The Krembil

September 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.

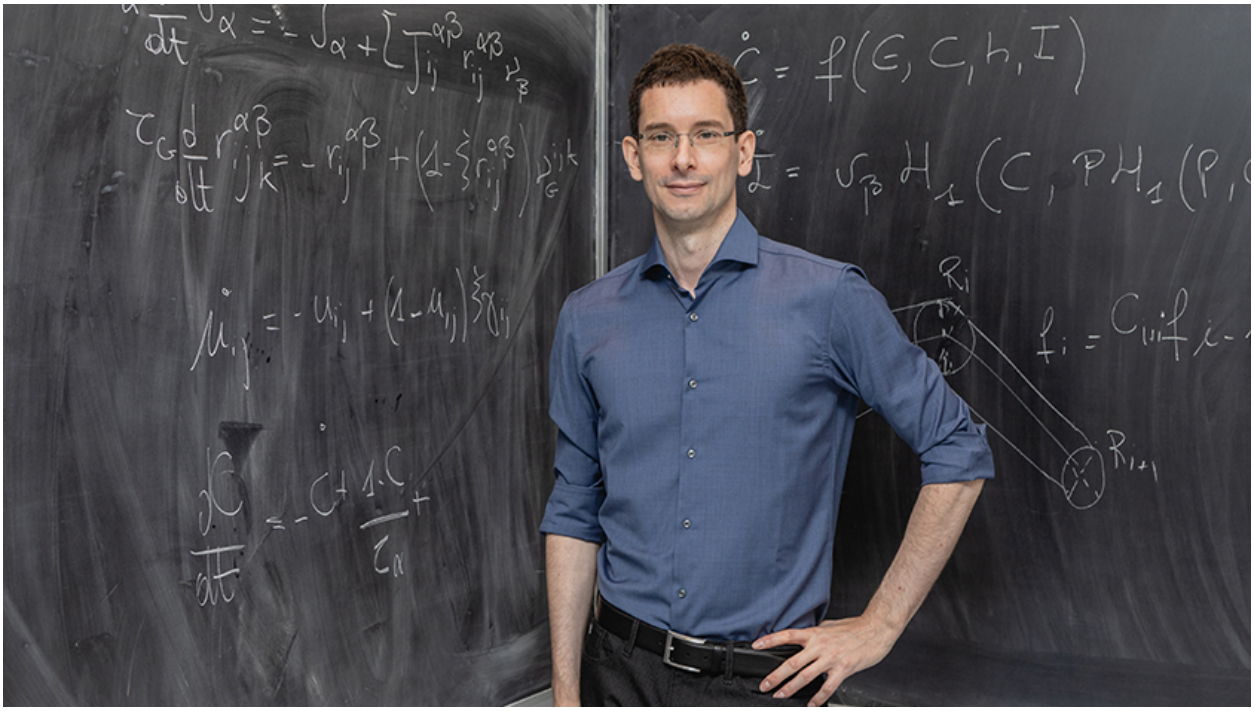
Stories in this month's issue:

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

News

Neuroscientist Joins Krembil

Dr. Maurizio De Pittà applies computational approaches to study neuron-glia interactions.



Dr. Maurizio De Pittà is a new Scientist at the Krembil Brain Institute.

The Krembil Research Institute is pleased to welcome Dr. Maurizio De Pittà as its newest Scientist at the Krembil Brain Institute. Dr. De Pittà is a computational neuroscientist with expertise in the biology and function of glia—non-neuronal cells in the nervous system.

Dr. De Pittà develops mathematical models to study the interactions between glia and neurons in the healthy and diseased brain. For example, recent research by Dr. De Pittà has uncovered how astrocytes—a subtype of glial cell—signal and contribute to neuron activity and cognition.

“Emerging evidence is revealing that neuron-glia interactions are involved in nearly every aspect of brain function and dysfunction,” explains Dr. De Pittà. “We are interested in clarifying the nature of these interactions, from the molecular to the

network level, in order to better understand how they give rise to behavioural outcomes."

At Krembil, Dr. De Pittà will continue to develop models of glial signaling and neuron-glia interactions and explore the roles that glia play in information processing, learning and memory, as well as neurodegenerative conditions such as Alzheimer disease.

"My ultimate goal is to improve how we diagnose and treat brain diseases," says Dr. De Pittà. "I look forward to working with translational scientists and clinicians at Krembil to develop a pipeline, from the surgical room to the lab, to identify disease markers and targets for therapeutic interventions."

In addition to his appointment at Krembil, Dr. De Pittà is a Principal Investigator of the ASTROTECH Consortium, a European network that aims to develop tools to study and manipulate glia in models of epilepsy, ischemia, glioma and depression.

