The Krembil

September 2019

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

Willkommen to Krembil

Visit by German AI delegation may spur new strategic collaborations with the institute.

Krembil researchers and staff, German AI experts and Judith Gerlach (third from right, first row), the Bavarian Minister of State for Digital Affairs, during the delegation's visit.

On September 12, Krembil hosted a delegation of artificial intelligence (AI) experts from Germany. The aim of the visit, which was organized by the State of Bavaria Office in Montreal, was to help German and Krembil researchers identify areas of mutual interest for future collaboration.

Judith Gerlach, the Bavarian Minister of State for Digital Affairs, led the delegation, which included 20 government, business and research leaders from Bavaria, a state in the southeast of Germany. Bavaria has one of the largest economies in Europe and is home to some of the continent's top universities, including Ludwig-Maximilians-Universität München (LMU) and the Technische Universität München (TUM).

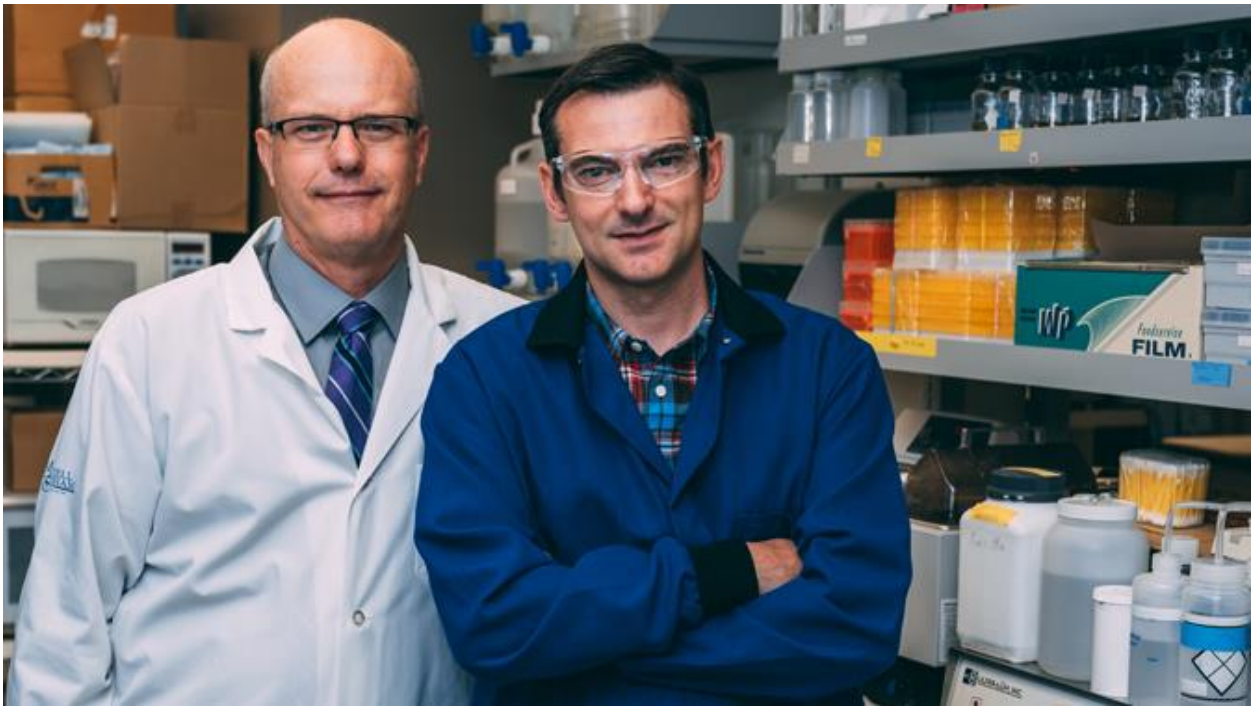
Notably, the group included several internationally recognized computational researchers, such as Prof. Dr. Matthias Schubert, the Chair of Database Systems and Data Mining at LMU; and Prof. Dr. Fabian Theis, Chair of Mathematical Models of Biological Systems at TUM and Head of the Helmholtz Institute of Computational Biology.

