The Krembil

September 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.

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Donald Weaver, PhD, MD, FRCPC, FCAHS
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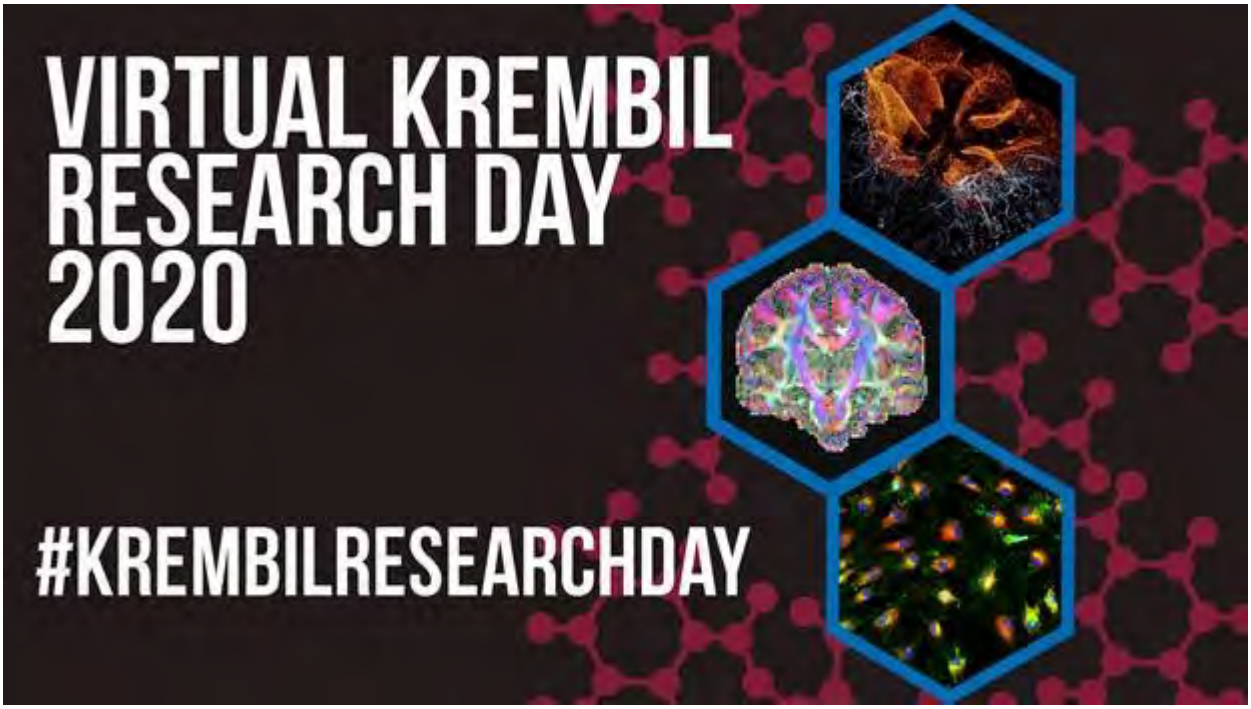
News

Virtual Krembil Research Day 2020

Krembil trainees are encouraged to persevere as scientists are needed now more than ever.



Krembil's annual Research Day was held a little differently this year. Investigators, trainees and staff pulled up a chair to celebrate the research achievements of their colleagues from the comfort of their home or office.

The event began with opening remarks from Dr. Brad Wouters, the Executive Vice President of Science and Research. "We are living through history right now and with all of you future scientists looking for answers, I know we are in good hands," Dr. Wouters stated.

Following these remarks, Krembil Director Dr. Donald Weaver delivered an inspiring message on the role of science today. "Science is a human activity that takes fear and transforms it into curiosity. And it is this curiosity that will lead to a cure."

During the rest of the event, Dr. Mary Pat McAndrews, Chair of the Trainee Affairs Committee, moderated three informative oral presentations addressing each of Krembil's three research pillars: brain and spine, bone and joint, and eye. Poster

presentations for this year were judged in advance of the live event but will remain viewable on the platform VoiceThread for a limited time here.