Dr. De Pittà completed his PhD in Computational Biology at the Maguy-Glass Laboratories of Physics of Complex Systems at Tel Aviv University before completing postdoctoral training in Artificial Biology at the National Institute for Research in Digital Science and Technology (Inria) in Lyon, France and Computational Neuroscience at the University of Chicago. Most recently, he was a La Caixa Junior Leader Postdoctoral Fellow at the Basque Center for Applied Mathematics in Bilbao, Spain.

Welcome to Krembil, Dr. De Pittà!

Krembil Magazine Launched

Toronto Life showcases research and clinical advancements from the Krembil Brain Institute.

The Krembil Brain Institute magazine features members of the diverse and multi-disciplinary Krembil community (clockwise from top left: PhD candidate Merrick Fallah, Krembil Scientist Dr. Olga Rojas, Advanced Practice Nurse Rosalie Magtoto and the Croxon family).

The 2021 Krembil Brain Institute magazine is live!

Launched in the September issue of *Toronto Life*, the magazine was distributed to nearly 40,000 subscribers across Canada. The magazine showcases the world-class multidisciplinary team at the Krembil Brain Institute and its groundbreaking research related to chronic and debilitating diseases of the brain and spine.

The stories in this issue highlight exciting research and clinical advancements currently underway at the Institute, as well as inspiring patients who have reclaimed their lives as a result of these advancements.

Patient-centred stories focus on how Krembil researchers and clinical partners are improving the detection and treatment of a wide range of nervous system conditions, including epilepsy, trigeminal neuralgia, chronic pain, stroke and spinal cord injury.

In addition to the printed magazine, *Toronto Life* shared digital versions of two feature stories, “Pushing the Limits” and “Codebreakers”, on their website. These stories introduce readers to the Krembil researchers who are working to develop cutting-edge neuromodulatory procedures and treatments for neurodegenerative conditions such as Alzheimer and Parkinson disease.

Click here to read the 2021 Krembil Brain Institute magazine.

Printed copies of the magazine are available at the Krembil Directorate Office (room 4KD478, Krembil Discovery Tower) and room 11MP302 at Toronto Western Hospital.

Side Benefits

Drugs used to treat prostate enlargement may reduce men's risk of developing Parkinson disease.

Approximately 0.4% of Canadians are affected by Parkinson disease—a progressive disorder that affects movement, balance and coordination. The risk for developing Parkinson disease increases with age.

A recent study led by Dr. Connie Marras, Clinician Scientist at the Krembil Research Institute, and Dr. Priti Gros, Clinical Fellow at Toronto Western Hospital, suggests that certain drugs used to treat prostate conditions may help to reduce men's risk of Parkinson disease.

The researchers examined data from various provincial and federal databases to identify adult males who were prescribed drugs to treat prostate enlargement, a noncancerous condition that interferes with urination.

Between 1997 and 2019, 265,745 males in Ontario filled prescriptions for at least one of four drugs commonly used to treat prostate enlargement: terazosin, doxazosin,

alfuzosin and tamsulosin. The first three of these drugs are known as phosphoglycerate kinase 1 (PGK1) activators, a class of drugs that improve the way cells manage energy.

“Previous research suggests that PGK1 activators have protective effects on the brain in experimental models of Parkinson disease,” explains Dr. Marras. “This may be because they improve the way that cells manage energy, and Parkinson disease is associated with impaired energy management in brain cells. We wanted to know if continued use of these drugs is associated with fewer new cases of Parkinson disease in the adult male population. We also wanted to see if the effects of these drugs differ from that of tamsulosin, a non-PGK1 activator.”

The researchers found that sustained use of all four drugs was associated with a lower risk of developing Parkinson disease in men over the age of 66. PGK1 activators were associated with a 6% reduction in disease incidence per year of use, and tamsulosin was associated with an 8% reduction per year of use.

“We found that regular use of PGK1 activators, as well as tamsulosin, was associated with reductions in the incidence of Parkinson disease. Further clinical studies are needed to determine how each of these drugs reduces an individual’s risk for developing Parkinson disease, and whether they may also be useful for treating the disease after it has developed,” says Dr. Marras.

This work was supported by ICES, the Bresler Family Research Fund and the UHN Foundation.

Gros P, Wang X, Guan J, Lang AE, Austin PC, Welk B, Visanji NP, Marras C. Exposure to Phosphoglycerate Kinase 1 Activators and Incidence of Parkinson's Disease. Mov Disord. 2021 Jul 9. doi: 10.1002/mds.28712.

Dr. Connie Marras (L) is a Clinician Scientist at the Krembil Research Institute and the senior author of the study; Dr. Priti Gros (R) is a Clinical Fellow at Toronto Western Hospital and the lead author of the study.

The Weight of Arthritis

The link between obesity and osteoarthritis: can we blame it on the knee?

