The Krembil

March 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.

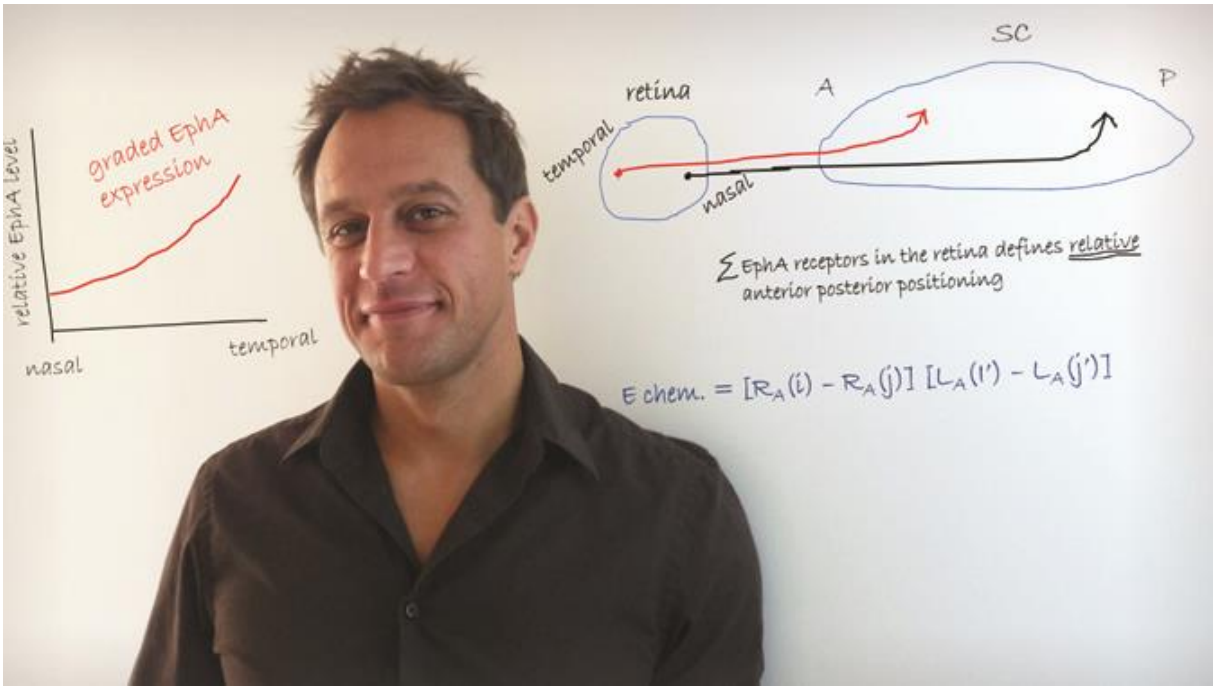
Stories in this month's issue:

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

News

New Recruit Enriches Vision Research

Krembil welcomes Senior Scientist Dr. Michael Reber, an expert on the brain's visual network.



Dr. Michael Reber (photographed in his laboratory at the Institute of Cellular & Integrative Neurosciences in Strasbourg, France).

In April 2018, Krembil's research community will welcome its newest member: Dr. Michael Reber, a neurobiologist with expertise in computational biology and mathematics.

Dr. Reber's research program examines the brain's visual network, which consists of interconnected 'webs' of cells that transmit and process visual information from the eyes. He uses a combination of experimental and mathematical models to reveal how the development and organization of the visual network is directed by particular molecules in the brain and eye.

Many of his studies have focused on a family of molecules known as ephrins. He and his colleagues have shown that gradients of ephrins direct the development of the visual network in the superior colliculus, a region in the middle of the brain. They have also found that disturbing ephrin gradients can lead to a duplication of some parts of the

visual network, which produces symptoms similar to those observed in attention deficit hyperactivity disorder.

Upon his arrival in Toronto, Dr. Reber will continue studying the brain's visual network. He will also begin examining how diseases of the retina and optic nerve affect its development. For example, he and Dr. Jeremy Sivak are planning to investigate how glaucoma, a leading cause of irreversible blindness, affects the visual network. Through another exciting project, he will validate the use of silk nanofibers to promote survival and repair of injured brain cells.

Before joining Krembil, Dr. Reber was an Associate Professor at the Institute of Cellular & Integrative Neurosciences in Strasbourg, France. He completed his PhD at Paris Diderot University in France and his postdoctoral fellowship at the Salk Institute in California.

Dr. Reber's recruitment was made possible by the generous support of Donald K. and Anna Johnson through the Toronto General & Western Hospital Foundation.

Strategic Support for Research

Research Strategy Development Specialist Joins Team at Krembil Directorate.

In February 2018, Carrie-Lynn Keiski became the new Krembil Research Strategy Development Specialist. In her new role, Carrie will support strategic research initiatives at Krembil, including the development of institutional grant applications and award nominations. She will also manage the Krembil newsletter and annual report.

