The Krembil

November 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 exciting news and innovative research happening at the Krembil Research Institute.

Stories in this month's issue:

Jaideep Bains, PhD
Director, Krembil Research Institute
University Health Network

News

Celebrating Arthritis Research

Researchers from around the world share arthritis discoveries and clinical innovations.

On October 13–14, UHN's Schroeder Arthritis Institute hosted the inaugural *International Conference on Arthritis: Convergence of Care, Education & Research*.

The free virtual event was broadcasted live worldwide and showcased cutting-edge research and innovations in clinical care for bone, joint, spine and autoimmune rheumatic diseases. The event brought together over 800 participants from around the world, including scientists, clinicians, patient partners and members of the public.

Attendees heard from 34 speakers including researchers, clinicians and educators with expertise in arthritis and related diseases. They also heard from patient partners who gave inspirational talks about their experiences living with arthritis.

The conference covered a wide range of topics and featured four keynote talks:

- The Burden of Musculoskeletal Disease on Society; Dr. Jasvinder Singh, University of Alabama

- Patient Phenotyping in Osteoarthritis: Data Driven Precision Medicine; Dr. David Hunter, The University of Sydney
- Molecular Phenotyping in Lupus; Dr. Virginia Pascual, Weill Cornell Medical College
- Multi-omic system based approach in Arthritis; Dr. Timothy Radstake, AbbVie

Missed the conference? Click here to access session recordings and information about the speakers.

“Arthritis is a global challenge that calls for a global response,” says Dr. Robert Inman, Co-Chair of the conference and Co-Director of the Schroeder Arthritis Institute.

“The event brought together speakers and attendees from across Canada and abroad, including the USA, Europe, Australia and Asia, and has set the bar for future conferences of its kind,” adds Dr. Mohit Kapoor, Co-Chair of the conference and Co-Director of the Schroeder Arthritis Institute.

The International Conference on Arthritis was hosted by the Schroeder Arthritis Institute, in partnership with Arthritis Society Canada, the Canadian Institutes of Health Research-Institute of Musculoskeletal Health and Arthritis, and the Departments of Surgery and Medicine at the University of Toronto, and was supported by the UHN Foundation.

Seeds of Science

Tune in to UHN's newest podcast—led by trainees for trainees.

UHN's Seeds of Science podcast is hosted by postdoctoral fellow Emily Mills and PhD student Rima El-Sayed at the Krembil Brain Institute.

UHN has over 1,300 research trainees—each with a different background, perspective and story to share.

Launched October 20, 2022, *Seeds of Science* is a trainee-led podcast that showcases how today's junior researchers are growing in their scientific careers.

Season one features six one-on-one interviews with UHN graduate students and postdoctoral fellows. The interviews are hosted by Dr. Emily Mills and Rima El-Sayed, who are trainees in the lab of Dr. Karen Davis at the Krembil Brain Institute.

Each episode delves into what it is like to be a budding scientist at Canada's top research hospital, while exploring each trainee's goals and achievements, their journeys in research so far, and their strategies for overcoming challenges in and outside the lab.

Click on the following link to listen and subscribe to season one:
https://seedsofscience.buzzsprout.com

"Trainees are an indispensable part of any research institution and we want to give them a platform to share and learn from one another," says Dr. Mills. "Not only are we

highlighting students' and fellows' incredible research, but also the more personal aspects of their journeys in science—their passions, the challenges that they face and what motivates them to keep going."

"Interviewing these exceptional trainees and hearing their unique perspectives on research and life at UHN has been an incredible experience," adds El-Sayed. "We are so thrilled to be able to put a spotlight on these young scientists and the exciting work that they do."

Seeds of Science episodes will air every other Thursday on Spotify, Apple Podcasts and Buzzsprout.

For more information about *Seeds of Science*, visit the Office of Research Trainees website.

Research

More than Supporting Cells

Study reveals that astrocytes, a type of non-neuronal brain cell, may play a role in cognition.