Obesity is a major modifiable risk factor for osteoarthritis, a progressive joint disease that causes pain and decreased mobility. Osteoarthritis commonly affects the knee, alone or together with other joints.

Researchers at UHN's Schroeder Arthritis Institute have demonstrated that the relationship between high body mass index (BMI) and hand osteoarthritis may be explained by the presence of osteoarthritis in the knee.

It is well known that individuals who are overweight or obese—those who have a BMI greater than 25 kg/m2—are more likely to develop osteoarthritis than normal weight individuals of the same age. Although the negative impact of obesity is most apparent at weight-bearing joints, such as the knee, some studies have linked obesity to osteoarthritis in non-weight-bearing joints, such as the joints of the hand. This finding has led to suggestions that hand osteoarthritis may be linked to body-wide changes that result from being overweight or obese, such as hormone disruptions and inflammation, not just increased stress on joints.

"An issue with a lot of clinical and epidemiological osteoarthritis research is that it treats the disease as though it affects only a single joint," cautions Dr. Elizabeth Badley, lead author of the study and a Senior Scientist at the Schroeder Arthritis Institute. "In reality, most people with osteoarthritis have symptoms at two or more different joint sites, and this needs to be taken into account in studies of osteoarthritis."

To determine whether the apparent connection between obesity and hand osteoarthritis can be attributed to osteoarthritis at other joint sites, the researchers examined the relationships between BMI and osteoarthritis affecting the hand, hip or knee alone, and combinations of these joints.

The research team leveraged the Canadian Longitudinal Study on Aging, which enabled them to analyze data from over 6,000 individuals with osteoarthritis. On first impression, high BMI appeared to be linked to a higher likelihood of having osteoarthritis affecting the knee, hip or hand. However, when the researchers examined individuals with all possible combinations of osteoarthritis at these joint sites, they found that BMI was linked only to osteoarthritis in the knee. This relationship was particularly strong for individuals with the highest BMI.

“Taken together, these findings suggest that the previously observed link between high BMI and hand osteoarthritis is likely explained by the presence of the disease at other joints, particularly the knee,” explains Dr. Badley. “The association between high BMI and knee osteoarthritis appears to be distinct from that between high BMI and osteoarthritis in other joints.”

The findings of this study highlight the importance of recognizing the multi-joint nature of osteoarthritis and considering multiple joints when studying the disease.

This study was conducted using data from the Canadian Longitudinal Study on Aging, and supported by the Canadian Institutes of Health Research, the Arthritis Society and the UHN Foundation.

Badley EM, Zahid S, Wilfong JM, Perruccio AV. The relationship between body mass index and osteoarthritis for single and multi-site osteoarthritis of the hand, hip, or knee: findings from the CLSA. Arthritis Care Res (Hoboken). 2021 Jun 13. doi: 10.1002/acr.24729.

Dr. Elizabeth Badley is a Senior Scientist at the Schroeder Arthritis Institute and Director of the Arthritis Community Research and Evaluation Unit.

The Power of Teamwork

Collaboration among different health care professionals shortens wait times for arthritis care.

Chronic lower back pain beginning in early adulthood may point to axial spondyloarthritis.

UHN researchers have found a way to shorten diagnostic wait times for patients with axial spondyloarthritis. The strategy involves a two-step screening process that occurs before patients see a rheumatologist.

Axial spondyloarthritis is a form of arthritis that primarily affects the spine and sacroiliac joint near the hip, causing lower back pain and stiffness. The condition is diagnosed by a rheumatologist based on the presence of persistent back pain and joint damage.

“Due to the shortage of rheumatologists in Canada, patients with this condition typically wait years between meeting with a primary care physician and receiving a formal diagnosis,” explains Dr. Yoga Raja Rampersaud, a Clinician Investigator at the Schroeder Arthritis Institute and senior author of the study.

In response to the long wait times for rheumatology care, Dr. Rampersaud’s team examined a patient screening approach that draws on experts other than rheumatologists. First, standard screening is carried out by a primary care physician. Then, secondary screening is carried out by an advanced practice clinician—a health care provider who is not a rheumatologist but is trained in arthritis care.

“Rheumatologists receive a high volume of referrals for patients with lower back pain, and many of these patients do not actually require specialized care," says Dr. Rampersaud. "We examined whether advanced practice clinicians can reduce diagnostic delays by better triaging patients. We also examined whether these advanced-practice clinicians can identify patients with axial spondylarthritis as effectively as rheumatologists.”

The researchers tested the screening process in more than 400 patients. All patients were initially screened by a primary care physician. Patients who had experienced lower back pain for least three months or more, beginning before they were 50 years of age, met the criteria for further screening. The secondary, more detailed screen was conducted by an advanced practice clinician at the Spondylitis Program at Toronto Western Hospital. Following the screening process, patients were referred to a rheumatologist for formal assessment and diagnosis.

