The Krembil

January 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:

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

News

Mental Health Matters

Krembil gets people talking and thinking about mental health on Bell Let's Talk Day.

Dr. Taufik Valiante and his trainees (pictured here) are taking a 'brain break' to do some mindfulness colouring on Bell Let's Talk Day at Krembil.

Mental illness is more common than most people think. By the age of 40, 50% of Canadians will have—or have had—a mental illness.

On January 29, Canada celebrated Bell Let's Talk Day, which aims to raise awareness of mental illness.

Krembil hosted a variety of events to recognize the importance of the day and promote mental health and well-being in its community. The events included:

- 'brain breaks' where participants could take a short break from their busy days to enjoy coffee, good conversation, a gratitude tree, mindfulness colouring and the Wellness Centre's Wellness Wagon;
- a talk delivered by a wellness ambassador about the importance of maintaining work-life balance and managing work-related stress; and
- a brief introduction to sitting meditation, a tool to improve focus and enhance feelings of well-being.

Bell Let’s Talk Day is an annual campaign to reduce the stigma attached to mental illness by promoting awareness, understanding and acceptance. Since being launched in 2010, the campaign has raised over $100 million to support mental health initiatives.

Thank you to Carley McPherson for playing a leading role in organizing Krembil’s events, and to all those who participated in and supported Bell Let’s Talk Day 2020.

Update on Alzheimer Disease

Krembil will host a public forum on Alzheimer disease on World Health Day 2020.

According to the Alzheimer Society of Canada, more than 500,000 Canadians are living with dementia. This number is expected to reach 937,000 by 2030.

World Health Day is a global event to raise awareness about health issues that deserve special attention. It is celebrated annually on April 7.

To mark World Health Day 2020, Krembil will host a public forum on Alzheimer disease, the most common form of dementia. The World Health Organization (WHO) estimates that more than 50 million people worldwide have dementia and that 10 million new cases are reported every year.

The forum, titled *The Future of Alzheimer Disease*, will aim to educate the public about advances in dementia research and care, to dispel common myths about Alzheimer disease and provide information to caregivers.

It will open with a keynote lecture delivered by the Canadian science broadcaster and writer, Jay Ingram. Mr. Ingram is most well known for hosting Discovery Channel's *Daily Planet* and CBC Radio's *Quirks & Quarks*.

The lecture will be followed by a question and answer session where a panel of dementia experts will answer questions from the audience. To date, the following experts (listed alphabetically) have agreed to sit on the panel:

- Dr. Andrea Iaboni is a geriatric psychiatrist and researcher at the KITE Research Institute. Her research focuses on developing new models of dementia care making use of physiological and behavioural data from environmental sensors.

- Dr. Saskia Sivananthan is a neuroscientist and the Chief Science Officer at the Alzheimer Society of Canada. From 2015 to 2018, she led the development of WHO's Dementia Action Plan.

- Dr. David Tang-Wai is a clinician and researcher who specializes in dementia. He is the co-Director of the Memory Clinic at the University Health Network (UHN).

- Dr. Donald Weaver is a dementia clinician at UHN and an international leader in computer-aided drug design. He has been developing novel drugs for dementia for almost 30 years. He is also the Director of the Krembil Research Institute.

Krembil's forum on Alzheimer disease will take place on the evening of April 7 in the BMO Education & Conference Centre at the Krembil Discovery Tower. More details about the forum will be distributed in the following months.

All are welcomed and encouraged to join us!

Research

Live or Let Die

New progress towards solving the puzzle of how a damaged cell decides whether to live or die.

Researchers at Krembil Research Institute are piecing together the complex processes that govern cell survival and death, and underpin Parkinson disease.

Mitochondria are the power plants of the cell. Almost all cells in our body depend on mitochondria to provide the energy they need to live. When its mitochondria malfunction or are damaged, a cell must either fight to stay alive or start planning its demise.

A team of researchers led by Drs. Suneil Kalia and Lorraine Kalia, Scientists at Krembil Research Institute, has found that a protein known as BAG5 is instrumental in determining whether a cell with damaged mitochondria will live or die.

BAG5 is part of a family of six proteins, named BAG1 to BAG6. Several members of this family are part of a network of interacting proteins recruited to the damaged mitochondria.

“Members of the BAG family play different roles in the process,” explains Dr. Suneil Kalia. “We found that BAG5 delays the decommissioning of severely impaired mitochondria, leading to the acceleration of cell death.”

Parkin, a protein implicated in Parkinson disease, is also recruited to damaged mitochondria. By understanding how BAG5, Parkin and other proteins work together to determine the fate of a cell, the researchers aim to reveal new approaches to treat Parkinson disease, a condition caused by the progressive death of brain cells.

To learn more about the research of Drs. Kalia and Kalia, please visit kalialabs.org

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canadian Institutes of Health Research (CIHR) and the Toronto General & Western Hospital Foundation. L Kalia holds a CIHR Clinician Scientist Award and EA Fon holds a Tier 1 Canada Research Chair in Parkinson’s Disease.

