# The Krembil

November 2020

*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:




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# News

# Unifying Research, Education & Care

***Generous $25 million donation enables creation of the Schroeder Arthritis Institute.***


*Krembil Senior Scientists (L-R) Drs. Mohit Kapoor and Robert Inman are Co-Directors of the Schroeder Arthritis Institute. (Photo by Tim Fraser)*

One in five Canadian adults is currently living with arthritis, a disease-causing inflammation of the joints, which can result in chronic, debilitating pain, reduced mobility and premature disability. Arthritis is the leading cause of disability globally.

To address this growing crisis, the **Schroeder Arthritis Institute** (link is external), launched with a **$25 million donation by philanthropists Walter and Maria Schroeder**, will help UHN's arthritis program become a world-class hub for innovation in research, education and patient care.

Krembil Senior Scientists Dr. Robert Inman and Dr. Mohit Kapoor serve as Co-Directors of the Institute. Dr. Inman is a leader in field of ankylosing spondylitis and Dr. Kapoor's research program is focused on advancing our understanding of osteoarthritis.

"Maria and I have put a great deal of thought into making this gift and ultimately we were persuaded by the vision and leadership of Dr. Kapoor and the arthritis team at

UHN," says Mr. Schroeder. "We want to be part of an effort that will finally put an end to unnecessary pain and suffering from arthritis and related conditions."

Funds will go toward supporting top scientific talent and providing critical salary and infrastructure resources for the entire research team, which includes 51 scientists and clinician-scientists, 113 trainees and 200 staff.

The Institute will encompass research, education and innovations in clinical activities within four clinical programs: Hand, Orthopedics, Osteoporosis and Rheumatology, with the core goal of pushing the boundaries of discovery, learning and patient care.

The Institute builds on the momentum of the arthritis team's progress in recent years, including innovations in surgical approaches for bone and joint diseases; new diagnostics and treatments in ankylosing spondylitis, lupus, osteoarthritis, osteoporosis, psoriatic arthritis, scleroderma and Sjogren's syndrome; as well as the development of predictive tools for orthopaedic surgery outcomes. This donation will extend these achievements by enabling the arthritis team to have global impact through the development of early diagnosis, innovative treatments and prevention.

"Our unique approach, creating alignment and synergy between our research and clinical teams, can only serve to help translate discoveries faster, and benefit patients sooner," says Dr. Brad Wouters, Executive VP, Science & Research, at UHN. "This gift will help solidify UHN's status as the largest research hospital in Canada and as a leader in arthritis research and clinical care, globally."

To read more, click here (link is external).

*Walter and Maria Schroeder's generous $25 million donation will help UHN's arthritis program become a world-class hub for innovation in research, education and patient care. (Photo by Cavouk)*

# Immunologist Joins the Krembil Team

***New scientist, Dr. Olga Lucia Rojas, studies the link between the gut and neuroinflammation.***

Krembil Research Institute welcomes its newest Scientist, Dr. Olga Lucia Rojas. As an immunologist, her focus is on understanding the role of intestinal immune cells in neuroinflammation and neurodegenerative disorders such as Alzheimer disease and multiple sclerosis (MS).

Recent research led by Dr. Rojas, published in *Cell* (link is external), uncovered the cellular mechanism behind the body's response to inflammation in autoimmune conditions. The findings revealed that a type of white blood cell, known as a plasma cell, in the gut can produce an antibody called Immunoglobulin A (IgA) that is key to fighting infection. These IgA-producing plasma cells can travel from the intestines to the central nervous system where they are found to supress brain inflammation during MS flare-ups.

Dr. Rojas is also working with a research team to understand the immune response to SARS-CoV-2. Their recent publication (link is external) showed that SARS-CoV-2 antibodies can be detected in saliva, suggesting the generation of a local immune response against SARS-CoV-2 in the oral cavity after infection. With ongoing collaborations, Dr. Rojas hopes to explore the impact of SARS-CoV-2 infection on neurodegenerative disorders as well.