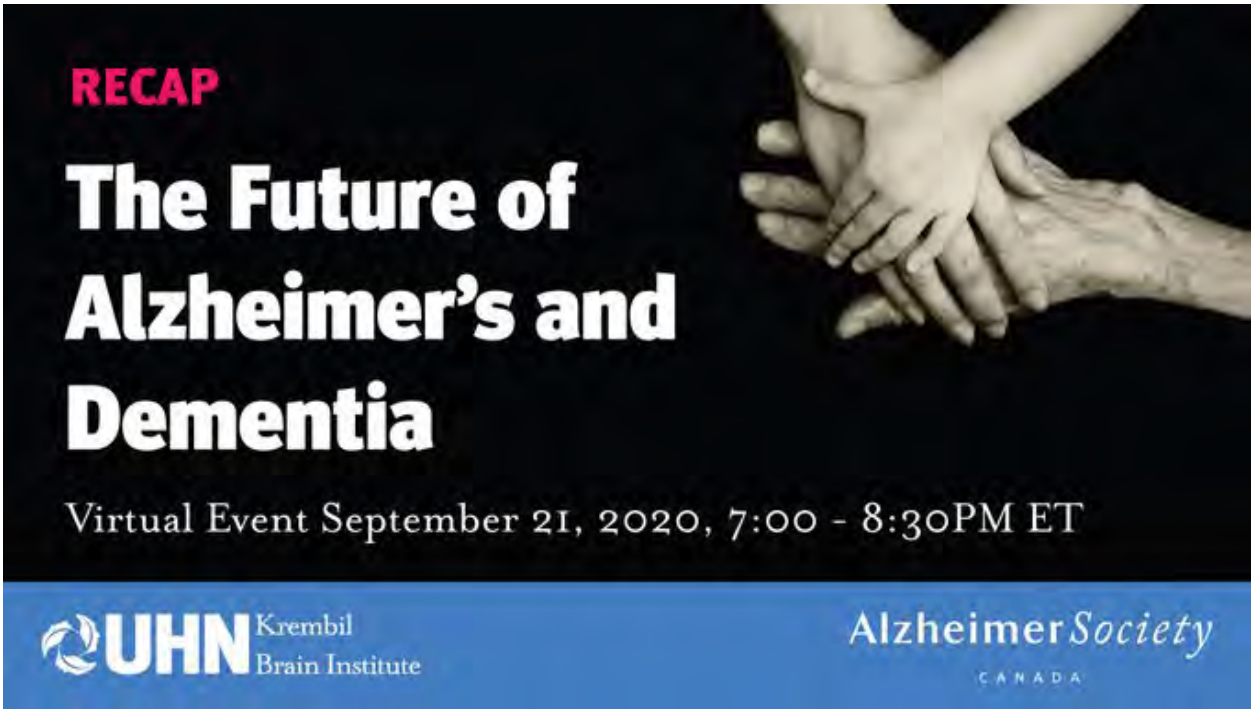
Prior to the award presentation, attendees were also treated to a video showcasing the rich history of research and mentorship at the former Toronto Western Research Institute and Krembil. Past trainees shared their unique experiences, some of their favourite memories and the most valuable lessons they learned along their journey.

Congratulations to the award winners and all of the presenters who participated in this year's Virtual Krembil Research Day!

You can view the full event recording here.

Coming Together for Dementia

Popular Krembil virtual event explored the future of dementia research and care.



On World Alzheimer's Day, Krembil Brain Institute, together with the Alzheimer Society of Canada, hosted a free, virtual event called *The Future of Alzheimer's and Dementia*. Over 300 viewers heard first-hand from those living with dementia and their loved ones, as well as from leading researchers and scientists.

More than 500,000 Canadians are living with dementia and Alzheimer disease. By 2031, that number is expected to rise to nearly one million Canadians. To help keep the spotlight on this urgent problem, the event was organized to bring together the broader community and to communicate the progress being made.