(L-R) Dr. Maurizio De Pittà, a Scientist at the Krembil Brain Institute, and Dr. Nicolas Brunel, a Distinguished Professor in Neuroscience at Duke University.

Scientists from the Krembil Brain Institute and Duke University have developed the first computational model of the role of glial cells in cognition. Their model reveals that interactions between neurons and glial cells may mediate working memory—the short-term storage of information that enables us to carry out tasks and make decisions without losing track of what we are doing.

Glial cells are abundant in the brain and play several important roles—from physically supporting neurons to transporting nutrients and removing waste. Scientists have recently discovered that a particular type of glial cell, known as an astrocyte, also interacts with and changes the activity of nearby neurons.

This study, published in *Proceedings of the National Academy of Sciences*, has shed light on how astrocytes interact with neurons to store information in the form of working memory.

“Modelling how information is stored in the healthy brain is necessary to uncover the cellular and molecular changes that cause memory deficits,” says Dr. Maurizio De Pittà, a Scientist at the Krembil Brain Institute and the lead author of the study.

The cellular basis of working memory is still an area of active investigation, but it involves information processing through distinct patterns of neuron activity and changes in the strength of the connections between neurons—called synapses. It was previously believed that neuron-neuron interactions alone could account for these features, but the researchers discovered a necessary role for glia.

To investigate how neuron-glial interactions give rise to working memory, the researchers modelled the activity of neuron networks with and without astrocytes. Their model revealed that chemical signalling by astrocytes leads to rapid changes in synaptic strength.

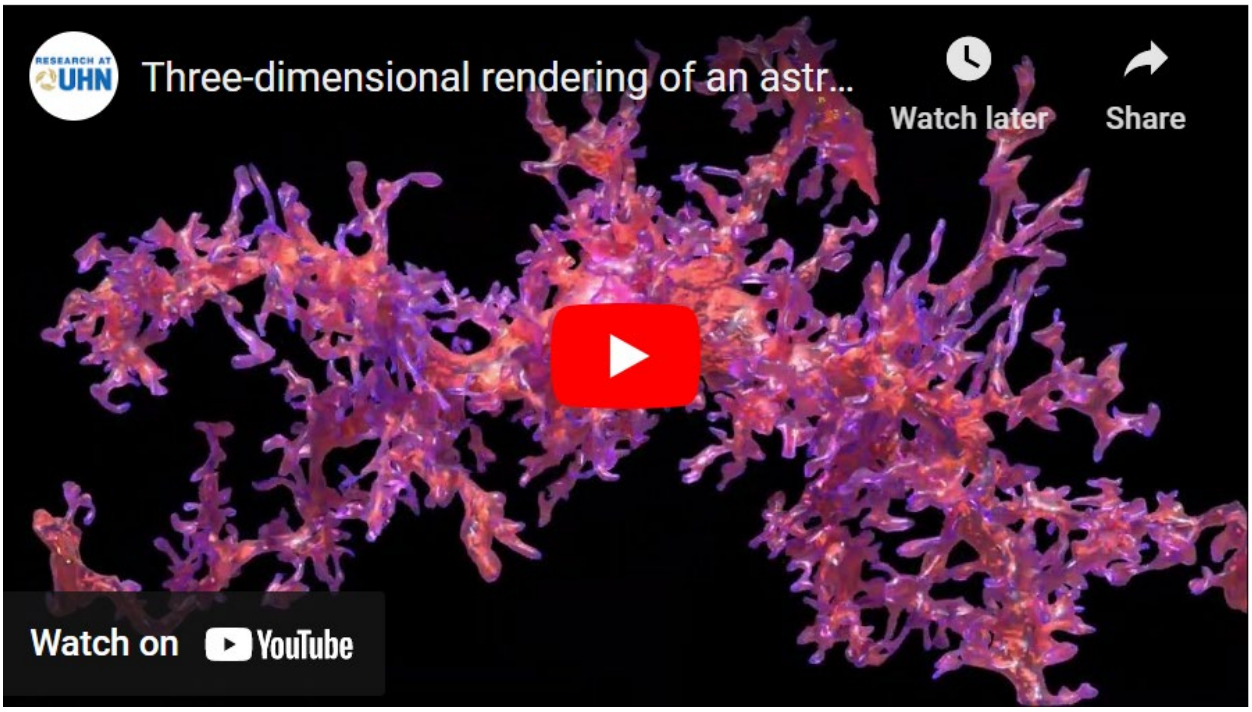
“By quickly increasing or decreasing synaptic strength, astrocytes modify neuronal activity patterns and cause subsets of neurons within a network to display different patterns at the same time,” explains Dr. De Pittà. “The co-existence of multiple activity patterns enables a single network to simultaneously encode different types of working memory.”