The researchers found that the two-step screening process reduced the overall time between pain onset and diagnosis. They also found an 82.7% agreement between disease assessments made by the advanced practice clinicians and those made by the rheumatologists.

“Our findings revealed that this two-step screening process can speed up diagnosis by quickly identifying patients who are most in need. These patients often spend months or years bouncing around the system before seeing the right provider, unfortunately too late. This networked team approach can be easily used to improve access to the right care in other forms of arthritis and other conditions,” says Dr. Rampersaud.

“By drawing on physiotherapists from the Spondylitis Program at Toronto Western Hospital, we were able to speed the detection and management of arthritis, and unlock an important pathway to improved patient outcomes.”

This work was supported by the Arthritis Society and the UHN Foundation. C Bombardier holds a Tier 1 Canada Research Chair in Knowledge Transfer for Musculoskeletal Care.

Passalent L, Sundararajan K, Perruccio AV, Hawke C, Coyte PC, Bombardier C, Bloom JA, Haroon N, Inman RD, Rampersaud YR. Bridging the Gap between Symptom Onset and Diagnosis in Axial Spondyloarthritis. Arthritis Care Res (Hoboken). 2021 Jul 15. doi: 10.1002/acr.24751.

Dr. Yoga Raja Rampersaud is a Clinician Investigator at the Schroeder Arthritis Institute and a Staff Orthopedic Surgeon at Toronto Western Hospital (photo credit: The Globe and Mail).

A Needle in a Haystack

Whole genome sequencing reveals rare genetic variations in adults with unexplained epilepsies.

The human genome—our complete set of genetic instructions—contains more than three billion DNA base pairs, which give rise to tens of thousands of genes. Identifying disease-causing genetic variations is incredibly challenging, like finding a needle in a haystack.

Epilepsy refers to abnormal electric brain activity that is seen in a wide range of brain disorders. Genetics often play a role in the development of epilepsy. Up to eight out of ten cases of epilepsy are thought to be caused by genetic abnormalities.

Although more than 900 genes have been linked to epilepsy syndromes, identifying the genetic mutations that are associated with specific types of epilepsy remains a challenge.

Researchers led by Krembil Clinician Investigator Dr. Danielle Andrade carried out a detailed analysis of the whole genome of patients with severe epilepsies that had not been previously linked to a genetic cause.

Whole-genome sequencing involves determining an individual's entire genetic code—including the approximately 1% of DNA that codes for proteins (known as genes) and the remaining 99% of DNA that is 'non-coding' and plays important regulatory roles.

“Most current methods for genetic analysis are limited in scope. Without sequencing the whole genome, genetic studies often miss mutations that cause disease,” explains Dr. Andrade. “We set out to address this issue by looking at the entire genomes of patients for whom the latest generation genetic testing has failed.”

The researchers analysed the genomes of 28 adult epilepsy patients recruited from the Adult Epilepsy Genetics Program at Toronto Western Hospital. They examined multiple types of genetic variants, including changes in single DNA base pairs, short sequence repeats and changes in the number of copies of genes.

In nearly a third of the patients included in the study, the researchers identified genetic variants that were either known or very likely to cause disease.

“Our study demonstrates that whole genome sequencing is a powerful tool that can help us connect the dots between an individual’s genetics and unexplained epilepsies,” says Dr. Andrade.

The team also identified certain genetic features in two patients with a rare form of epilepsy called Lenox Gastaut Syndrome. Specifically, they found abnormal repetitions of DNA sequences in the non-coding regions their genomes—suggesting that they could be linked to the disease. This is the first report of this type of genetic variant in individuals with this disease, highlighting the importance of analysing the whole genome when studying the genetic basis of epilepsy.

“By uncovering the genetic basis of these severe cases of epilepsy, this work moves us closer to developing better diagnostic tests and personalized therapeutics to improve the lives of our patients.”

This work was supported by the McLaughlin Foundation, the Ontario Brain Institute, the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada and the UHN Foundation. Yuen RKC is a SickKids Catalyst Scholar in Genetics and an Azrieli Future Leader in Canadian Brain Research. Pearson CE holds a Tier 1 Canada Research Chair in Disease-Associated Genome Instability at the University of Toronto.

Qaiser F, Sadoway T, Yin Y, Ali QZ, Nguyen CM, Shum N, Backstrom I, Marques PT, Tabarestani S, Munhoz RP, Krings T, Pearson CE, Yuen RKC, Andrade DM. Genome sequencing identifies rare tandem repeat expansions and copy number variants in Lennox-Gastaut Syndrome. Brain Comms. 2021 Sep 14. doi: 10.1093/braincomms/fcab207.

Dr. Danielle Andrade is a Clinician Investigator at the Krembil Brain Institute and Director of UHN's Epilepsy Genetics Research Program.