The Krembil

January 2019

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

The Year in Review

A message from Dr. Donald Weaver, Director of the Krembil Research Institute.

Dr. Donald Weaver, Director, Krembil Research Institute. Photo courtesy of the Globe and Mail.

Together, we achieved many successes in 2018, including publishing our research in high-impact journals and securing new research funding. These achievements were made possible through the hard work and dedication of the Krembil community. As such, I thank each of you for your important contributions over the past year.

Our Institute also experienced several noteworthy changes in 2018.

We recruited talented individuals to support our strategic research priorities. Senior Scientist Dr. Michael Reber and Scientist Dr. Milad Lankarany are leading new research programs in vision and neuroscience, respectively. Our new Senior Public Affairs Advisor, Heather Sherman, is promoting our scientific achievements—through press releases and stories—to the public. And Dr. Carrie-Lynn Keiski is helping our researchers develop grant applications.

The Krembil Brain Institute (KBI) was created to bring together neuroscience researchers and clinicians across the University Health Network. Its launch was followed by the release of a magazine describing some of the exciting research at KBI.

Krembil researchers established important partnerships to help convert their research findings into new treatments for disease. My Krembil-based company Treventis and French pharma company Servier inked a research agreement to develop a new treatment for Alzheimer disease. Likewise, MaRS Innovation and Evotec are partnering with Dr. Jeremy Sivak to develop a new treatment for glaucoma.

Not only was the Centre for Medicinal Chemistry and Drug Discovery operationalized in 2018, but it also achieved its first commercial success. The Centre was instrumental in securing Dr. Sivak's partnership with Evotec and MaRS Innovation and will perform the project's medicinal chemistry activities.

These changes in staff, structure and partners will help us move closer to our goal of developing new diagnostics and therapies to ease the suffering of those affected by arthritis or diseases of the eye and brain.

I look forward to working together in 2019!

Relentlessly yours,
Don Weaver

Director, Krembil Research Institute

Pitching Like a Pro

Krembil will host a competition to help researchers better showcase their work to the public.

Researchers should always have an ‘elevator pitch’ about their work handy to pique the interest of any listener. This way, they will always be prepared for a chance encounter with a science journalist looking for their next story or a philanthropist looking for a new investment opportunity.

An elevator pitch is a short verbal description of an idea or project that is meant to deliver the most meaningful and engaging information to a listener in a matter of minutes. Instead of providing an overview, a pitch should act as an ‘intellectual teaser’ that leaves an audience wanting more.

To help researchers, trainees and staff craft great pitches about their research, Krembil will be hosting a ‘Pitch Perfect’ competition on April 9, 2019.

What can participants expect at Pitch Perfect 2019?
Participants will present a three-minute pitch to a panel of judges from UHN Public Affairs—the pitch experts. The pitch must be about a recent or upcoming project and should convey what the project is, why it was or will be undertaken and what it will achieve if successful. The judges will provide feedback on each pitch.

What are the judges looking for?
A good pitch uses plain, non-scientific English that is easy to understand by the general public. Its content engages and inspires not only fellow researchers, but also someone with little knowledge of science or research. Importantly, it is delivered in a creative and visually appealing way, without relying solely on traditional PowerPoint slides.

More details on Pitch Perfect 2019
Date: Tuesday, April 9, 2019
Time: 1:00-3:00pm
Location: Room 2WW401, 2nd floor West Wing, Toronto Western Hospital
Registration: an email will be sent out shortly with details on how to sign up.

Research

One Mutation Spanning Two Countries

What do Finns and Canadians have in common? A gene mutation that causes Parkinson disease.

In Finland, a small Nordic country (pictured above), all PD patients with the A53E mutation are believed to have inherited the mutation from a common ancestor.

Finland is known for its snowy landscapes and herds of reindeer.

In 2014, Finland became famous for a very different reason: researchers discovered Finnish people carrying a new type of mutation—known as A53E—in the *SNCA* gene that causes Parkinson disease (PD).