De Snoo ML, Friesen EL, Zhang YT, Earnshaw R, Dorval G, Kapadia M, O'Hara DM, Agapova V, Chau H, Pellerito O, Tang MY, Wang X, Schmitt-Ulms G, Durcan TM, Fon EA, Kalia LV, Kalia SK. Bcl-2-associated athanogene 5 (BAG5) regulates Parkin-dependent mitophagy and cell death. Cell Death Dis. 2019 Dec 2. doi:10.1038/s41419-019-2132-x.

Left to Right: Dr. Lorraine Kalia, Scientist, Krembil Research Institute; and Dr. Suneil Kalia, Scientist, Krembil Research Institute.

Less Stigma for More Health

Minimizing harm by identifying and targeting negative beliefs about people who use opioids.

A key feature of stigma is that it socially discredits those who are its targets, thereby diminishing a person's power within society.

Opioids are causing significant harm to Canadians.

Opioids refer to a broad group of pain-relieving drugs. Some of these are illegal like heroin, whereas others are legal and can be prescribed to manage severe chronic pain. According to the Public Health Agency of Canada, opioids were implicated in 4,614 deaths and 5,349 hospitalizations across Canada in 2018.

Dr. Daniel Buchman led a study to improve our understanding of the different types of stigma that affect opioid users.

Stigma refers to negative public attitudes and beliefs about a group of people who share a specific demographic quality. Further, these beliefs and attitudes can cause individuals in the group to be marginalized and labeled as 'deviant' by others. People who use opioids and people living with opioid use disorder are often the target of stigma, and labels such as 'addict' and 'junkie' are examples of stigmatizing language that could lead to discrimination.

"It is well established that stigma worsens the health of targeted individuals by deterring them from seeking and/or accepting help for their condition," says Dr. Buchman, a

Clinician Investigator at Krembil Research Institute and a Bioethicist at Toronto Western Hospital. “Stigma can also be a major source of chronic stress in people’s lives.”

As part of the study, he and his colleagues analyzed 51 academic papers about opioid-related stigma. They reported the existence of numerous types of stigma, which the team grouped into four distinct categories. These included stigmas towards people who are taking methadone and other medications for opioid use disorder; stigmas related to the use of opioids for chronic pain; stigmas related to attitudes among health care professionals; and self-stigmas in which feelings of self-blame, shame and despair prevent a person from seeking help for their opioid use.

“People who consume opioids are often marginalized by society,” explains Dr. Buchman. “Identifying the different types of stigma that these individuals face will help policymakers develop targeted strategies that will minimize the harm caused by opioid consumption.”

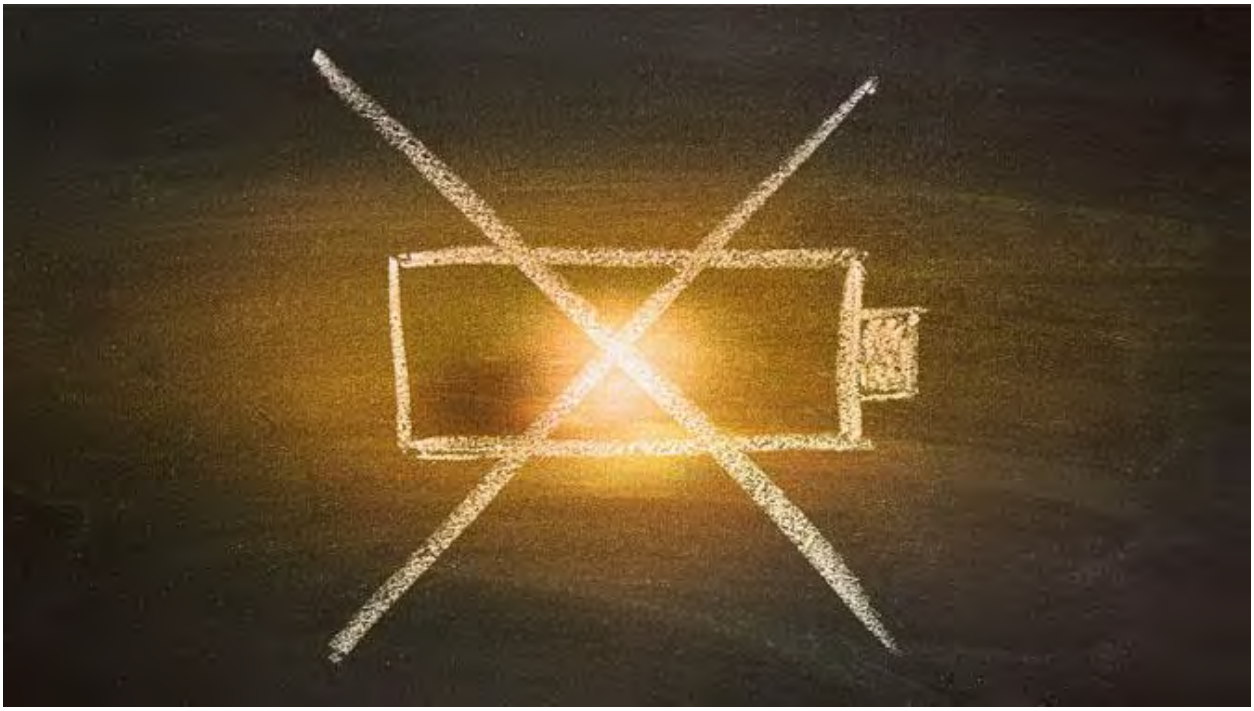
This work was supported by the University Health Network.

