

The Krembil

July 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:

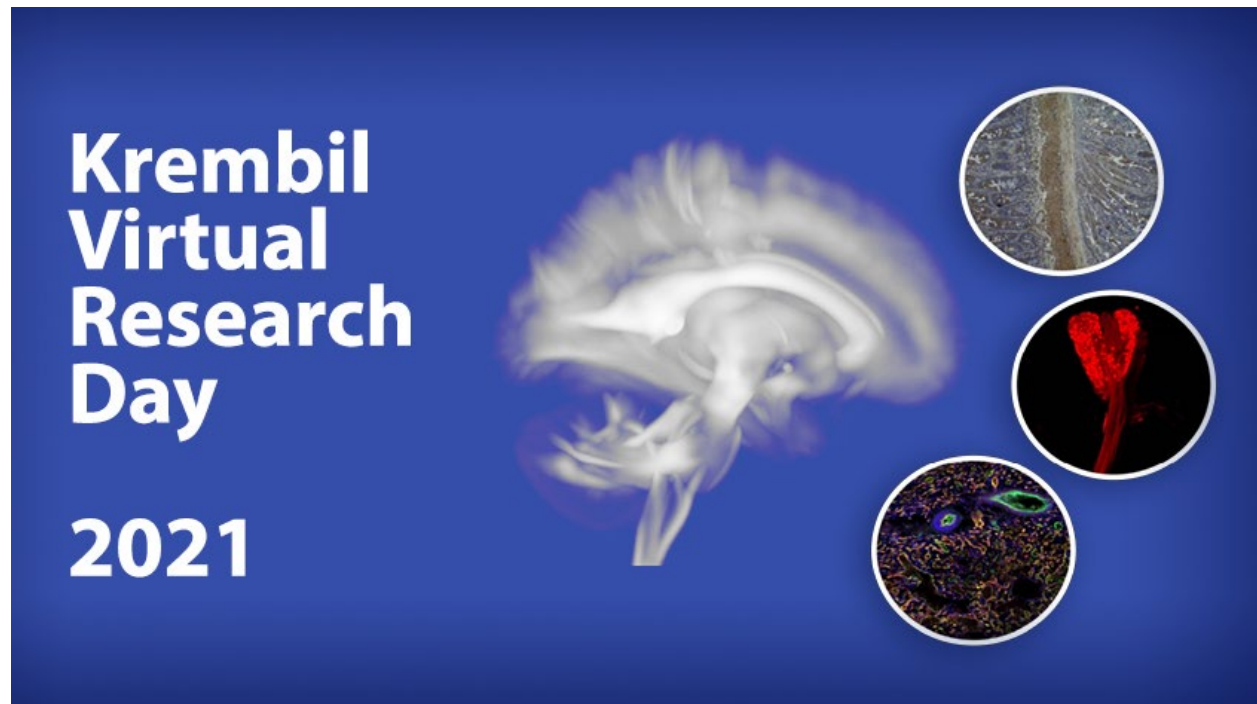
- [Krembil Research Day 2021](#)
- [Vision Researcher Joins Krembil](#)
- [Sleep Disorder a Key Factor](#)
- [Signalling Inflammation](#)
- [A Question of Quality](#)
- [Stimulating the Brain](#)



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

Krembil Research Day 2021

Trainees share their discoveries in neuroscience, vision and arthritis research.



This year's virtual Krembil Research Day was attended by more than 175 people.

Each summer, Krembil Research Day brings together the Institute's investigators, trainees and staff to celebrate research achievements across Krembil's three research pillars: brain and spine, vision, and bone and joints.

This year's event was hosted on the virtual meeting platform Gather, which offered attendees a new and unique way to connect amid restrictions to in-person meetings. Outside of oral presentations hosted on Zoom, attendees were able to explore the event space, walk the rows of poster boards and engage with colleagues, familiar and new.

The event kicked off with opening remarks from Dr. Bradly Wouters, the Executive Vice President of Science and Research; followed by Dr. Mary Pat McAndrews, Chair of the Krembil Research Institute Trainee Affairs Committee. Trainees were then treated to a video featuring Krembil investigators thanking them for their hard work and perseverance throughout this challenging year (watch the video [here](#)).