Several Krembil researchers and staff met with and presented their work to the delegation. The presenters included Drs. Mark Reed (Staff Scientist, Centre for Medicinal Chemistry and Drug Discovery), Frances Skinner (Senior Scientist, brain), Starlee Lively (Scientific Associate, arthritis), Mayuri Gupta (Postdoctoral Fellow, brain) and Jeremy Sivak (Senior Scientist, vision).

One promising area of collaboration identified by the group was the application of AI to accelerate the discovery and development of new medicines for chronic diseases.

A Partnership to Make New Medicines

New drug discovery program launched is based on Krembil discovery.



Dr. James Eubanks (left) and Dr. Mark Reed (right) are partnering with the Toronto Innovation Acceleration Partners to develop a new treatment for Rett syndrome.

The Toronto Innovation Acceleration Partners (TIAP), formerly known as MaRS Innovation, are collaborating with Krembil Senior Scientist Dr. James Eubanks at the University Health Network (UHN) to develop a new treatment for Rett syndrome, a rare developmental disorder found almost exclusively in girls and women.

Infants with Rett syndrome develop and grow normally until the age of 8 to 12 months when symptoms begin appearing. Although the symptoms vary in type and severity, most of the girls and women with the disorder cannot speak or use their hands purposefully. Many also experience seizures that are difficult to control with medications. Presently, there is no cure for Rett syndrome, and the available treatments can only help alleviate symptoms.

Researchers have known for many years that most cases of Rett syndrome are caused by mutations in the *MECP2* gene; however, the mechanisms that link these genetic changes to the syndrome's diverse symptoms are not well understood.

"We believe that we have discovered an important piece of the puzzle," says Dr. Eubanks, who has been studying the disorder for over 20 years.

Using experimental models, Dr. Eubanks and his team have shown that *MECP2* mutations lead to abnormally high levels of the TRPM2 protein in the brain, which interfere with normal brain development and function. Although this mechanism is likely to be only one of several contributing to the disorder and its symptoms, the researchers have accumulated compelling evidence that it is an important contributor and represents a promising therapeutic target for Rett syndrome.

TIAP will initially invest up to $400,000 to help translate Dr. Eubanks' discovery into a new treatment for Rett syndrome. The funds will support the creation and evaluation of drug-like compounds that target TRPM2, dampening its activity, in the brain of Rett patients. Dr. Mark Reed, a medicinal chemist and head of Krembil's Centre for Medicinal Chemistry and Drug Discovery, will oversee the work, which will be split between the Centre and the Charles River Discovery site in the United Kingdom. The new partnership will also give Drs. Eubanks and Reed access to TIAP's commercialization services to support further development of any promising treatments.

"This is a unique and exciting opportunity to really help patients by developing a treatment that is more effective than what is currently available to them," says Dr. Eubanks.

Source: https://www.globenewswire.com/news-release/2019/07/15/1882478/0/en/MaRS-Innovation-Launches-New-Drug-Discovery-Program-Targeting-Rare-and-Disabling-Developmental-Disorder.html

Top Award for Neuroscientist

Dr. Kovacs receives international award for his research in neurodegenerative diseases.

Krembil's Dr. Gabor G. Kovacs received the 2019 Franz Burda Award from the International Association of Parkinsonism and Related Disorders. Dr. Kovacs, who recently joined UHN, is an internationally renowned neuropathologist and researcher in the field of neurodegenerative diseases.

The award recognizes his research focused on a protein known as alpha-synuclein. This protein accumulates in the brains of patients with a family of neurodegenerative diseases known as synucleinopathies, which include Parkinson disease.

Dr. Kovacs joined UHN in the spring of 2019 and is co-leading UHN's new program devoted to the study of progressive supranuclear palsy—a rare and severely disabling neurodegenerative disease. He is a Senior Scientist at the Krembil Research Institute, a Professor in the Department of Laboratory Medicine and Pathobiology at the University of Toronto and a Principal Investigator at the Tanz Centre for Research in Neurodegenerative Diseases. His research program uses human brain tissues to investigate the mechanisms underpinning nerve cell death in certain neurodegenerative diseases. He has published more than 260 peer-reviewed articles and written 19 book chapters.

"Toronto has an incredibly high concentration of talented scientists and neurologists involved in neurodegeneration research. It also has a very collegial atmosphere that promotes collaboration and the sharing of research facilities. Combined, these factors

are key for making new insights and discovering treatment strategies to help people living with these devastating diseases," says Dr. Kovacs.

