Centre at the Toronto Western Hospital.

Hung PS, Zhang JY, Noorani A, Walker MR, Huang M, Zhang JW, Laperriere N, Rudzicz F, Hodaie M. Differential expression of a brain aging biomarker across discrete chronic pain disorders. Pain. 2022 Feb 23. doi: 10.1097/j.pain.0000000000002613.



Magnetic resonance imaging of a brain, revealing structural features (false colouring applied). Chronic pain has been linked to abnormalities in the cortex, which lines the outermost layer of the brain.

New Take on an Old Disease

Researchers reframe Alzheimer disease as an autoimmune disorder and uncover new drug targets.

Dr. Donald Weaver is the Director of the Krembil Research Institute and a Senior Scientist at the Krembil Brain Institute.

Alzheimer disease is a common neurodegenerative disorder that causes losses in memory and cognitive function, and eventually death. Treatments for the disease are limited, in part because the mechanisms that trigger the underlying destruction of brain cells are unknown.

An international collaboration led by Dr. Donald Weaver, Director and Senior Scientist at the Krembil Research Institute, has provided a new explanation for how Alzheimer disease develops.

The explanation revolves around a protein building block called amyloid beta, which accumulates in the brains of people with Alzheimer disease and leads to the death of neurons. Despite a growing understanding of amyloid beta, researchers still do not know what causes it to accumulate, and existing treatments targeting it are neither universally accepted nor suitable for all patients.

“We reframed Alzheimer disease as a disorder of the immune system, wherein amyloid beta triggers an immune response that attacks healthy brain cells,” explains Dr.

Weaver. “By viewing the disease as an autoimmune disorder, we have united competing theories of what causes the disease into one compelling picture.”

Through a series of experiments and computer simulations of the interactions between amyloid beta and cells, the research team created a four-step model for the development of the disease:

Step 1. In a manner similar to known immune responses, brain cells release amyloid beta in response to invaders such as bacteria and viruses and to traumatic events such as mechanical injury to nearby cells.

Step 2. The amyloid beta behaves similarly to other agents released by the immune system, inserting itself into the membranes of the invading organisms or damaged cells. This action helps to destabilize the unwanted cells and clear them from the body.

Step 3. The amyloid beta mistakenly acts on healthy brain cells because their membranes share traits with those of bacteria and damaged cells.

Step 4. The attacked brain cells degrade and release more amyloid beta, and the cycle repeats itself.

Dr. Weaver’s team proposes that the repetitive release of amyloid beta fuels a self-perpetuating cycle that ultimately causes the progressive neuron degeneration seen in Alzheimer disease.

With their new model, the team sought to identify targets for drugs that could disrupt the cycle. They screened more than 1,100 molecules that naturally occur in the brain as potential targets.

The researchers discovered that biological products made from the amino acid tryptophan are particularly effective in preventing the accumulation of amyloid beta. They then compiled a library of natural and synthetic compounds that might be good candidates for use in therapy because of their similarities to these biological products.

“By uncovering a new dimension to Alzheimer disease and identifying potential therapeutic compounds, this research could lead to a new treatment that can target the underlying driver of the disease to prevent further cognitive changes,” says Dr. Weaver.

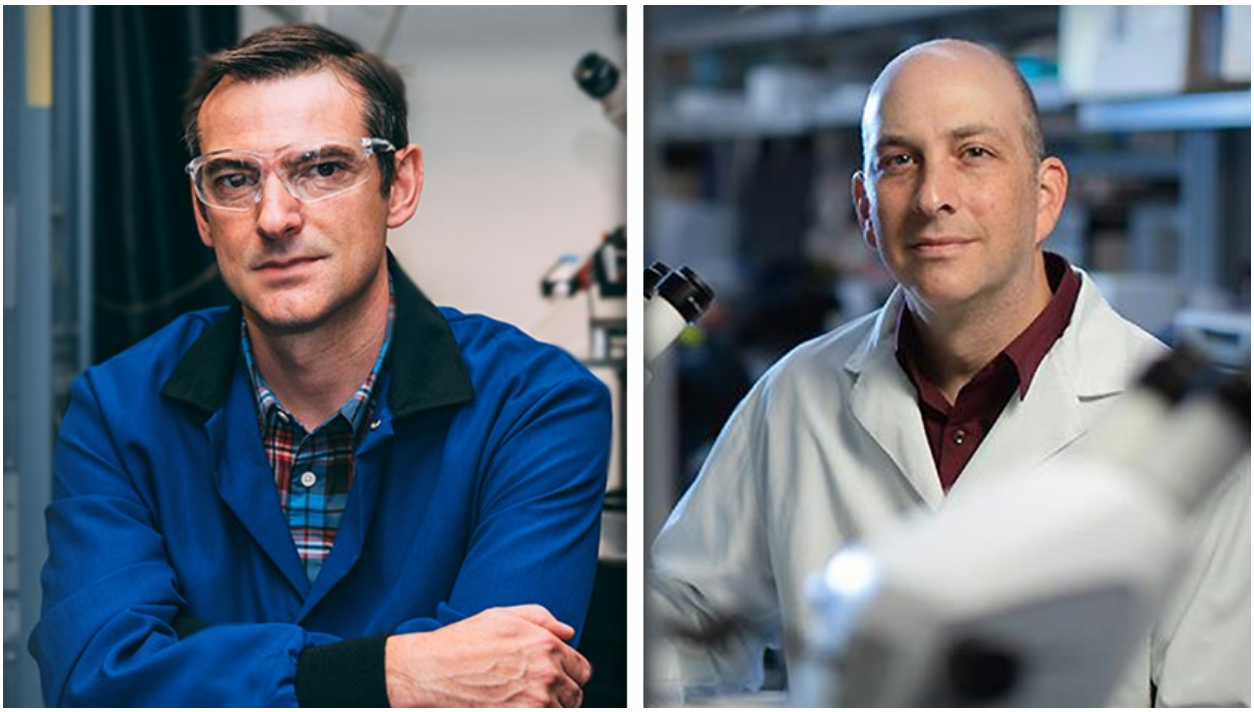
This work was supported by the BrightFocus Foundation, Canadian Institutes of Health Research, Alzheimer’s Society of Canada, Ontario Brain Institute, Canada Foundation for Innovation, Sobey Family and Sobey Foundation, Weston Brain Institute, Michael Albert Garron Foundation, Dalhousie Medical Research Foundation, Atlantic Canada Opportunities Agency, Krembil Foundation and UHN Foundation. Dr. Donald Weaver is a Professor of Chemistry, Medicine and Pharmaceutical Science at the University of Toronto.