Commenting on the dedication of Krembil trainees, Dr. McAndrews says, “I remain in awe of the dedication and resilience of all our trainees and research teams, particularly as you have navigated with grace and grit through the acute, post-acute and long-haul phases of COVID-19 disruption to our research enterprise and life in general.”

Throughout the day, attendees enjoyed seven talks and 60 poster presentations.

Following the final poster session, attendees were treated to a second video featuring graduate students and postdoctoral fellows sharing who they are, what they do and why they value events like Research Day (watch the video [here](#)).

The event concluded with closing remarks from Dr. Donald Weaver, Director of the Krembil Research Institute.

The Krembil community thanks the many individuals who made this year’s Research Day a resounding success, including Krembil’s Trainee Affairs Committee, Administration Team and Public Affairs team, UHN’s Education Technology & Media Services and all those who volunteered as presentation judges. Krembil also thanks Mr. Jim Leech and Ms. Deborah Barrett for their sponsorship of the event, and the Nadler Family for their generous donation for prizes awarded to presentation winners.

PRESENTATION AWARDS

Awards for best oral and poster presentations have been awarded to the following trainees:

Oral presentation postdoctoral category

- Scott Rich (Valiante Lab)

Oral presentation graduate student category

- First place: Brian Wu (Kapoor Lab)
- Second place: Nadeem Murtaza (Singh Lab)
- Third place: Akshay Gurdita (Wallace Lab)

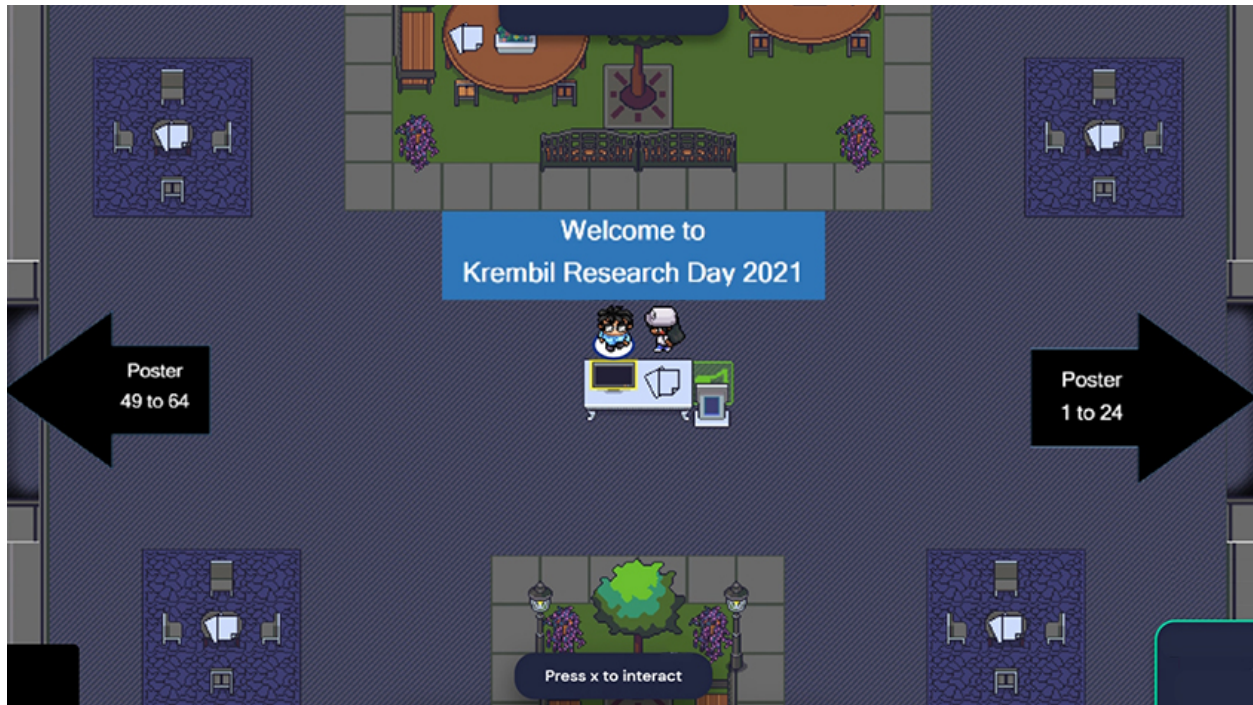
Poster presentation postdoctoral category

- First place: Maximilian Scherer (Milosevic Lab)
- Second place: Ivan Martinez (Kovacs Lab)
- Third place: Camille Fauchon (Davis Lab)

Poster presentation graduate student category

- First place: Ain Kim (Kovacs Lab)
- Second place: Areeb Jafrani (Kovacs Lab)
- Third place: Savannah Kilpatrick (Singh Lab)

Congratulations to the winners and all those who presented their work!