Prior to joining UHN, Dr. Kovacs was an Associate Professor at the Medical University of Vienna in Austria and the leader of the Hungarian and Austrian Reference Center for Human Prion Diseases. His recruitment was made possible by the generous support of The Rossy Foundation and the Edmond J. Safra Foundation.

Research

Leaving Their Mark on the Brain

Repeated concussions in former athletes linked to high levels of tau protein.

The National Football League (NFL) reported that its players sustained at least 214 concussions during games and practices in the 2018 season.

Concussions are a common type of injury in contact sports, such as football and hockey. They are caused by a blow or jolt to the head or body that damages the brain.

Athletes with a history of repeated concussions are at an increased risk of developing a neurodegenerative condition known as chronic traumatic encephalopathy (CTE). The condition impairs mental function and memory and can cause behavioural changes, such as aggression or depression.

“We do not fully understand how CTE develops or why it develops in some people with multiple concussions but not others. Diagnosing the condition is also a challenge because many of its symptoms overlap with those of other neurodegenerative diseases, such as Alzheimer disease,” says Dr. Carmela Tartaglia, a Clinician Investigator at Krembil Research Institute.

To begin addressing these gaps in knowledge, a team of researchers led by Dr. Tartaglia recently published a study examining 22 former professional athletes—including hockey and football players, as well as a snowboarder—who sustained multiple concussions throughout their careers.

The researchers measured the levels of total tau and beta-amyloid proteins in the cerebrospinal fluid of each athlete. These proteins are frequently used in the diagnosis of Alzheimer disease. The researchers also assessed the athletes' brain structure using magnetic resonance imaging and brain function through neuropsychological tests.

They discovered that the former athletes could be divided in two groups based on their total tau levels: one group had significantly higher tau in their cerebrospinal fluid than healthy participants without a history repeated concussions, whereas the other group had levels comparable to those in healthy participants. The researchers also found that athletes in the high tau group displayed impairments in their mental function and changes in their brain structure, both of which are indicative of neurodegeneration.

"Our findings suggest that high total tau levels could be a sign of neurodegeneration in individuals who have sustained multiple concussions," says Dr. Tartaglia. "Detecting evidence of neurodegeneration is the first step towards being able to provide a treatment. Not everyone with multiple concussions gets CTE or other neurodegenerative diseases, so being able to detect those with evidence of disease is important for targeting treatment to the right person."

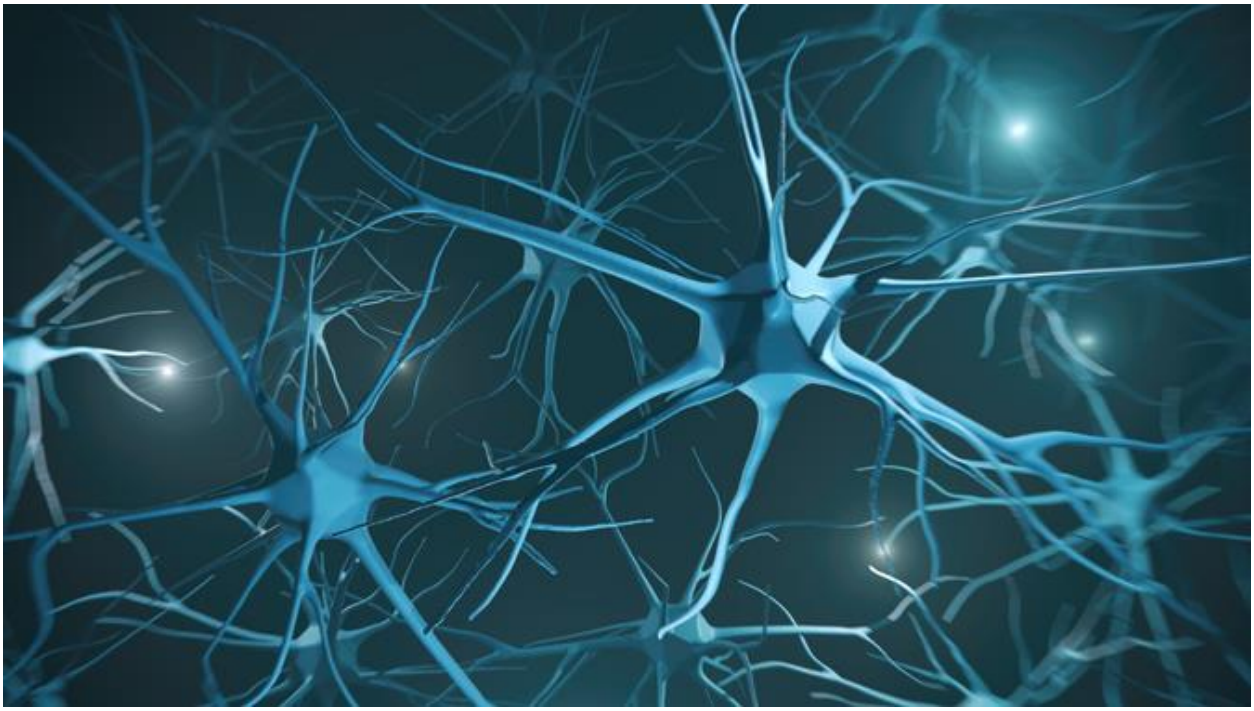
This work was supported by the PSI Foundation, the Canadian Institutes of Health Research and the Toronto General & Western Hospital Foundation. Dr. Tartaglia holds the Marion and Gerald Soloway Chair in Brain Injury and Concussion Research.