PD is a neurodegenerative disease characterized by progressive problems with movement. Many people with PD will also experience impaired mental function. Some hereditary forms of the disease are caused by mutations in the *SNCA* gene and may develop at a younger age than non-hereditary forms. To date, at least 6 different *SNCA* mutations have been detected in PD patients.

Until recently, the A53E mutation had only been found in Finnish families with PD.

In November 2018, Dr. Lorraine Kalia, a neurologist and Scientist at the Krembil Research Institute, reported the discovery of a Canadian family with PD caused by the A53E mutation. This work was done in collaboration with colleagues at the Krembil, the Morton and Gloria Shulman Movement Disorders Clinic and Edmond J. Safra Program in Parkinson's Disease at Toronto Western Hospital, and the Tanz Centre for Research in Neurodegenerative Diseases at the University of Toronto.

Using genetic tests and the family's medical history, Dr. Kalia and her colleagues found that the A53E mutation is likely to have occurred spontaneously and was not inherited from a Finnish ancestor. The tests also suggest that the pattern of methyl molecules on the patients' DNA might contribute to the earlier appearance of symptoms in PD patients with *SNCA* mutations. Methyl molecules are found on the DNA of all people and help to control the activity of their genes.

Given that the *SNCA* gene provides the instructions for making the protein α-synuclein, Dr. Kalia and her colleagues also examined the effect of the A53E mutation on the protein's behaviour in test tubes and in cells. They showed that the mutated proteins had an increased tendency to form 'clumps' and 'fibres', similar to those found in the brains of PD patients. These clumps and fibres are believed to be toxic to brain cells and thus are key contributors to neurodegeneration.

Of the findings, Dr. Kalia says, "They show that the A53E mutation should not be ruled out as a cause of Parkinsonism outside of Finland. They also provide new insights into the mechanisms underpinning Parkinson disease, as well as other neurological diseases involving α-synuclein."

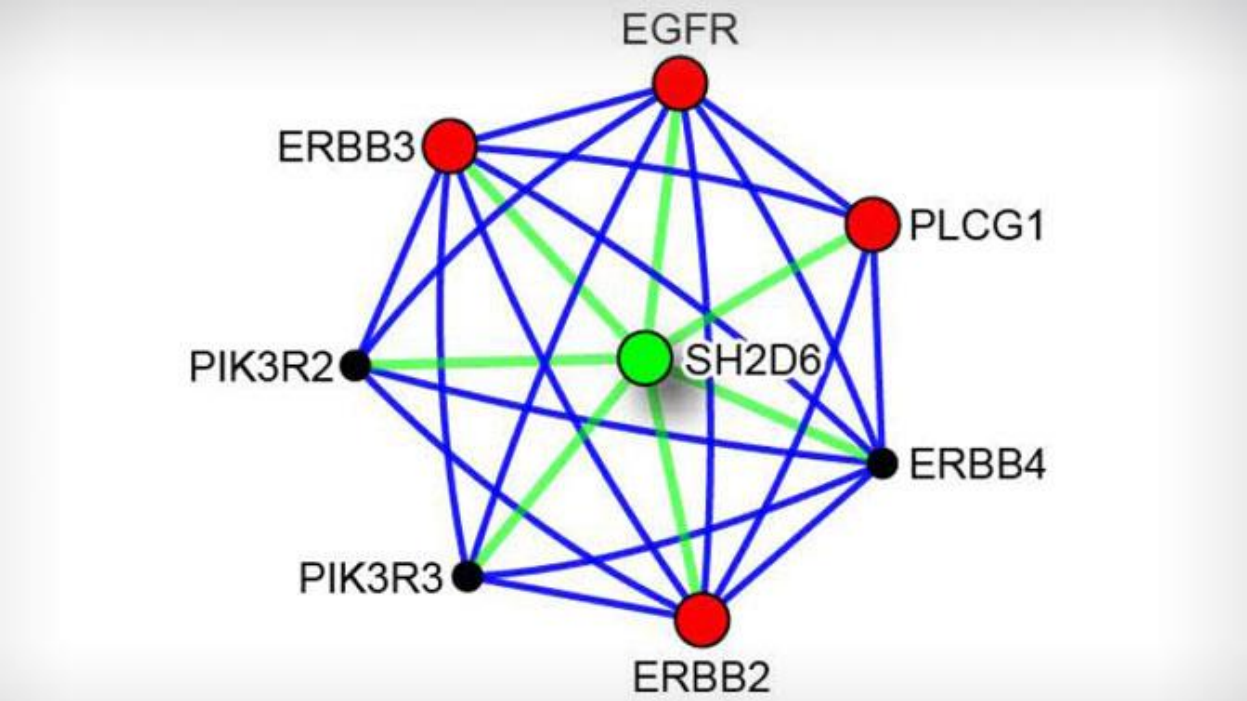
This work was supported by the Canadian Institutes of Health Research, the Canadian Consortium on Neurodegeneration in Aging, and the Toronto General & Western Hospital Foundation (TGWHF).