Following opening remarks from Dr. Kevin Smith, UHN's CEO and President, viewers learned about the lived experience of Leonard & Naome Howe—community members that are living with dementia. The Howe's shared their story and optimism for the future of dementia research. "I want to share my story because I want to help others and I believe that others can be helped," says Leonard Howe. "We'll get there."

Panelist Dr. Donald Weaver, neurologist and Co-Director of UHN's Krembil Brain Institute, echoed the need to help one another: "We have to work collectively if we are going to find the solutions that are required."

Award-winning science broadcaster and best-selling author Jay Ingram set the stage with a keynote address that explored his knowledge and perspectives on Alzheimer disease. Next began the panelist discussion, which highlighted the latest dementia

research advancements, prevention strategies, caregiver support, and the impacts that COVID-19 has had. Also, Dr. Saskia Sivananthan, Chief Research & KTE Officer with the Alzheimer Society of Canada, discussed the stigma surrounding dementia diagnoses and the benefits of dementia-friendly communities.

Notably, the event brought to light the importance of including people with lived experience in dementia research. Dr. Andrea Iaboni, Geriatric Psychiatrist and Clinician-Scientist at KITE Research Institute commented, “As researchers and doctors, we often have a deficit focus—we think about the problems and the symptoms. But what people living with dementia bring is a focus on problem-solving, strengths, adaptation and learning to thrive while living with dementia. Involving people [living with dementia] from very early stages is essential.”

Thank you to those that tuned in for the event and the panelists and speakers for providing critical insight into the future of dementia research and care, as well as highlighting our collective responsibility to reduce stigma. “Getting this conversation going, that’s why we brought you together tonight,” said Dr. Weaver. “Dementia and Alzheimer's disease in particular is quickly becoming a global health threat that we cannot afford to ignore."

You can view the full event recording here.

Neurophysiologist Joins Krembil

Dr. Luka Milosevic, biomedical engineer and neurophysiologist, returns to UHN.

Dr. Luka Milosevic is a new Scientist at the Krembil Research Institute and Assistant Professor with the Institute of Biomedical Engineering at the University of Toronto.

This month, former UHN trainee Dr. Luka Milosevic joins the Krembil Research Institute as their newest Scientist. Dr. Milosevic is a biomedical engineer, researcher and intraoperative neurophysiologist.

Dr. Milosevic's research has provided his field with a deeper understanding of how electrical impulses that are generated during deep brain stimulation (DBS) regulate brain activity. Most notably, he found that DBS can induce long-lasting changes to brain activity that persist after stimulation—a key finding in the search for new treatments for neurological disorders, such as Alzheimer disease and Parkinson disease.

Dr. Milosevic also plays a clinical role monitoring patients' brain activity during surgeries to guide the placement of DBS devices.

"It is very fulfilling knowing that with our research and with each surgery we are helping to improve the quality of life and independence of the individuals we treat."

Start-up funding will help Dr. Milosevic build a research program with a diverse team of talented trainees. His team will leverage the access to intracranial human brain recordings in order to gain a deeper understanding of physiological processes

underlying disorders of the nervous system, with the overall aim of developing novel therapeutic brain stimulation approaches.

Dr. Milosevic is cross-appointed to the Institute of Biomedical Engineering at the University of Toronto as an Assistant Professor and will collaborate with CRANIA and The KITE Research Institute as an Affiliate Scientist.

“Krembil is the world-leading center for deep brain stimulation research and is home to unique and state-of-the-art research facilities, such as the CRANIA neuromodulation suite. I’m looking forward to collaborating with the incredibly talented scientists at Krembil and contributing positively to the lives of individuals living with neurological conditions.”

Most recently, Dr. Milosevic was a Postdoctoral Fellow at the Institute for Neuromodulation and Neurotechnology at the University of Tübingen in Germany. He received a PhD in Biomedical Engineering from the University of Toronto, where he was supervised by Dr. Milos Popovic, Director of The KITE Research Institute, and Dr. William Hutchison, Senior Scientist at the Krembil Research Institute.