Taghdiri F, Multani N, Tarazi A, Naeimi SA, Khodadadi M, Esopenko C, Green R, Colella B, Wennberg R, Mikulis D, Davis KD, Goswami R, Tator C, Levine B, Tartaglia MC. Elevated cerebrospinal fluid total tau in former professional athletes with multiple concussions. Neurology. 2019 Jun 4. doi: 10.1212/WNL.0000000000007608.

Dr. Carmela Tartaglia, Clinician Investigator, Krembil Research Institute.

Making the Right Connections

Researchers discover a new mechanism that regulates the development of brain networks.



A neuron, which is the basic working unit of the brain, uses electrical pulses to communicate information to other neurons in its network.

A new study from the Krembil Research Institute suggests that a protein known as VLK plays an important role in brain development. The findings of the study were recently published in the prestigious journal *Nature Chemical Biology*.

The adult brain consists of 86 billion nerve cells known as neurons, which are highly interconnected and form multiple overlapping networks. The activity of these networks underpins all of the brain's functions and processes.

How neurons establish the right connections to build these networks during brain development is not fully understood.

"We found several scientific clues suggesting that the VLK protein, which was discovered only five years ago, might be involved in this process, so we decided to take a closer look," explains Krembil Senior Scientist Dr. Philippe Monnier, who led the team of researchers who conducted the new study.

VLK is a protein secreted by neurons into their environment. Its function is to add chemical groups known as phosphates onto other proteins, which alters the activity of the recipient protein.

The researchers examined the effect of VLK on the growth and development of the network of neurons that connects the eyes to the tectum, which is a region of the brain that processes visual information.

They found that VLK attached phosphate groups to a specific protein that is found on the surface of the growing neurons. The resulting pattern of phosphates on the neuron's surface modulated the direction of the cell's growth, enabling it to establish connections to neurons in the tectum.

"Our findings indicate that VLK, which appears to modify many other proteins that guide the growth and connections of neurons, is likely to have broad and profound effects on brain development, function and disease," says Dr. Monnier.

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

Harada H, Farhani N, Wang XF, Sugita S, Charish J, Attisano L, Moran M, Cloutier JF, Reber M, Bremner R, Monnier PP. Extracellular phosphorylation drives the formation of neuronal circuitry. Nat Chem Biol. 2019 Aug 26. doi: 10.1038/s41589-019-0345-z.

Dr. Philippe Monnier, Senior Scientist, Krembil Research Institute.

Neural Code Breakers

Study highlights similarities between the nervous system and digital communication technology.

Cell phones, digital television and wireless internet use multiplexing—combining multiple signals into one and transmitting it over a single channel—to share information.

The human nervous system and your cell phone use similar strategies to communicate.

A cell phone converts a speaker's voice into a radio signal that is transmitted by a tiny antenna to another cell phone, where the radio signal is converted back into a voice.

The human nervous system—a network of billions of nerve cells in the brain and spinal cord, which also projects throughout the body—converts information into electrical pulses that are transmitted through the network to their destination, where the pulses are converted back into information.