The researchers hope to eventually create a high-fidelity model—or ‘digital twin’—of the brain’s neuron-glia circuits. This model will help to identify markers of normal and abnormal neuron-glial interactions, which currently cannot be measured in the living human brain.

“Changes in working memory are often warning signs of major brain disorders, such as Alzheimer disease and Parkinson disease,” explains Dr. Brunel, a Professor at Duke University and the co-author of the study. “Our ultimate goal is to model neuron-glia circuits to figure out what is going wrong in these disorders and develop therapies that target glial signalling.”

This work was supported by the European Union Marie Skłodowska-Curie Actions. Dr. Maurizio De Pittà’s lab is supported by the Krembil Research Institute, the European Research Commission, the Krembil Foundation and the UHN Foundation. Dr. Maurizio De Pittà is an Assistant Professor in the Department of Physiology at the University of Toronto.

De Pittà M, Brunel N. Multiple forms of working memory emerge from synapse-astrocyte interactions in a neuron-glia network model. Proc Natl Acad Sci U S A. 2022 Oct 25. doi: 10.1073/pnas.2207912119.



A three-dimensional rendering of an astrocyte. Digital reconstruction made by Anaïs Lupu, a graduate student in Dr. De Pittà's lab, and inspired by data from Dr. Corrado Calì at the University of Turin, Italy (Calì et al., 2019, Progress in Neurobiology).

Treating Parkinson Disease

Study examines medication type and the time-to-development of disabling complications.

(L-R) Dr. Anthony Lang is a Senior Scientist at the Krembil Brain Institute and senior author of the study; Dr. Diana Olszewska was formerly a Movement Disorders Fellow at Toronto Western Hospital and the first author of the study.

A recent study led by Dr. Anthony Lang, a Senior Scientist at the Krembil Brain Institute, found that the development of severe motor complications associated with medications for Parkinson disease does not depend on the type of medication that a doctor initially prescribes.

Parkinson disease is a progressive brain disease marked by uncontrollable movements, such as shaking. The disease results from a loss of neurons that produce dopamine—an important chemical messenger in the brain.

Parkinson disease is typically treated with levodopa, a drug that is converted into dopamine in the brain. Although it is highly effective, this drug often causes motor complications of its own, particularly in younger individuals. For this reason, doctors often use a dopamine agonist—a drug that mimics dopamine activity in the brain but carries a lower risk of motor complications—as a first treatment for younger patients, before prescribing levodopa.

Despite dopamine agonists' lower risks of motor complications for younger individuals, these drugs have important behavioural side effects and it is unclear whether initial treatment with a dopamine agonist meaningfully delays the disabling motor complications caused by levodopa.

To address this gap in knowledge, the research team examined patients who underwent deep brain stimulation surgery at Toronto Western Hospital between 2004 and 2022. Deep brain stimulation is a surgical treatment for Parkinson disease that is typically recommended when drug-induced motor complications become a source of disability.

Of the 438 patients examined, 312 were first treated with levodopa and 126 first received a dopamine agonist. Across groups, half of the patients had lived with Parkinson disease for ten years or more before they underwent deep brain stimulation for disabling motor complications.

The team found no association between the type of medication first used and the time it took for individuals to develop disabling motor complications.