Research

More than Face Value

Machine learning enables in-depth mapping of abnormalities caused by trigeminal neuralgia.

Trigeminal neuralgia is often considered to be among the most painful disorders known to medicine. It is more common in women and can be associated with other conditions, such as multiple sclerosis.

An extensive network of branching nerves enables the face to feel a wide range of sensations.

However, when these nerves become damaged or irritated—as is the case in a condition known as trigeminal neuralgia—they can become a source of chronic and excruciating bursts of pain. For individuals with the condition, even simple actions like chewing food can trigger debilitating pain.

Krembil Scientist and neurosurgeon Dr. Mojgan Hodaie, together with her research team, has mapped out key differences in the nerves of people suffering from trigeminal neuralgia to better understand the disease.

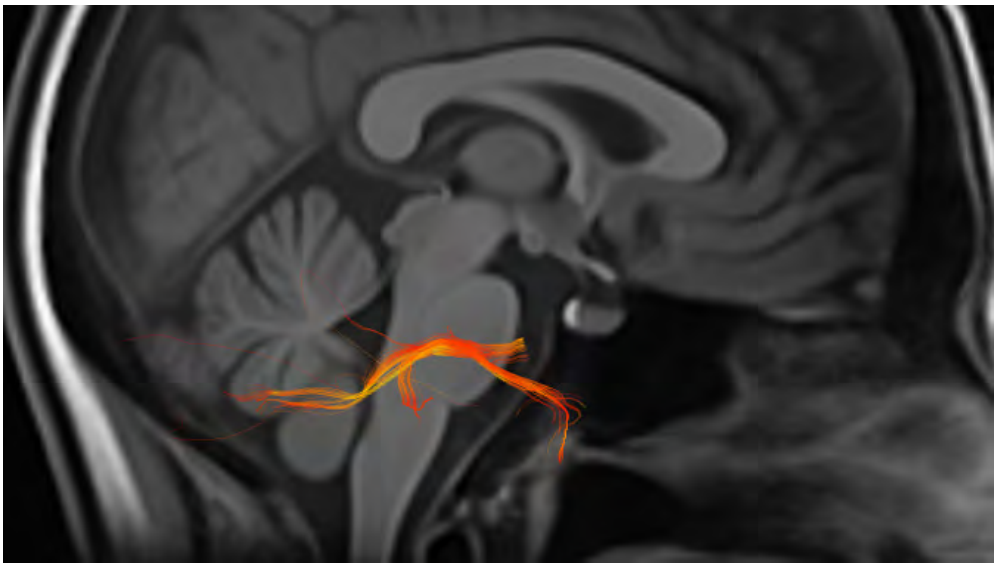
“This is the first in-depth survey of microarchitectural abnormalities in nerves associated with trigeminal neuralgia,” says Dr. Hodaie. “We traced the entire nerve pathway—from peripheral segments of the trigeminal nerve to where its branches gather, all the way to the brain.”

Using magnetic resonance imaging (MRI), the research team collected detailed images of the tissues in the faces of patients with or without the condition. To study whether the disease causes structural differences in the trigeminal nerve or its connections, the researchers used programs to automatically generate 3D models of the nerve pathways from the MRI data for all the subjects, with little human intervention.

Because these 3D models were highly complicated, Dr. Hodaie’s team applied machine learning algorithms—a form of artificial intelligence—to pick out the hidden differences. These algorithms enabled the team’s computer to learn which features corresponded to patients with trigeminal neuralgia and pinpoint where the differences occurred.

The team’s analysis revealed abnormalities in the nerves of individuals with trigeminal neuralgia that could be used to distinguish them from healthy subjects with more than 80% accuracy. For patients with pain in only one side of the face, these abnormalities could likewise be used to distinguish the unaffected and affected sides.