Researchers do not fully understand how these electrical pulses communicate complex information, such as the variety of colours and shapes seen by the eyes or the different notes perceived by our ears while listening to music. It is widely believed that the nervous system uses multiple 'languages' or codes to translate this information into electrical pulses.

Krembil Scientist Dr. Milad Lankarany recently published a study revealing a new type of code used by the nervous system to transmit information from the skin to the brain.

Prior to joining Krembil, he completed this research during his postdoctoral fellowship with Dr. Steven Prescott at The Hospital for Sick Children.

For the study, the researchers examined the electrical pulses received by a network of 30 brain cells in response to skin being touched. They found that the pattern of the electrical pulses encoded at least two different types of information about the touch stimulus. The synchronous pulses encoded information about abrupt changes in the touch stimulus. In contrast, asynchronous pulses conveyed information about the amount of pressure applied to the skin while being touched.

“When a communication system transmits multiple types of information through a single channel, we say that it is capable of ‘multiplexing’,” explains Dr. Lankarany. “Cell phones also multiplex by sending multiple radio signals—each corresponding to a conversation—over the same radio channel. Multiplexing is another feature that our nervous system has in common with digital telecommunication systems.”

Next, the researchers plan to examine how these electrical pulses—and the information they carry—are shared with other regions of the brain, where they will be decoded.

This work was supported by the National Institutes of Health, the Natural Sciences and Engineering Research Council of Canada, the Canadian Institutes of Health Research, the Fonds de recherche du Québec – Santé, The Hospital for Sick Children and the Government of Ontario.

Lankarany M, Al-Basha D, Ratté S, Prescott SA. Differentially synchronized spiking enables multiplexed neural coding. Proc Natl Acad Sci U S A. 2019 May 14. doi: 10.1073/pnas.1812171116.

Dr. Milad Lankarany, Scientist, Krembil Research Institute.

Going Above and Beyond

Specially trained physiotherapists could help diagnose arthritis faster.

Axial spondyloarthritis, a type of arthritis that affects the spine, typically begins before the age of 45. Symptoms can start appearing as early as the age of 15.

Up to 84% of Canadians will experience low back pain at some point in their life.

Back pain can be caused by many things, and patients sometimes have to wait a long time before they can see a specialist to have the cause of their back pain diagnosed—years in some cases. This is much too long for some back pain-causing conditions such as axial spondyloarthritis (SpA).

SpA is a form of arthritis that affects the spine and can produce back pain and stiffness. If left untreated, it can lead to severe pain, back deformities and significant disability.

One of the factors that delays diagnosis is the lack of access to rheumatologists, who are doctors specialized in the care of arthritis and other diseases that affect the musculoskeletal system.

A new study led by Krembil Clinician Investigator Laura Passalent examined whether an alternative model of care could help accelerate the detection of SpA for those living with back pain.

The alternative model involved using physiotherapists to supplement the role of rheumatologists. The physiotherapists were provided with additional training to

determine whether back pain is likely to be caused by SpA. While physiotherapists typically diagnose and treat different types of injuries, diagnosing SpA is traditionally outside of the scope of their role.

As part of the study, the specially trained physiotherapists assessed 57 patients with back pain for SpA. The records of the same patients were also independently assessed by three rheumatologists.

Ms. Passalent and the other researchers involved in the study found that the diagnoses offered by the physiotherapists agreed with those provided by the rheumatologists up to 80% of the time. The assessment offered by each of the three rheumatologists also matched up to 80% of the time. These findings indicate that the specially trained physiotherapists are comparable to rheumatologists at diagnosing SpA.

“Our study suggests that health care practitioners extending their role, with suitable training, could help reduce bottlenecks in the health care system and improve access to care for SpA patients,” says Ms. Passalent.

This work was supported by the Canadian Initiative for Outcomes in Rheumatology cAre (CIORA).

Passalent L, Hawke C, Lawson D, Omar A, Alnaqbi K, Wallis D, Steinhart H, Silverberg M, Wolman S, Derzko-Dzulynsky L, Haroon N, Inman RD. Advancing early identification of axial spondyloarthritis: An interobserver comparison of extended role practitioners and rheumatologists. J Rheumatol. 2019 May 1. doi: 10.3899/jrheum.180787.

Laura Passalent, Clinician Investigator, Krembil Research Institute.