The web-conferencing platform Gather enabled attendees to navigate the virtual meeting space and interact with their colleagues for a more engaging conference experience.



Krembil trainees Mandana Movahed (top left), Nadeem Murtaza (top right), Wilford Wang (bottom left) and Alexandra Chatzikalymniou (bottom right) shared their research activities and how important it is to connect with colleagues through events like Research Day.

Vision Researcher Joins Krembil

Dr. Brian Ballios studies stem cell therapies for inherited and acquired eye diseases.



Dr. Brian Ballios is a new Scientist at the Donald K. Johnson Eye Institute.

The Krembil Research Institute is pleased to welcome Dr. Brian Ballios as its newest Scientist at the Donald K. Johnson Eye Institute.

Dr. Ballios' research is focused on developing stem cell therapies for inherited and acquired retinal diseases, such as age-related macular degeneration and retinitis pigmentosa. These diseases result in progressive vision loss for which existing treatments can only slow progression.

“As a physician, I am struck by the immense personal toll of eye disease,” explains Dr. Ballios. “It is very motivating to conduct research that has the potential to make tremendous improvements in patients’ quality of life. I find inspiration in these patients’ journeys and share their eagerness for cures.”

Leveraging his background in engineering and medicine, Dr. Ballios developed the world’s first injectable biomaterial-based delivery system for transplanting stem cells into the retina. This work launched a new field of study into the use of biomaterials to improve cell transplantation in the retina. He also developed methods to efficiently generate light-sensitive cells from stem cells to replace the cells lost in retinal degeneration.

At Krembil, Dr. Ballios' research program will bring together diverse fields that include retinal neurobiology, stem cell biology and bioengineering. He will continue to develop methods to generate light sensitive cells from stem cells and promote their survival and integration into the damaged eye. He will also develop accurate models of human inherited retinal disease and investigate the unique features of these conditions to improve the effectiveness of cell therapies.

“Coming to UHN is about joining an ecosystem of discovery. We have the best-of-the-best clinicians and vision science researchers,” says Dr. Ballios. “The Donald K. Johnson Eye Institute and the Krembil Research Institute bring together these leaders with a shared goal: to restore vision and improve the lives of patients.”

In 2017, Dr. Ballios was the inaugural recipient of Fighting Blindness Canada's *Clinician-Scientist Emerging Leader Award*. His research has also been funded by the BrightFocus Foundation and the Retina Foundation of Canada. This year, he was awarded a Career Development Award from the Foundation Fighting Blindness U.S. He is currently the *J. Ardeth Hill – Fighting Blindness Canada* Professor in Ocular Genetics at the University of Toronto.

At the University of Toronto, Dr. Ballios completed his Doctor of Medicine and Doctor of Philosophy degrees through the combined MD/PhD program, a clinical residency in Ophthalmology and postdoctoral training in the Department of Ophthalmology and Vision Sciences. At Massachusetts Eye and Ear and Harvard University, he completed a clinical fellowship in Inherited Retinal Diseases.

Welcome to Krembil, Dr. Ballios!

Research

Sleep Disorder a Key Factor

Those at risk for obstructive sleep apnea are more likely to get COVID-19 and be hospitalized.



This study used the STOP questionnaire to assess the risk of sleep apnea. The questionnaire comprises four simple questions relating to snoring, tiredness, observed apnea and blood pressure.

A recent study from UHN revealed that individuals at high risk for obstructive sleep apnea are more likely to be diagnosed with COVID-19 and are twice as likely to be hospitalized or treated in intensive care.

Approximately one in ten adults have obstructive sleep apnea. However, 85% to 90% of these individuals are not aware that they have the disease and are not diagnosed. Those with the condition experience broken sleep and interrupted breathing during sleep, which can lead to low blood oxygen levels.