"Every idea and experiment that we create is a challenge brimming with unanswered questions. I am motivated by my colleagues, students and patients to continue this

important research with the aim of improving disease outcomes and quality of life for so many," says Dr. Rojas.

At Krembil, Dr. Rojas will focus on understanding the role of gut bacteria in the production of IgA-producing plasma cells and the mechanisms by which gut-derived immune cells can impact the development and progression of neurodegenerative disorders. Her research has significant implications for new therapeutic approaches for disorders that currently have no cure, such as Parkinson disease.

"My ultimate research goal is to benefit patients," says Dr. Rojas. "At Krembil, I will be able to collaborate closely with clinicians, scientists and patients. This unique environment makes it the best place to translate basic research from the lab to a clinical setting."

Dr. Rojas received her MD and PhD from the Pontificia Universidad Javeriana in Colombia before completing a postdoctoral fellowship in Jennifer Gommerman's lab in the Department of Immunology at the University of Toronto.

Research

# Having it Both Ways

***Krembil researchers validate new, highly specific & sensitive criteria for classifying lupus.***

*The new criteria for classifying whether a patient has lupus have been endorsed by the European League Against Rheumatism and the American College of Rheumatology.*

Clinical researchers rely on robust selection criteria when identifying patient groups for their research studies. In recent years, Dr. Sindhu Johnson, a Clinician Scientist at Krembil Research Institute, has been jointly leading a global collaboration to develop new, more effective criteria to identify individuals with lupus (also known as systemic lupus erythematosus).

Lupus is an autoimmune disease in which the immune system attacks the body's healthy tissues and organs, causing pain and damage. "The disease can develop and present itself in many ways," says Dr. Johnson. "This makes it difficult to grasp and define."

In 2019, Dr. Johnson's team, which spanned continents and included fellow Krembil researchers Drs. Dafna Gladman, Jorge Sanchez-Guerrero, Murray Urowitz and Zahi Touma, published their new criteria (link is external). The researchers carefully weighed results from lab tests for antibodies and proteins along with other clinical factors, such as the occurrence of fevers or seizures, to devise their classification system.

While the new criteria were proven successful for a general population, the research community still needed to know how they fared for specific patient groups. For instance, would the criteria work equally well for males and females?

Dr. Johnson's team then sought to validate the criteria against sex, ethnicity and disease stage and have now published their results.

The team evaluated the new criteria for sensitivity—correctly identifying patients *with* lupus—and specificity—correctly identifying patients *without* lupus. The criteria performed exceptionally well across all patient groups, with both quantities ranging from 89 to 100%.

This combination of excellent sensitivity and specificity is a leap forward because previous criteria have been only top-performing in one measure. For instance, criteria published in 2012 by the Systemic Lupus International Collaborating Clinics Group offered a sensitivity of 83% and a specificity of 93% for women, whereas Dr. Johnson's criteria achieved 97% and 94%.

A key finding from the validation study was that the criteria were robust for patients with early disease. This will enable the more timely inclusion of patients in clinical trials and observational studies.

*This work was supported by the European League Against Rheumatism; the American College of Rheumatology; the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health; and Toronto General & Western Hospital Foundation.*

*Johnson SR, Brinks R, Costenbader KH, Daikh D, Mosca M, Ramsey-Goldman R, Smolen JS, Wofsy D, Boumpas DT, Kamen DL, Jayne D, Cervera R, Costedoat-Chalumeau N, Diamond B, Gladman DD, Hahn B, Hiepe F, Jacobsen S, Khanna D, Lerstrøm K, Massarotti E, McCune J, Ruiz-Irastorza G, Sanchez-Guerrero J, Schneider M, Urowitz M, Bertsias G, Hoyer BF, Leuchten N, Tani C, Tedeschi SK, Touma Z, Schmajuk G, Anic B, Assan F, Chan TM, Clarke AE, Crow MK, Czirják L, Doria A, Graninger WB, Halda-Kiss B, Hasni S, Izmirly PM, Jung M, Kumánovics G, Mariette X, Padjen I, Pego-Reigosa JM, Romero-Diaz J, Rúa-Figueroa Í, Seror R, Stummvoll GH, Tanaka Y, Tektonidou MG, Vasconcelos C, Vital EM, Wallace DJ, Yavuz S, Meroni PL, Fritzler MJ, Naden R, Dörner T, Aringer M. Performance of the 2019 EULAR/ACR classification criteria for systemic lupus erythematosus in early disease, across sexes and ethnicities (link is external). Ann Rheum Dis. 2020 Oct. doi: 10.1136/annrheumdis-2020-217162.*