Picillo M, Lizarraga KJ, Friesen EL, Chau H, Zhang M, Sato C, Rooke G, Munhoz RP, Rogaeva E, Fraser PE, Kalia SK, Kalia LV. Parkinsonism due to A53E α-synuclein gene mutation: Clinical, genetic, epigenetic, and biochemical features. Mov Disord. 2018 Nov 13. doi: 10.1002/mds.27506.

Dr. Lorraine Kalia, Scientist, Krembil Research Institute.

Putting Labels on Protein Behaviour

UHN researchers expand database of interactions between proteins to accelerate drug discovery.



In a graphical representation of a protein interaction network, each point corresponds to a protein and each line represents a relationship.

Imagine going to a museum where none of the artifacts are labelled. Without any knowledge of the context in which the artifacts were used or where they came from, an exhibit would look like a collection of random objects.

In the past several decades, researchers have amassed large collections of information describing the components of cells and how they work together. However, much of the context has been missing from this information, which has prevented researchers from fully understanding the role of a cell's components in health and disease.

To help address this, Dr. Igor Jurisica, Senior Scientist at Krembil Research Institute, has been 'putting labels' on the interactions between proteins, the cellular machinery that performs much of the essential functions of the cell. In 2005, he created a database of protein interactions that has evolved and expanded over the years. In 2015, it included proteins from humans and five other species, as well as the tissues in which specific interactions occur.

His team recently reported a substantial expansion of their database in the journal *Nucleic Acids Research*. The new features include protein interactions for 12 more species to support biomedical, veterinary and agricultural research, and three new types

of context information: where these protein interactions occur in the cell, the diseases they are associated with, and whether they might respond to a potential drug.

“The Integrated Interactions Database, or IID, is one of the broadest and largest physical interaction databases,” explains Dr. Jurisica. “We’ve also included features that enable researchers to map the networks of protein interactions for each species, identify the key proteins in these networks and determine the conditions under which an interaction network is physiologically important.”

With this additional information, the 4.8 million protein-protein interactions in the database will help researchers better understand the molecular mechanisms behind diseases and treatments, and develop new drugs faster.

This work was supported by the Krembil Foundation, Ontario Research Fund, Natural Sciences and Engineering Research Council of Canada, Canada Foundation for Innovation, Canada Research Chairs Program, Toronto General & Western Hospital Foundation and IBM.

Kotlyar M, Pastrello C, Malik Z, Jurisica I. IID 2018 update: context-specific physical protein-protein interactions in human, model organisms and domesticated species. Nucleic Acids Res. 2018 Nov 8. doi: 10.1093/nar/gky1037.

Dr. Igor Jurisica, Senior Scientist, Krembil Research Institute.

Location is Everything

Better brain treatment targeting improves outcomes for individuals with essential tremor.

Improving clinical outcomes for patients with essential tremor requires specific targeting of areas in the brain, which can be aided by precise image-guided techniques

Much like how location can directly affect the price of a home, targeting specific areas of the brain can have an effect on the success of certain brain treatments. However, delivering treatment to the exact location in the brain that will provide the most benefit remains a daunting challenge.