Meier-Stephenson FS, Meier-Stephenson VC, Carter MD, Meek AR, Wang Y, Pan L, Chen Q, Jacobo S, Wu F, Lu E, Simms GA, Fisher L, McGrath AJ, Fermo V, Barden CJ, Clair HDS, Galloway TN, Yadav A, Campágna-Slater V, Hadden M, Reed M, Taylor M, Kelly B, Diez-Cecilia E, Kolaj I, Santos C, Liyanage I, Sweeting B, Stafford P, Boudreau R, Reid GA, Noyce RS, Stevens L, Staniszewski A, Zhang H, Murty MRVS, Lemaire P, Chardonnet S, Richardson CD, Gabelica V, DePauw E, Brown R, Darvesh S, Arancio O, Weaver DF. Alzheimer's disease as an autoimmune disorder of innate immunity endogenously modulated by tryptophan metabolites. Alzheimers Dement (N Y). 2022 Apr 6. doi: 10.1002/trc2.12283.

The burning of each match sparks the next match, similar to how each cycle of neuron degeneration induced by amyloid beta provokes the next in the new model of Alzheimer disease.

Drug Development

Krembil researchers synthesize a molecule with potential to treat inflammatory diseases.



(L) Dr. Mark Reed is Director of the Centre for Medicinal Chemistry and Drug Discovery and senior author of the study. (R) Dr. Jeremy Sivak is a Senior Scientist at the Donald K. Johnson Eye Institute and a co-author of the study (Photo: The Globe and Mail).

Scientists at the Krembil Research Institute's Centre for Medicinal Chemistry and Drug Discovery (CMCDD) report a new total synthesis of natural product lipoxin B4 (LXB4), a molecule with neuroprotective properties.

LXB4 is a small lipid molecule that dampens inflammation. Krembil Senior Scientist Dr. Jeremy Sivak and his team found that this molecule is produced in the retina and protects retinal neurons against the damaging effects of increased eye pressure and inflammation in experimental models of glaucoma—one of the leading causes of blindness in people over the age of 60.

"We have been exploring whether we can stimulate the body to produce more LXB4 or deliver a synthetic version of the molecule directly into the retina to treat glaucoma," says Dr. Sivak.

After discovering LXB4's key roles in retinal disease, Dr. Sivak's team focused on strategies to reproduce the molecule in the lab so that they could study its biological

effects. To do this, they partnered with medicinal chemist Dr. Mark Reed, a Staff Scientist at the Krembil Research Institute and Director of CMDD.

Starting with readily accessible chemical building blocks, Dr. Reed's team used a series of medicinal chemistry methods to create the complex molecule from scratch. The team confirmed the molecule's precise chemical structure for the first time and demonstrated that it has significant neuroprotective activity in a test of retinal neuron survival.

Dr. Reed says, "Our team has shown that LXB4 can be produced in large quantities synthetically and can easily be modified to change its activity. This opens the door to studies that explore how LXB4 functions, which will ultimately shed light on how to enhance its action to treat inflammatory and neurodegenerative diseases."

In addition to the molecule serving as a potential treatment for glaucoma, a deeper understanding of LXB4 could unlock new treatments for a host of diseases in which inflammation is a contributing factor, such as lupus, asthma, cancer and Alzheimer disease.

"Drug development is a complex undertaking—it often takes over 10 years to bring a new drug to market," says Dr. Reed. "The close collaboration between scientists and in-house medicinal chemists at Krembil is enabling us to accelerate this process and translate discoveries into life-changing therapies."

This work was supported by a LAB150 grant administered through Toronto Innovation Acceleration Partners, the Krembil Foundation and the UHN Foundation. Nuclear magnetic resonance (NMR) spectrometers were funded by the Canada Foundation for Innovation and the Princess Margaret NMR Core Facility was supported by the Princess Margaret Cancer Foundation. Dr. Jeremy Sivak holds the Graham Trope Chair in Glaucoma Research and is an Associate Professor in the Department of Ophthalmology and Vision Sciences at the University of Toronto.

Lee CF, Brown CE, Nielsen AJ, Kim C, Livne-Bar I, Parsons PJ, Boldron C, Autelitano F, Weaver DF, Sivak JM, Reed MA. A Stereocontrolled Total Synthesis of Lipoxin B4 and its Biological Activity as a Pro-Resolving Lipid Mediator of Neuroinflammation. Chemistry. 2022 May 1. doi: 10.1002/chem.202200360.

Medicinal chemistry is a discipline focused on the design and development of drugs and other pharmaceutical compounds. Medicinal chemists play an important role in drug discovery by synthesizing compounds for testing in preclinical studies.