"This is the only study to date to examine the link between the particular Parkinson disease medication first used to treat the disease and the time to development of serious motor complications that warrant surgery," says Dr. Lang.

"These results are important because there are still practitioners who initiate dopamine agonists first, especially putting younger patients at risk of neuropsychiatric side effects, with the incorrect belief that they are delaying the need for deep brain stimulation surgery in the long run."

Dr. Diana Olszewska, a former Movement Disorders Fellow at Toronto Western Hospital and the first author of the study, says the findings reveal the need for more studies and novel treatments. "While more research is needed to determine how these drugs affect patients' quality of life before symptoms worsen, it is clear that there is a real need for new therapies that carry lower risks of complications."

This work was supported by the UHN Foundation. Dr. Anthony Lang is a Professor of Medicine at the University of Toronto.

Olszewska DA, Fasano A, Munhoz RP, Gomez CCR, Lang [no-lexicon]AE[/no-lexicon]. Initiating dopamine agonists rather than levodopa in early Parkinson's disease does not delay the need for deep brain stimulation. Eur J Neurol. 2022 Sep 3. doi: 10.1111/ene.15539.

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 Joint Discovery

Researchers reveal a mechanism for osteoarthritis in an overlooked portion of the joints.

PhD graduate Dr. Ghazaleh Tavallaee (left) and Scientific Associate Dr. Starlee Lively (right) are co-first authors of the study.

A research team led by Dr. Mohit Kapoor, Co-Director and a Senior Scientist at the Schroeder Arthritis Institute, has uncovered a new biological mechanism underlying osteoarthritis, an often painful and disabling form of joint deterioration.

The new findings focus on the synovium, the specialized connective tissue that surrounds and lubricates freely movable joints, such as the knee. As osteoarthritis progresses, this tissue becomes inflamed and thickened, contributing to joint stiffness and pain.

“Most of the research into osteoarthritis has focused on what is going on in the joint cartilage and bone. Changes to the synovium have been traditionally thought of as secondary effects,” says Dr. Kapoor. “We now know that the synovium is actively involved in osteoarthritis, but we still do not know exactly how.”

Dr. Kapoor’s lab previously discovered that a particular microRNA—a molecule that regulates the production of proteins from genes—is elevated in the synovial fluid of patients with knee osteoarthritis. This finding spurred the team to investigate whether this microRNA—*miR-27b-3p*—affects disease progression.

Using lab models of osteoarthritis and samples of knee synovia from patients with varying degrees of disease severity, the researchers discovered that elevated levels of *miR-27b-3p* coincide with more severe changes in the synovium, such as a build-up of collagen—a structural protein that makes up connective tissues.

Next, the research team showed that they could control the production of collagen and other key structural proteins by manipulating the levels of *miR-27b-3p* in experimental models. By doing this, they could even induce an osteoarthritis-like state in healthy synovial tissue.

To explore how the microRNA affects joints, the team searched for the genetic targets of *miR-27b-3p*. They found that numerous genes are under the molecule's influence, including some key genes that are most closely associated with collagen regulation and osteoarthritis.

In particular, they discovered that *miR-27b-3p* consistently affects one gene that leads to the production of proteins that make up the scaffolding outside cells (i.e., the extracellular matrix). They also identified a way to counter this effect: a drug called rosiglitazone reduces the ability of the microRNA to regulate this gene.

"This study shines a light on a less appreciated part of the joint—the synovium—and shows how microRNA can affect collagen production in the synovium and even drive progression of this debilitating form of arthritis," says Dr. Ghazaleh Tavallaee, co-lead author of the study and a PhD graduate of Dr. Kapoor's lab.

"We have also uncovered mechanisms that could lead to new treatment approaches, ones that may be able to prevent the build-up of extracellular materials that thicken and stiffen joints in osteoarthritis," adds the second co-lead author, Dr. Starlee Lively, a Scientific Associate in Dr. Kapoor's lab.