“Our approach was unique in that we were able to explore the effect of undiagnosed sleep apnea on COVID-19 severity in a large and diverse group of individuals in the

general population,” says Dr. [Frances Chung](#), the senior author of the study and a Clinician Investigator at the Krembil Brain Institute.

A group of over 20,000 individuals from 14 different countries participated in the study. Participants completed a series of established questionnaires to assess the quality of their sleep, their risk for obstructive sleep apnea, and to assess levels of anxiety and depression.

In addition to providing insights into potential link between obstructive sleep apnea and COVID-19, the results of the study indicated that:

- Males were three times more likely than females to be hospitalized for COVID-19
- Individuals with diabetes were three times more likely to be hospitalized for COVID-19
- Participants who reported experiencing depression were nearly twice as likely as those without depression to be hospitalized for COVID-19

While the above findings are in line with previous studies, a few of the results contradicted existing literature. “Surprisingly, we did not observe a link between physician-diagnosed obstructive sleep apnea and worse COVID-19 outcomes. This finding may be explained by the fact that those who are aware of their condition are likely managing it with effective treatments, such as continuous positive airway pressure therapy,” says Dr. Chung.

“We also failed to observe statistically relevant links between certain established risk factors for COVID-19 severity, such as hypertension or chronic inflammatory lung disease. This is likely because the participants in our study were younger and had fewer chronic health conditions than participants in previous studies.”

Taken together, the results of this study highlight the importance of screening individuals with COVID-19 for obstructive sleep apnea to help health care professionals determine which COVID-19 patients are at risk for developing severe symptoms.

How you can help advance COVID-19 research

With the success of the first worldwide study, Dr. Chung’s team is looking for participants to complete a second survey on the effects of long lasting COVID-19 symptoms (Long COVID).

The survey is open to everyone aged 18 years and older—regardless of whether you have experienced COVID-19 symptoms. The time it will take to complete the survey depends on whether participants have experienced symptoms:

For those who have not had COVID-19, the survey will take 15 to 20 min.

For those who have had COVID-19 in the past year, it will take 40 to 50 min.

Participation in the study is voluntary and completely anonymous (no identifiable information is gathered). If you are interested in participating, please click on the following link or scan the QR-code:

https://educationhelsinki.eu.qualtrics.com/jfe/form/SV_eIZTDNuj65Kfmg6



If you have any questions about participation in this research study, please contact the Principal Investigator, Dr. Frances Chung, University Health Network, University of Toronto, at 416 670-4253 or frances.chung@uhn.ca.

This work was supported by the UHN Foundation. Chung F holds the ResMed Research Chair of Anesthesia, Sleep and Perioperative Medicine at University Health Network. Morin CM holds a Tier 1 Canada Research Chair in Sleeping Disorders at Université Laval.

*Chung F, Waseem R, Pham C, Penzel T, Han F, Bjorvatn B, Morin CM, Holzinger B, Espie CA, Benedict C, Cedernaes J, Saaresranta T, Wing YK, Nadorff MR, Dauvilliers Y, De Gennaro L, Plazzi G, Merikanto I, Matsui K, Leger D, Sieminski M, Mota-Rolim S, Inoue Y, Partinen M; International COVID Sleep Study (ICOSS) group. [The association between high risk of sleep apnea, comorbidities, and risk of COVID-19: a population-based international harmonized study](#). *Sleep Breath*. 2021 Apr 28:1–12. doi: 10.1007/s11325-021-02373-5.*



Dr. Frances Chung is the lead author of the study and a Clinician Investigator at the Krembil Brain Institute.

Signalling Inflammation

Study identifies two proteins linked to joint inflammation and treatment outcomes in arthritis.



A hallmark feature of axial spondyloarthritis is inflammation of the sacroiliac joint—the joint that connects the lower spine and the pelvis. This inflammation frequently results in severe back pain and stiffness.

Researchers at the Schroeder Arthritis Institute have identified proteins that signal joint inflammation and may predict treatment outcomes in individuals with axial spondyloarthritis.

This form of arthritis mainly affects joints of the spine and pelvis. Although treatments exist to suppress disease flare-ups and reduce symptoms, there are few molecular markers that scientists and clinicians can use to accurately identify chronic inflammation or predict treatment success.

To improve management of the condition, the research team examined whether proteins in patients' blood can be used to detect joint inflammation and predict how patients will respond to treatments.