Carrie has been a member of UHN's Strategic Research Initiatives Development team for more than four years. During this time, she supported the development of a variety of grant applications for the Ontario Research Fund, the Canada Foundation for Innovation, the Canada Research Chairs program and the Canadian Institutes of Health Research. She has worked with scientists across UHN and has written grants and news stories in different research areas, such as rehabilitation for spinal cord injury, the role of immune cells in cardiovascular disease and health services research.

As an undergraduate, she took classes in a wide range of topics including genetics, brain and behaviour, microbiology and epidemiology. She completed a PhD in Biochemistry at the University of Toronto, and then subsequently worked at the bench for a few years at the University's Department of Chemistry. Throughout her academic and professional career, Carrie has also taken several classes in writing, editing and scientific communication.

Carrie is looking forward to working more closely with Dr. Weaver, the Krembil Directorate team and the rest of Krembil's research community.

Research

But Why Does It Work?

Researchers make progress in solving mystery surrounding deep brain stimulation.

Electrical activity in the brain underpins mental functions—such as thinking and problem solving—and behaviours, and is disrupted in diseases like epilepsy and Parkinson disease.

It takes a lot of courage for a patient to receive a treatment requiring a neurosurgeon to drill a hole in their skull and insert electrodes into their brain. That courage reaches heroic levels when the answer to how the treatment works is still unclear.

Deep-brain stimulation (DBS) is a treatment that uses implanted electrodes to provide small electric jolts to targeted areas of the brain. It's highly effective at controlling the tremors and slowed movements of Parkinson disease and is typically prescribed when drug therapies fail or lead to unacceptable side effects. Though precisely what the electrical stimulation of DBS is doing to the brain to alleviate those symptoms is not known.

To address this knowledge gap, Krembil Senior Scientist Dr. William D. Hutchison and PhD student Luka Milosevic led a study examining brain activity following bursts of electrical pulses in 22 patients with DBS installed to treat Parkinson disease.

The researchers found evidence that DBS induces the release of a chemical known as a gamma-aminobutyric acid (GABA)—which is known to inhibit or reduce electrical activity between brain cells—into the area of the brain where the electrodes are implanted. GABA then acts on neighbouring brain cells to dampen their activity and alter their connections with other cells. The researchers believe that these mechanisms, combined with the unique makeup of different brain regions, help to explain why DBS can cause varying behavioural effects when applied to different parts of the brain.

These findings suggest that DBS helps to control Parkinson symptoms by reducing the abnormal activity and connections of brain cells in affected areas.

Studies such as this one improve our understanding of this complex treatment modality, increasing the odds that DBS can be safely used to treat more patients and more consistently control symptoms such as tremor in Parkinson disease and seizures in epilepsy.

This work was supported by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council and the Dystonia Medical Research Foundation. A Lozano is a Tier 1 Canada Research Chair in Neuroscience.

Milosevic L, Kalia SK, Hodaie M, Lozano AM, Fasano A, Popovic MR, Hutchison WD. Neuronal inhibition and synaptic plasticity of basal ganglia neurons in Parkinson's disease. Brain 2018 Jan 1. doi: 10.1093/brain/awx296.

Sign of Success

Three-month period after surgery foretells longer-term improvement in osteoarthritis knee pain.

More than 780,000 total knee replacement surgeries are carried out in Canada and the United States every year—that is more than one surgery every minute.

Older age, female sex, obesity and injury are associated with an increased risk of osteoarthritis, a disease characterized by degeneration of cartilage and significant pain. The knee joints are among the most commonly affected by osteoarthritis.

For individuals with knee osteoarthritis who cannot find pain relief or improve their physical function with non-pharmacological or pharmacological treatments, total knee replacement surgery is the only treatment option.

Total knee replacement is generally recognized as one of the most effective of surgical procedures. However, up to 30% of patients who receive it can show limited improvement in pain and physical function one year after surgery.

To gain further insight into this phenomenon, Krembil Scientist Dr. Anthony Perruccio and Krembil Clinician Investigator Dr. Rajiv Gandhi conducted a study involving more than 550 osteoarthritis patients who underwent knee replacement surgery.

As part of the study, the researchers looked at changes in pain and physical function before the surgery and then at three months, one year and two years postoperatively.

As expected, a majority of the patients had reduced pain and improved physical function at the two-year mark; however, most of these changes had occurred in the first three months following surgery—suggesting that the success of the surgery can largely be predicted at this earlier time point.

“Previous studies have focused on examining the outcomes of knee surgery in patients with osteoarthritis one to two years after the surgery at which point most, if not all, of the changes in pain and physical function have occurred,” explains Dr. Perruccio.

“Because there are ongoing interactions between patients and their health care providers during the three months following surgery, this may be an important time to consider strategies to increase the likelihood of better longer-term outcomes. We hope that our study will stimulate more research to look at earlier time points following surgery so we can find factors that can be modified to improve patient outcomes.”

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

Gandhi R, Mahomed NN, Cram P, Perruccio AV. Understanding the Relationship Between 3-Month and 2-Year Pain and Function Scores After Total Knee Arthroplasty for Osteoarthritis. J Arthroplasty. 2017 Dec 6. pii: S0883-5403(17)31056-2. doi: 10.1016/j.arth.2017.11.051.