The latter analysis also revealed a peculiarity: patients with pain in only one side of their face still had some abnormalities on both sides. This intriguing result, along with other findings, lays the foundation for future research and the development of therapeutic strategies to target the observed differences.



A 3D model of the right-side trigeminal nerve (orange) overlaying an MRI scan of the head. The trigeminal nerve branches into three divisions, which supply nerves to areas of the face such as the jaw, cheeks, nose, sinuses, eyelids, brow and forehead.

This work was supported by the Multiple Sclerosis Society of Canada and Toronto General & Western Hospital Foundation.

Chen DQ, Zhong J, Chu PPW, Fei Li CM, Hodaie, M. Trigeminal Neuralgia Diffusivities using Gaussian Process Classification and Merged Group Tractography. Pain. 2020 Jul 21. doi: 10.1097/j.pain.0000000000002023.

Losing Sleep after Critical Illness

Study links sleep problems after release from intensive care unit with cognitive decline.

It is often recommended that adults receive seven to nine hours of sleep to function optimally. However, those recovering from a critical illness may experience frequent awakenings throughout the night, which could have an impact on their cognitive ability.

Most patients often complain of not getting a good night's rest in the hospital. However, those who are treated for critical illnesses in the intensive care unit (ICU) continue to experience trouble sleeping for a short while after discharge.

A new study suggests that sleep fragmentation, or the tendency to wake up repeatedly throughout the night, may be linked to a decline in cognitive performance—ie, the brain's ability to acquire and process information—in ICU survivors at one week of discharge from the unit.

"About half of patients show signs of cognitive impairment after a critical illness," says Dr. Elizabeth Wilcox, Clinician Investigator at Krembil Research Institute and lead author of the study. "While we know that poor sleep is linked to cognitive impairment, we wanted to see whether these factors affected patients after discharge from the ICU and for how long."

The study enrolled 150 participants from five ICU wards across Toronto's academic hospitals. All participants were on a ventilator for at least three days. Of the 102

individuals who survived discharge from the ICU, more than half were found to have cognitive impairment after one week.

To assess sleep quality and duration, the researchers used a technique called actigraphy, which is a non-invasive approach that tracks movement. Study participants used a wrist-worn device to track their activity during sleep. Sleep activity was measured at one week, six months and one year following ICU discharge and standardized cognitive tests were performed at each follow-up.

Their analysis revealed that fragmented sleep was associated with cognitive impairment at seven days post-ICU. However, no link was found at six or twelve months.

“Although we were unable to find an association between fragmented sleep and cognitive impairment at six months or one year following discharge, further studies are needed to see whether the effects of poor sleep on cognition linger,” explains Dr. Wilcox. “Added support to help patients regain healthy sleep patterns after discharge from the ICU may benefit patients and help with their recovery.”

This work was supported by the Physician Services Incorporated Foundation and the Toronto General & Western Hospital Foundation.

Wilcox ME, McAndrews MP, Van J, Jackson JC, Pinto R, Black SE, Lim AS, Friedrich JO, Rubenfeld GD. Sleep fragmentation and cognitive trajectories after critical illness. Chest. 2020 Jul 24. doi: 10.1016/j.chest.2020.07.036.

A Promising Candidate

Early data suggest that furosemide may reduce the severity of COVID-19 infection.

Furosemide is widely available worldwide and is inexpensive to produce. It has been used as a diuretic to treat high blood pressure for decades.

In response to a coronavirus infection, the body's immune system mounts an inflammatory response against the virus. However, sometimes this inflammatory response is so sudden and strong that it becomes fatal.

Dr. Donald Weaver, a Senior Scientist and Director of Krembil Research Institute, recently showed in a pre-clinical study that furosemide, a small-molecule drug, has the potential to treat COVID-19 by reducing the harmful inflammation caused by the infection.

Furosemide is a diuretic commonly prescribed to treat high blood pressure, fluid build-up in the lungs and chronic kidney disease. It can be administered orally, intravenously, and by inhalation. It is also safe, readily available and part of WHO's Essential Medicines List.