*The international collaboration jointly led by Dr. Sindhu Johnson spanned 21 centres with expertise in lupus across 16 countries, including Mexico, Japan, Croatia, Turkey and Canada.*

# A Case for Research

***Study proposes research roadmap to improve knowledge of spontaneous hydrocephalus in adults.***

*Normal Pressure Hydrocephalus causes difficulty walking, loss of bladder control and cognitive impairments and is often mistaken for Alzheimer disease or Parkinson disease.*

The brain is bathed in a protective fluid called cerebrospinal fluid. In a condition known as hydrocephalus, the fluid fails to drain properly from cavities in the brain called ventricles and puts pressure on the surrounding tissue.

The type of hydrocephalus that is most commonly seen in adults—normal pressure hydrocephalus—can be caused by an infection, tumour or head trauma. However, the condition is often deemed idiopathic, which means that the cause of the fluid accumulation is unknown.

To shed light on this elusive form of hydrocephalus, a research team led by Krembil Clinical Investigator Dr. Alfonso Fasano highlighted the current knowledge gaps in diagnosis and treatment, and proposed a research roadmap to address them.

“There are currently no standardized diagnostic criteria for normal pressure hydrocephalus and it often goes misdiagnosed because the symptoms can be similar to neurodegenerative conditions such as Parkinson disease,” explains Dr. Fasano. “We must take a research-oriented approach to defining diagnostic guidelines and understanding treatment outcomes.”

The researchers highlighted the actions needed to advance our understanding of the condition, which are listed below:

● Develop unified international diagnostic criteria

● Conduct population-based studies to reveal how the disease develops and progresses in a variety of individuals

● Build international biobanks where samples from diverse patient populations can be stored and shared

The roadmap also emphasizes the need for better ways to assess how normal pressure hydrocephalus is treated. Currently, the condition is treated through shunting—a procedure in which a small tube is inserted into the brain to drain excess fluid. A key problem is that the test used to decide whether shunting should be used is unreliable. To address this, the roadmap calls for rigorous clinical trials (ie, randomized controlled trials) that involve a variety of different patients. These trials will help to reveal more effective ways to decide which patients should receive the procedure.