McCradden MD, Vasileva D, Orchanian-Cheff A, Buchman DZ. Ambiguous identities of drugs and people: A scoping review of opioid-related stigma. Int J Drug Policy. 2019 Dec. doi: 10.1016/j.drugpo.2019.10.005.

Dr. Daniel Buchman, Clinician Investigator, Krembil Research Institute.

Intrigued by Fatigue

New study helps to alleviate worries that tiredness is a warning sign of disease progression.



Systemic autoimmune rheumatic diseases (SARDs) are relatively rare, but potentially debilitating disorders. They include diseases such as lupus, Sjogren's disease and scleroderma.

The immune system is the body's defense against infectious invaders like bacteria and viruses. However, in autoimmune diseases, the immune system dysfunctions and attacks the body itself.

In her latest study, Dr. Joan Wither, a Senior Scientist at Krembil Research Institute, examined whether tiredness is a harbinger of disease progression in a family of autoimmune diseases known as systemic autoimmune rheumatic diseases (SARDs). SARDs occur when the immune system mistakenly attacks the body's joints and connective tissues, and can lead to debilitating inflammation, pain and tiredness.

The first sign of a SARD is the presence of a specific type of antibody, which is a protein produced by the immune system. Doctors have worried that people with these antibodies who are also experiencing profound tiredness are at an increased risk of progressing to a more severe stage of disease.

As part of the study, Dr. Wither and her team analyzed a combination of questionnaires administered to SARD patients, as well as their blood test results and medical records. The researchers found that individuals with the antibodies and tiredness did not have a greater likelihood of progressing to a SARD.

Instead, they found that approximately one third of patients who participated in the study might be affected by a different disease with similar symptoms: fibromyalgia. Fibromyalgia is a condition with heightened sensitivities to pain and tiredness and is thought to stem from a disorder in the nervous system.

“Based on our findings, clinicians can now reassure their patients that fatigue is not necessarily a sign that their condition is progressing,” says Dr. Wither.

These findings will also improve the diagnosis and treatment of people with elevated tiredness.

This work was supported by the Krembil Foundation, the Canadian Institutes of Health Research, the Oscar and Eleanor Markovitz Fund for Scleroderma Research, the Freda Fejer Fund for Scleroderma Research, the Autoimmunity Research Centre of the University Health Network, The Arthritis Centre of Excellence and the Department of Medicine of the University of Toronto, The Arthritis Society of Canada and the Toronto General & Western Hospital Foundation.

Hafiz W, Nori R, Bregasi A, Noamani B, Bonilla D, Lisnevskaia L, Silverman E, Bookman AAM, Johnson SR, Landolt-Marticorena C, Wither J. Fatigue severity in anti-nuclear antibody-positive individuals does not correlate with pro-inflammatory cytokine levels or predict imminent progression to symptomatic disease.Arthritis Res Ther. 2019 Nov 4. doi: 10.1186/s13075-019-2013-9.

Dr. Joan Wither, Senior Scientist, Krembil Research Institute.

Keeping Score

New study shows that some symptoms of lupus are more likely to occur in groups.

Designing drugs to treat neurological conditions that can enter the brain requires careful consideration of a combination of features, such as molecular structure and weight.

Mathematical models are used to predict many natural phenomena around us, including population growth, the weather and the movement of planets. In medicine, scientists are using models to predict the ability of drugs to reach certain locations in the body, particularly the brain.

The blood–brain barrier (BBB) acts as a barricade that prevents harmful toxins and substances in the blood from reaching the brain. While this barrier is necessary for preserving a healthy brain, a major drawback is that new drugs developed to treat neurological disorders, such as Alzheimer disease, might not be able to cross into the brain at high enough levels to be effective.

A study led by Dr. Donald Weaver, Director of the Krembil Research Institute, revealed a new strategy that can facilitate the design of medications for neurological disorders. His group developed a computational model called ‘BBB Score’ that predicts the likelihood of a drug penetrating through the BBB using information about the drug’s physical and chemical properties.

The new score was proven to be better at predicting entry for selected drugs than other conventional approaches. These findings suggest that the ‘BBB Score’ could be used to supplement other models currently used in drug development programs. It has been

classified in F1000Prime as a technical advance and being of special significance in its field.

“The BBB Score is a much needed tool that will improve the effectiveness of drug development efforts, while saving time and resources,” says Dr. Weaver.

This work was supported by the Krembil Foundation. DF Weaver holds a Tier 1 Canada Research Chair in Protein Misfolding Diseases.

Gupta M, Lee HJ, Barden CJ, Weaver DF. The blood—brain barrier (BBB) score. J. Med. Chem. 2019, 62 (21), 9824-9836. doi: 10.1021/acs.jmedchem.9b01220.

Dr. Donald Weaver, Director, Krembil Research Institute.