Reading into Central Vision Loss

New measures provide more informative assessment of reading performance in central vision loss.

Reading is an essential skill for performing daily activities. It also provides myriad benefits such as improving communication skills, increasing empathy levels and expanding vocabulary.

Reading is a gift that keeps on giving. As soon as we learn how to read, we keep reading every day for the rest of our lives. We use this skill to learn, relax and communicate with others. And when we lose the ability to read, it negatively impacts our emotional wellbeing and quality of life.

“Central vision loss can impair a person’s ability to read. It’s characterized by the appearance of a blurred or distorted area in the center of a person’s field of vision. This area can become so blurred that a person’s central vision is completely eliminated,” explains Dr. Tarita-Nistor, a Scientific Associate at the Krembil Research Institute.

Recently, a team led by Drs. Tarita-Nistor and Esther González (Affiliate Scientist at Krembil) evaluated the effectiveness of two new measures of reading performance—the reading accessibility index (ACC) and a quality of reading grid—in patients with central vision loss. The ACC assesses a person’s ability to read text sizes found in everyday life, such as those in newspapers and books, whereas the quality of reading grid classifies the speed at which a person reads different sizes of text.

The study included 24 participants with normal vision and 61 patients with central vision loss. The researchers used a variety of reading parameters, such as the maximum

reading speed and the smallest print size that can be read, to calculate each participant's ACC score and assess their reading ability using the quality of reading grid.

The researchers found that the ACC scores of people with normal vision were consistently high and strongly associated with indicators of good reading performance. Whereas, the scores were significantly lower in patients with central vision loss and strongly associated with indicators of poor reading performance. They also showed that the quality of reading grid provided a better understanding of the type of reading impairment affecting each patient, suggesting that it may be a good tool to evaluate improvement after reading rehabilitation.

These findings show that the ACC is a good measure of overall reading performance in patients with central vision loss and, when combined with the quality of reading grid, provides detailed information about a patient's reading impairments. These new measures could not only improve the diagnosis of reading impairments in patients with central vision loss, but also help researchers develop more effective rehabilitation strategies for it.

This work was supported by an anonymous donor, the Vision Sciences Research Program and the Toronto General & Western Hospital Foundation.

Tarita-Nistor L, González EG, Mandelcorn MS, Brent MH, Markowitz SN, Steinbach MJ. The reading accessibility index and quality of reading grid of patients with central vision loss. Ophthalmic Physiol Opt. 2018 Jan. doi: 10.1111/opo.12429.

Rock-Steady Hands Win the Game

Researchers identify factors that can predict the success of surgery to control tremors.

Common symptoms of tremor include rhythmic shaking in the hands, arms, head, legs and torso, all of which can prevent affected individuals from participating in routine and leisure activities

At some point today, most people have likely drank a glass of water, tied their shoelaces or written something down on a piece of paper. But, for those experiencing tremors, the ability to perform these routine activities is difficult.

Tremors are a type of movement disorder characterized by involuntary and rhythmic shaking of certain parts of the body. They can appear on their own or can be the symptom of a neurological disorder such as Parkinson disease, stroke or traumatic brain injury. Drugs can help reduce the severity of tremors in some people, but can be ineffective in others, who will often then turn to surgical treatments to ease their tremors.

A surgery known as deep brain stimulation (DBS) has been successfully used to treat tremors. DBS involves implanting electrodes into certain regions of the brain to deliver electrical stimulation. Like any surgery, there are risks; however, these risks may be outweighed by the expected benefits of the surgery. A better understanding of the factors that can predict the long-term benefit of DBS would help patients decide whether the surgery is right for them. To date, these predictive factors remain elusive.

To address this gap in knowledge, Krembil Clinician Investigator Dr. Alfonso Fasano initiated a study to determine the characteristics associated with positive long-term

outcomes in people who underwent DBS. His research team analyzed the medical records of 52 patients and used advanced approaches to identify clinical factors that can predict the effectiveness of DBS in reducing tremors.

The team found that patients who benefitted from DBS tended to be of older age; have Parkinson disease as their cause of tremor; display more severe tremors prior to DBS; did not respond to a certain class of drugs normally prescribed to treat tremors; and exhibited specific signatures of brain activity. They also found that positioning the electrode in a specific way during surgery improved outcome.

“This study represents the first attempt to create recommendations for the selection of tremor patients who are most likely to benefit from DBS using readily available clinical data,” explains Dr. Fasano. “Future studies involving more patients will enable the development of novel tools that will help patients and surgeons make more informed medical decisions.”

This work was supported by the Dystonia Medical Research Foundation Canada and the Toronto General & Western Hospital Foundation. A Lozano is a Tier 1 Canada Research Chair in Neuroscience.

Sandoe C, Krishna V, Basha D, Sammartino F, Tatsch J, Picillo M, di Biase L, Poon YY, Hamani C, Reddy D, Munhoz RP, Lozano AM, Hutchison WD, Fasano A. Predictors of deep brain stimulation outcome in tremor patients. Brain Stimul. 2018 Jan 2. doi: 10.1016/j.brs.2017.12.014.