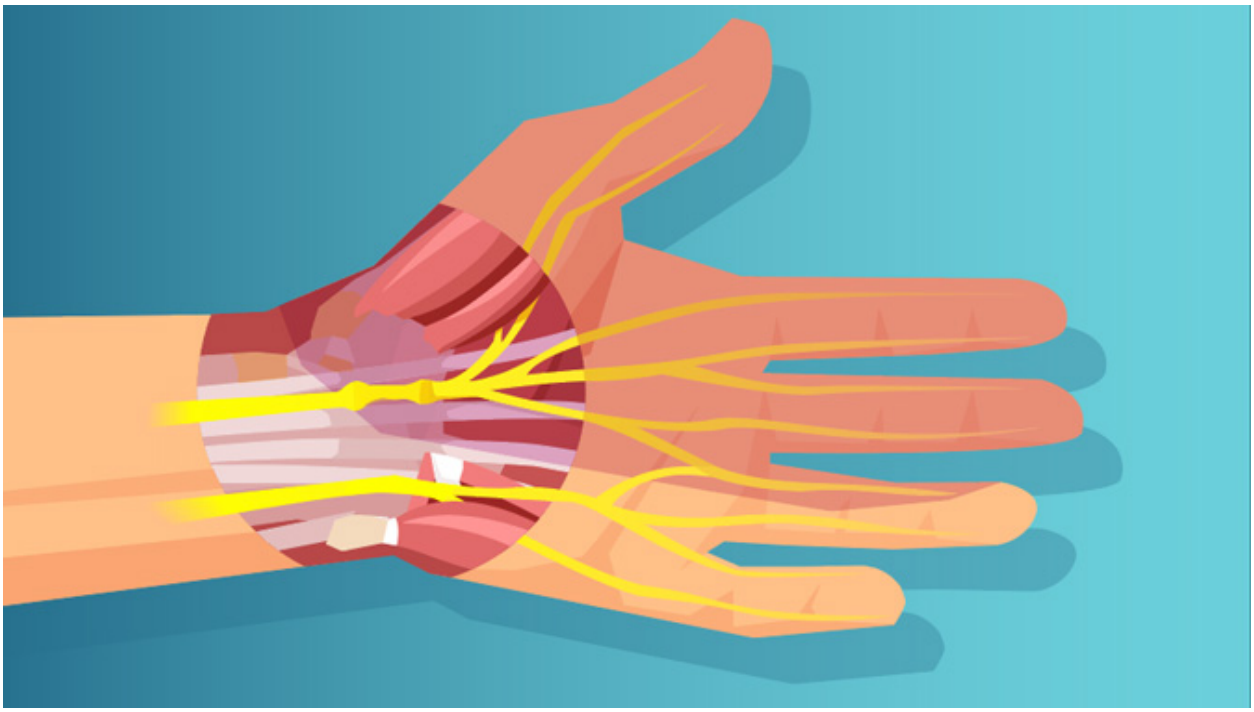
“In order to better treat those affected by this disorder, we need a stronger understanding of the underlying factors,” says Dr. Fasano. “A unified approach is the best way forward. By working together, the research community is uncovering the molecular and biological mechanisms at play so we can improve the quality of life for patients living with this condition.”

*Fasano A, Espay AJ, Tang-Wai DF, Wikkelsö C, Krauss JK. Gaps, Controversies, and Proposed Roadmap for Research in Normal Pressure Hydrocephalus* (link is external) *[published online ahead of print, 2020 Sep 22]. Mov Disord. 2020;10.1002/mds.28251. doi:10.1002/mds.28251*

Lead author, Dr. Alfonso Fasano, is a Clinical Investigator at Krembil and Professor of Neurology at the University of Toronto.

# Well in Hand

***Study explores how the brain restores hand function after a hand transplant.***



*Many steps are involved in hand transplant surgery, including the attachment of bones, nerves, arteries, veins and tendons.*

Many steps are involved in hand transplant surgery, including the attachment of bones, nerves, arteries, veins and tendons.

Hand transplantation is very rare because the procedure is highly complex. The first hand transplant surgery in Canada (link is external) was performed in 2016 at the Toronto Western Hospital; it involved 18 surgeons and took around 14 hours to complete.

A research team at Krembil Research Institute had the opportunity to follow the patient's recovery journey after hand transplant surgery. The individual had a forearm and hand amputation ten years prior to receiving the transplant at UHN.

The findings were recently published in the journal *Neurology* by Krembil Senior Scientist Dr. Robert Chen and Clinician Investigator Dr. Steven McCabe. The exploratory study reveals that the brain changes and networks are rewired as the recipient gains function in the transplanted hand.

"The brain is remarkably flexible. By around a month after surgery, the recipient began to feel sensations from the transplant and could move the transplanted hand. By around half a year to one year, the recipient was able to use the hand to perform a variety of daily tasks," says Dr. McCabe.

The brain's outer layer of neural tissue—the cerebral cortex—is mapped to different parts of our body. These connections help to coordinate body movement and the sense of touch. To explore these connections after the transplant, the team used non-invasive diagnostic methods, including functional magnetic resonance imaging and transcranial magnetic stimulation, to determine how the brain-body map shifts and changes after surgery and during rehabilitation.