It takes many years to bring a new drug to market. To accelerate the development of treatments for COVID-19, Dr. Weaver's team had turned to the strategy of repurposing existing drugs.

Searching through a library of 1,136 small molecules produced by the body, the research team found one molecule with significant anti-inflammatory potential known as 3-hydroxyanthranilic acid (3-HAA). They then looked for approved drugs that are similar in structure to 3-HAA.

Of the few candidates that were shortlisted, furosemide was the most promising. Cell culture studies revealed that furosemide inhibited the production of pro-inflammatory molecules and promoted the production anti-inflammatory molecules.

“Our pre-clinical study suggests that furosemide may be a candidate for repurposing as an inhaled therapy against COVID-19,” says Dr. Weaver.

“Furosemide has been shown to reduce bronchial inflammation associated with asthma in previous clinical studies. We are currently pursuing a clinical study to assess whether it can reduce the severity of COVID-19 infection.”

This work was supported by the Canada Research Chair Program and the Toronto General & Western Hospital Foundation. D Weaver holds a Tier 1 Canada Research Chair in Drug Design for Protein Misfolding Disorders.
Wang Z, Wang Y, Vilekar P, et al. Small molecule therapeutics for COVID-19: repurposing of inhaled furosemide. PeerJ. 2020 Jul 7. doi:10.7717/peerj.9533.

A Matter of Perception

Disagreement found between self-reported and performance-based measures of physical function.

Osteoarthritis is a form of arthritis caused by biomechanical and biochemical processes that can lead to joint inflammation and cartilage degradation where bones meet. As the cartilage thins, the bones can rub together causing pain, stiffness and swelling. The knee is one of the most common joints affected by osteoarthritis.

Total knee replacement surgery is a last-resort treatment for people whose osteoarthritis can no longer be managed through other approaches.

Although reduced physical function is a key decider for whether surgery is the right treatment, there is currently no clinically standardized way to measure physical function in individuals with knee osteoarthritis. A team of Krembil researchers compared and contrasted two ways that are often used to assess function: a physical test and a self-reported questionnaire.

The study, published in *PloS ONE*, revealed that self-reported physical function scores in younger individuals tended to be worse compared to performance-based scores. In older adults, self-reported and performance-based scores were more consistent.

“An osteoarthritis diagnosis can be perceived as untimely and upsetting for middle-aged adults (45-65 years of age), particularly as they tend to be more engaged in activities such as working and activities with young children. These perceptions and experiences

of disruption to normal activities may be expressed by worse self-reported function relative to measured physical function," explains Krembil Scientist Dr. Anthony Perruccio who led the study with then graduate student Jessica Wilfong.

Disagreement between self-reported and performance-based scores was also found in individuals with more intense knee pain. Additionally, discordance, depending on sex and obesity, was associated with:

- more symptomatic joints
- fewer additional complicating conditions or diseases
- higher levels of pain catastrophizing (ie, the tendency to focus on pain, ruminate about it or feel helpless towards managing it)

The performance test used by the research team involved timing how long it took patients to stand up from a chair, walk a short distance and return to the chair to sit. Longer times indicated worse functionality. They compared the results of the performance test with how patients ranked their functionality on a questionnaire.

"Our research shows that self-reported and performance-based measures provide distinctive and complementary information that lend to a holistic understanding of a patient's physical functionality and how it impacts their life," says Dr. Perruccio.

Study lead Dr. Anthony Perruccio, Scientist at the Krembil Research Institute. Photo credit: The Globe and Mail.

This work was supported by the Toronto General & Western Hospital Foundation through the University Health Network Arthritis Program.

Wilfong JM, Badley EM, Power JD, Gandhi R, Rampersaud YR, Perruccio AV. Discordance between self-reported and performance-based function among knee osteoarthritis surgical patients: Variations by sex and obesity. PLoS ONE. 2020 Jul 30. doi: 10.1371/journal.pone.0236865.