“By identifying proteins in the blood that reflect disease status, we have the potential to address a major care gap for patients. This information could be used to develop a simple blood test to measure disease flare-ups or gauge the effectiveness of treatments. The approach could also shed light on underlying disease mechanisms—

leading the way to new therapies," explains Dr. [Robert Inman](#), senior author of the study and Co-Director and Senior Scientist at the Schroeder Arthritis Institute.

The researchers monitored 286 individuals with the disease for between 4 and 12 years, and measured blood levels of two proteins—lipocalin 2 (LCN2) and oncostatin M (OSM). The team focused on these proteins because previous studies from the Inman lab (examining an experimental model of axial spondyloarthritis) had implicated them in inflammation and bone remodelling, the hallmark features of the disease. They then examined the relationship between the levels of the two proteins and patients' responses to treatment, as well as inflammation—determined by imaging of the sacroiliac joint near the hip.

The team found that most patients with the disease had higher levels of LCN2 and OSM than normal. Also, individuals who had high levels of these proteins over longer periods of time were more likely to have joint inflammation. Patients with different protein levels responded differently to certain treatments, but persistent elevation of either protein was generally linked to poorer treatment outcomes.

Over the course of the study, back pain resolved in 60% of patients. Despite their lack of pain, approximately half of these patients continued to have elevated levels of LCN2 or OSM. Interestingly, over 85% of these patients also exhibited joint inflammation, indicating that protein levels might be more sensitive measures of disease activity than self-reported symptoms.

"This study has shed light on how LCN2 and OSM contribute to joint inflammation in this form of arthritis. Our hope is to advance the use of these proteins to better predict treatment outcomes," says Dr. Inman. "Also, because these proteins appear to reflect disease activity better than pain severity, measuring protein levels could help us develop preventative and proactive treatment strategies to better manage the disease."

This work was supported by the Canadian Institutes of Health Research and the UHN Foundation.

Tsui FWL, Lin A, Sari I, Zhang Z, Tsui HW, Inman RD. [Serial Lipocalin 2 and Oncostatin M levels reflect inflammation status and treatment response in axial spondyloarthritis.](#) *Arthritis Res Ther.* 2021 May 14. doi: 10.1186/s13075-021-02521-y.



The senior author of the study, Dr. Robert Inman, is Co-Director and Senior Scientist at the Schroeder Arthritis Institute. He is also Co-Director of the Spondylitis Program and Deputy Physician in Chief for Research at University Health Network. (Photo by Tim Fraser)

A Question of Quality

Study highlights the need for standardized methodology in survey-based surgery research.



Researchers often use surveys to collect information about health care professionals' thoughts, opinions and practices. The information gained from these surveys is regularly used to develop important medical policies and guidelines.

Researchers at UHN's Krembil Research Institute and Princess Margaret Cancer Centre have identified the need for improved standards for survey-based research in the field of general surgery.

“Many people see surveys as a quick and easy approach to collecting data, but it is actually quite challenging to develop a high-quality survey that provides meaningful insights,” explains Dr. [Fayez Quereshy](#), a co-author of the study and a Krembil Clinician Investigator. “Unfortunately, few guidelines exist to help researchers design surveys that are targeted to health care professionals.”

In survey research, scientists typically collect information about a population of interest using questionnaires. Survey studies allow researchers to obtain data quickly and at a low cost, but the conclusions drawn from surveys are only as strong as the quality of the survey methodology.

To explore the quality of survey research in the field of general surgery, the research team examined the methodology of more than 270 survey studies published in surgical

journals over the past 18 years. The team was led by Dr. [Sami Chadi](#), a Clinician Investigator at the Princess Margaret Cancer Centre, and research fellow and PhD candidate Dr. Keegan Guidolin.

The researchers examined several factors related to the overall quality of a survey's methodology, including whether the authors used an existing questionnaire or developed their own, whether they followed specific steps when developing their questionnaire and how they reported survey details.

The study revealed several shortcomings in how surveys are carried out and described. For example, only 14% of studies used a previously developed and accepted questionnaire, and more than 20% of studies did not explain how the questionnaires were developed. Additionally, 63% of studies failed to report how the researchers managed incomplete questionnaires.