"We did not observe changes in the mapping of the cerebral cortex to the arm that did not receive surgery," says Dr. Chen. "Interestingly, the area of the cerebral cortex that is mapped to the arm that received surgery shifted to adapt to the transplanted hand, and this adaptation began before the recovery of hand function."

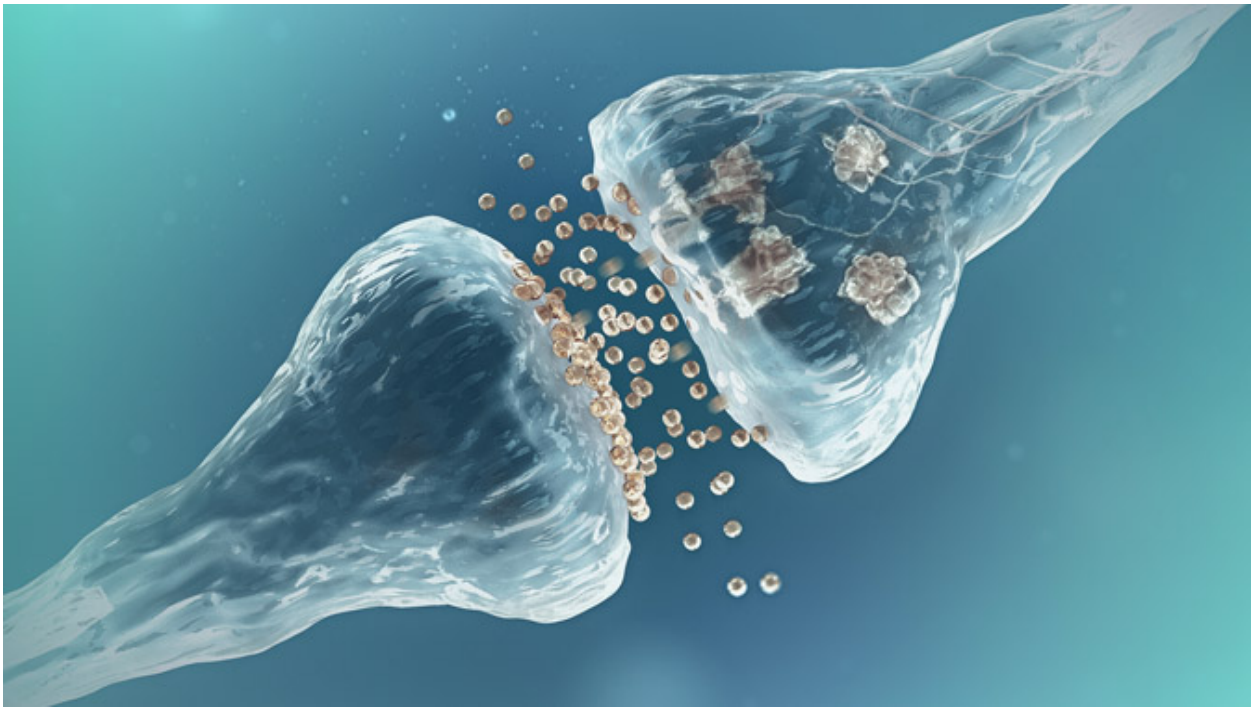
These observations suggest that the adaptions in the cerebral cortex shortly after surgery may be key to a successful recovery and the restoration of hand function after transplantation surgery.

*This work was supported by the Canadian Institutes of Health Research and the Toronto General & Western Hospital Foundation.*

*Ni Z, McCabe S, Novak C, Baltzer HL, Jegatheeswaran G, Isayama R, Vesia M, Gunraj C, Saha U, Hallett M, Chen R. Plastic changes in the brain after human hand allotransplantation (link is external). Neurology. 2020 Sep 22. doi: 10.1212/WNL.0000000000010583.*

# The Importance of Being Open

***Study implicates syntaxin as a gatekeeper of information in the brain and spinal cord.***



*Electric nerve impulses are passed from neurons to other cells through the release of neurotransmitters across a narrow gap between the cells called a synapse (pictured).*

Researchers at the Krembil Research Institute have revealed that a protein—known as syntaxin—could hold the key for new therapies for a variety of neurological disorders.