This work was supported by the Natural Sciences and Engineering Research Council of Canada, the Canadian Institutes of Health Research, the Canada Foundation for Innovation, the Ontario Research Fund, Arthritis Society Canada, IBM, the Ian Lawson van Toch Fund, the Krembil Research Institute, the Schroeder Arthritis Institute and the UHN Foundation. Dr. Mohit Kapoor is a Professor in the Departments of Surgery and Laboratory Medicine & Pathobiology at the University of Toronto, and a Tier 1 Canada Research Chair in Mechanisms of Joint Degeneration.

Tavallaee G#, Lively S#, Rockel JS, Ali SA, Im M, Sarda C, Mitchell GM, Rossomacha E, Nakamura S, Potla P, Gabrial S, Matelski J, Ratneswaran A, Perry K, Hinz B, Gandhi R, Jurisica I, Kapoor M. Contribution of microRNA-27b-3p to synovial fibrotic responses in knee osteoarthritis. Arthritis Rheumatol. 2022 Jul 6. doi: 10.1002/art.42285. #These authors contributed equally.

Osteoarthritis, which affects nearly 14% of Canadians, is the most common form of arthritis and is a leading cause of disability.

Moving the Needle

CRISPR gene editing shows potential to treat familial Alzheimer disease in human cells.

(L-R) Drs. Evangelos Konstantinidis, a recent PhD graduate at Uppsala University in Sweden, and Martin Ingelsson, a Senior Scientist at the Krembil Brain Institute and a Visiting Professor in the Department of Public Health and Caring Sciences at Uppsala University.

Researchers led by Krembil Brain Institute Senior Scientist Dr. Martin Ingelsson have used CRISPR-Cas9 to tackle a gene mutation that causes early-onset Alzheimer disease.

Alzheimer disease is a progressive brain disorder and the leading cause of dementia worldwide. Despite decades of efforts to develop a cure, most available drugs only treat symptoms and do nothing to stop disease progression.

Genomic studies have revealed that early-onset, familial forms of the disease result from changes in numerous genes, including *presenilin 1* (*PSEN1*). This gene and its corresponding protein, PS1, are involved in the production of amyloid beta (Aβ), which builds up and forms amyloid plaques in the brains of people with Alzheimer disease.

Evangelos Konstantinidis, a recent PhD graduate at Uppsala University and the first author of the study, describes PS1 as part of the molecular scissors that produce Aβ from its precursor protein, resulting in Aβ aggregation into plaques. “The precursor

protein can get cut in different spots, forming molecules of different sizes. Gene mutations that alter the structure of PS1 can increase the production of a larger and more aggregation-prone form of Aβ—called Aβ42 for its 42 amino acids, compared to the more prevalent Aβ40."

The research team used the gene editing technology CRISPR-Cas9 to disrupt a particular mutation in the *PSEN1* gene. They did this in fibroblasts—the cells that make up human skin and connective tissue.

Although Alzheimer disease is a condition of the brain, the hallmark increase in Aβ42 levels is present in cells throughout the body of people who carry this mutation. The team tested their gene editing approach in the laboratory, using cells from six people with the mutation, as well as two healthy family members and two healthy unrelated people.