To help address this challenge, researchers at Krembil Research Institute explored an emerging technique, known as magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy, for the treatment of essential tremor—a debilitating brain disorder that causes uncontrollable shaking. This study was done in collaboration with Sunnybrook Health Sciences Centre.

The approach uses high-resolution MR imaging to precisely target a tiny area of the brain called the thalamus. This brain region is responsible for relaying important motor and sensory signals in the brain and is a key target for essential tremor therapies.

By examining patients who underwent MRgFUS thalamotomy, the study found that clinical outcomes were largely dependent on the specific regions that were targeted within the thalamus. Just as in the real estate market, location seems to play a critical role in the clinical outcomes of these patients.

The researchers further mapped out areas that were associated with the best treatment responses, as well as those linked with an increased risk of detrimental side effects. Using standard assessment methods, the research team found that use of MRgFUS led to a ~42% improvement in tremor scores three months after treatment. The study also suggested that when smaller areas of the brain were targeted, side effects were less severe.

“These findings are a significant step toward improving the effectiveness of MRgFUS thalamotomy and will enable us to refine areas to target therapy so that we can improve outcomes and reduce adverse effects for patients,” says Dr. Andres M. Lozano, a neurosurgeon at Toronto Western Hospital and Krembil Senior Scientist.

This work was supported by Insightec and the Toronto General & Western Hospital Foundation. Dr. Lozano holds a Tier 1 Canada Research Chair in Neuroscience.

Boutet A, Ranjan M, Zhong J, Germann J, Xu D, Schwartz ML, Lipsman N, Hynynen K, Devenyi GA, Chakravarty M, Hlasny E, Llinas M, Lozano CS, Elias GJB, Chan J, Coblentz A, Fasano A, Kucharczyk W, Hodaie M, Lozano AM. Focused ultrasound thalamotomy location determines clinical benefits in patients with essential tremor. Brain. 2018 Dec 1. doi: 10.1093/brain/awy278.

Dr. Andres M. Lozano, Senior Scientist, Krembil Research Institute. Photo courtesy of the Globe and Mail.

Sparking Curiosity

Research study provides new insight on what makes us more open to new experiences.

An inquiring mind and a preference for novelty spurred some of our ancestors to explore new environments and make new discoveries.

We all have a natural curiosity that drives us to try new experiences. It is part of the reason our ancestors tried new things, even when the outcomes were not clearly beneficial.

However, research shows that our preference for novelty is not always straightforward and that we are occasionally biased toward the familiar.

Dr. Moshe Eizenman, a Professor in the department of Ophthalmology and Vision Sciences at the University of Toronto and an Affiliate Scientist at the Krembil Research Institute, recently conducted a study to explore this bias.

As part of the study, participants performed visual and audio tasks—either alone or together—while they were presented with novel and previously displayed images that were shown following short or long delays. During this time, their eye movements were recorded and analyzed to determine how likely they were to be paying attention to each of the images.

The research team found that participants who performed the visual and audio tasks together were less likely to pay attention to a new image when there were long delays, but not when there were short delays.

“To allocate more attention to novel images, our brain first has to differentiate between previously seen images and new images. This is done by two distinct memory systems. One memory system recognizes previously seen images by remembering details of the images; this system was affected by the long-delays in our study,” explains Dr. Eizenman. “The second memory system does not remember the details of images but it can indicate if those images were previously seen; this system was not affected when subjects performed two tasks at once.”

“A hallmark of human behaviour has always been our desire to explore. This study provides new insight into the effects of multitasking on the automatic, subconscious processes that support and drive our curiosity,” says Dr. Eizenman.

The study was supported by the National Science and Engineering Research Council of Canada, the University of Toronto Vision Science Research Program and the Toronto General & Western Foundation.

Eizenman M, Chung J, Yu M, Jia H, Jiang P. Attention, novelty preference and the visual paired comparison task. Exp Eye Res. 2018 Nov 13. pii: S0014-4835(18)30381-6. doi: 10.1016/j.exer.2018.11.009.