The study was led by Krembil Senior Scientist Dr. Shuzo Sugita and was recently published in *Nature Communications* (link is external).

Syntaxin plays a key role in how neurons—specialized cells in the brain and nervous system—transmit information throughout the body. Neurons communicate with other cells at narrow gaps known as synapses, where neurotransmitters are released. These neurotransmitters serve to 'bridge the gap' between the cells by passing on the signal.

The release of neurotransmitters is key to the process known as synaptic transmission, which enables the flow of electrical information between the brain, spinal cord and body.

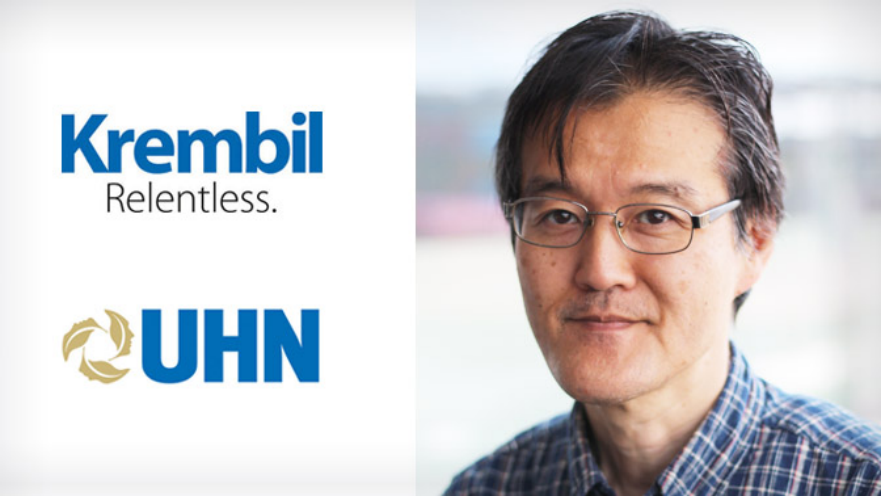
At the molecular level, syntaxin serves as a switch and changes shape from a 'closed' to an 'open' state. Once in the 'open' state, syntaxin acts in concert with other proteins to enable the release of the neurotransmitters. When syntaxin or other proteins involved in this process are defective, certain neurological disorders can arise.

“Using an experimental model, we introduced a version of syntaxin that was locked in the ‘open’ state. This version of syntaxin was able to overcome losses in proteins that are implicated in a wide spectrum of childhood epilepsy and autism spectrum disorders,” says Dr. Sugita.

These findings position syntaxin as a key player in synaptic transmission, and suggest that drugs, and other small molecules, could be developed to push syntaxin to the ‘open’ state as part of a strategy to treat certain neurological diseases.

*This work was supported by the Natural Sciences and Engineering Research Council of Canada, the Canadian Institutes of Health Research, The Welch Foundation, National Natural Science Foundation of China, the United States National Institute of Neurological Disorders and Stroke, the Dengfeng Initiative of the Global Talents Recruitment Program, and the Toronto General & Western Hospital Foundation.*

*Tien CW, Yu B, Huang M, Stepien KP, Sugita K, Xie X, Han L, Monnier PP, Zhen M, Rizo J, Gao S, Sugita S. Open syntaxin overcomes exocytosis defects of diverse mutants in C. elegans* (link is external)*. Nat Commun. 2020 Nov 2;11(1):5516. doi: 10.1038/s41467-020-19178-x.*




*The senior author of the study, Dr. Shuzo Sugita (pictured), is a Senior Scientist at UHN’s Krembil Research Institute.*