Based on their findings, Drs. Chadi and Quereshy recommend that researchers apply standardized methods when they conduct surveys. They encourage researchers to adapt existing questionnaires whenever possible and follow steps to assess questionnaire clarity and completeness when developing their own. They also encourage researchers to describe key survey details such as response rate and methods for managing missing data when they publish their results.

"We need to ensure that the results of surgery-related surveys are reliable," says Dr. Chadi. "Survey studies often inform policy changes, so they can have far-reaching effects."

This work was supported by The Princess Margaret Cancer Foundation and the UHN Foundation.

Guidolin K, Wexner SD, Jung F, Khan S, Deng SX, Kirubarajan A, Quereshy F, Chadi S. [Strengths and weaknesses in the methodology of survey-based research in surgery: A call for standardization.](#) *Surgery*. 2021 Feb 16. doi: 10.1016/j.surg.2021.01.006.



*(L) Dr. Sami Chadi is a Clinician Investigator at the Princess Margaret Cancer Centre.
(R) Dr. Fayez Quereshy is a Clinician Investigator at the Krembil Research Institute
(Photo by Tim Fraser).*

Stimulating the Brain

Researchers map and model the effects of deep brain stimulation on different brain regions.



Deep brain stimulation is a therapy that uses microelectrodes implanted in the brain to adjust the electrical activity of neurons in the surrounding area.

A team of UHN researchers recently characterized how cells in four different brain regions respond to deep brain stimulation.

During deep brain stimulation, microelectrodes implanted in the brain emit pulses of electricity to change the activity of neurons. This procedure is currently approved for treating Parkinson disease, epilepsy and several other movement disorders. The electrical pulses can be adjusted in terms of their frequency, intensity and duration to reduce abnormal neuron activity, which eases the symptoms of the disorders.

“There are still many unknowns regarding how deep brain stimulation changes brain activity,” explains Dr. [Luka Milosevic](#), the lead author of the study and a Scientist at the Krembil Brain Institute. “We wanted to understand how stimulation changes the activity of neurons in different brain regions. This understanding will enable us to improve the effectiveness of deep brain stimulation and apply the procedure to other conditions, such as addiction and depression.”

The researchers studied the activity of 115 neurons from four brain regions involved in movement control in patients with either Parkinson disease or essential tremor—a

neurological disorder that causes involuntary shaking. They programmed the electrodes to deliver stimulation pulses at various frequencies, up to 200 pulses per second, and monitored whether this stimulation increased or decreased neuron activity. The team also developed a mathematical model to predict how neurons in each region would respond to electrical stimulation.

The findings revealed that how neurons respond to electrical stimulation depends on their location within the brain and the frequency of stimulation that they receive.

Electrical pulses had opposite effects in different regions, depending on the local concentration of chemicals that stimulate or suppress neuron activity. Low-frequency stimulation suppressed activity in regions with higher levels of inhibitory chemicals, but increased activity in regions with higher levels of excitatory chemicals. However, prolonged high-frequency stimulation suppressed activity in all regions. This was likely because neuronal communication could not keep up with stimulation impulses delivered at high frequencies (a phenomenon called “synaptic fatigue”).

Overall, the researchers concluded that both anatomical and physiological properties of the brain must be taken into consideration to be able to predict how electrical stimulation will change neuron activity in specific brain regions. Furthermore, it seems that high-frequency deep brain stimulation may elicit its beneficial therapeutic effect in Parkinson disease and essential tremor by disrupting the unhealthy signals generated by neurons in the areas of the brain known to be associated with these disorders.

“These findings have enabled us to gain a deeper understanding of how deep brain stimulation benefits patients and will help us fine-tune existing and future therapies. Moreover, our experimental findings and our computational model will support the development of new stimulation methods in other regions of the brain and for other neurological disorders,” says Dr. Milosevic.

This work was supported by the Natural Sciences and Engineering Research Council of Canada, donation from Dean Connor and Maris Uffelmann, donation from Walter and Maria Schroeder, the Dystonia Medical Research Foundation and the UHN Foundation.

Milosevic L, Kalia SK, Hodaie M, Lozano AM, Popovic MR, Hutchison WD, Lankarany M. [A theoretical framework for the site-specific and frequency-dependent neuronal effects of deep brain stimulation](#). *Brain Stimul.* 2021 May 12. doi: 10.1016/j.brs.2021.04.022.



Dr. Luka Milosevic, Scientist at the Krembil Brain Institute, is the lead author of the study.