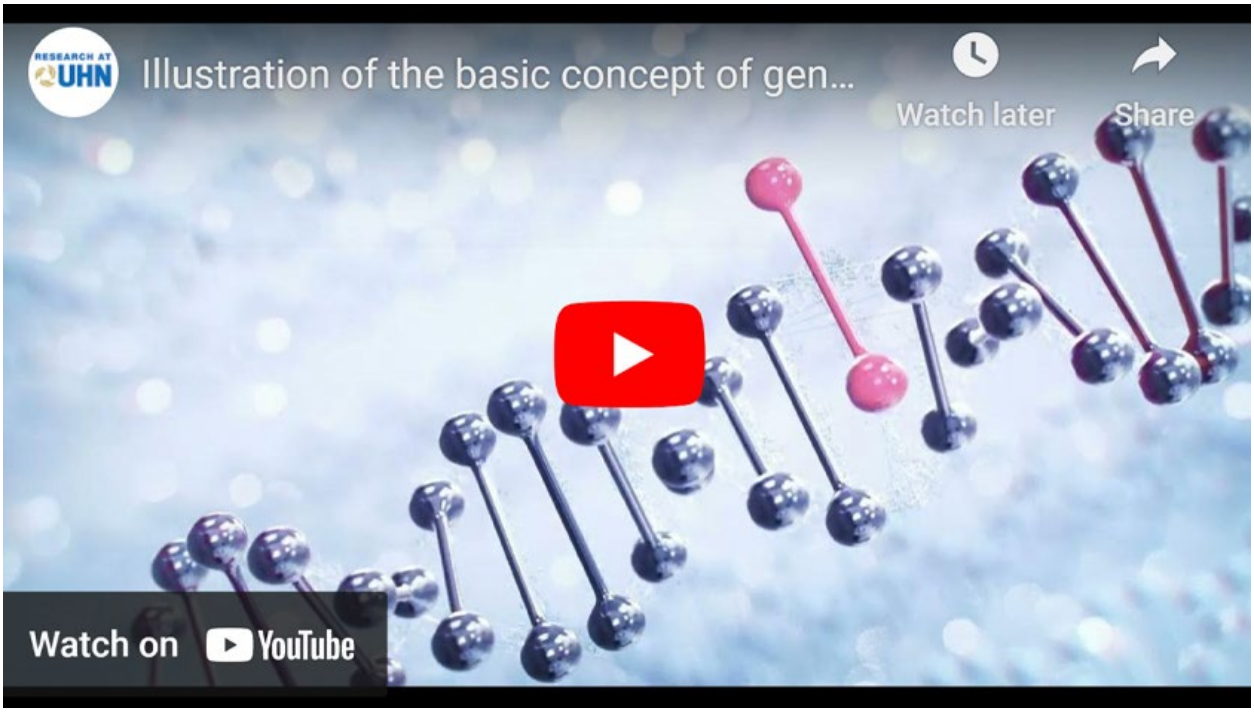
The gene editing led to a reduction in Aβ42 and partially restored the normal Aβ42/40 ratio. It did this by correcting the shape of the abnormal PS1 protein and lowering its levels.

Importantly, the team did not detect any off-target effects of the gene editing.

"Because we are using molecular tools to identify and delete a specific disease-causing gene sequence, it is possible that we might disrupt similar sequences elsewhere in the DNA," cautions Dr. Ingelsson. "We examined ten sequences that were most likely to be disrupted, and we saw no changes. This tells us that our approach does a good job of distinguishing between sequences, and it could eventually be a safe and effective treatment for people with this mutation."

This work was supported by the Swedish Research Council, the Swedish Alzheimer Foundation, the Swedish Brain Foundation, the Åhlén Foundation, the Gamla Tjänarinnor Foundation, the Gun and Bertil Stohne's Foundation, the German Research Foundation, Massachusetts General Hospital, the National Institutes of Health and the UHN Foundation. Dr. Martin Ingelsson is a Scientist at the Tanz Centre for Research in Neurodegenerative Diseases at the University of Toronto.

Konstantinidis E, Molisak A, Perrin F, Streubel-Gallasch L, Fayad S, Kim DY, Petri K, Aryee MJ, Aguilar X, György B, Giedraitis V, Joung JK, Pattanayak V, Essand M, Erlandsson A, Berezovska O, Ingelsson M. CRISPR-Cas9 treatment partially restores amyloid-β 42/40 in human fibroblasts with the Alzheimer's disease PSEN1 M146L mutation. Mol Ther Nucleic Acids. 2022 Mar 28. doi: 10.1016/j.omtn.2022.03.022.



CRISPR-Cas9 gene editing works by precisely cutting DNA at a target location—typically a disease-causing gene sequence—and letting the cell's natural DNA repair machinery fix the damage.