The Krembil

May 2017

The Krembil is the official newsletter of the Krembil Research Institute (formerly the Toronto Western 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

Recap of 2017 Krembil Research Day

(R-L) Trainee Affairs Committee Chair, Dr. Frances Skinner; Keynote Speaker Dr. Eve Marder; Krembil Director Dr. Donald Weaver; the 2017 trainee presentation award winners; and Trainee Affairs Committee Member Dr. Mary Pat McAndrews (far left).

The 17th Annual Krembil Research Day was held on May 10th, 2017 at the Chestnut Residence & Conference Centre. Opening remarks were provided by UHN's Executive VP of Science and Research, Dr. Bradly Wouters, and Krembil Research Institute Director Dr. Donald Weaver.

Throughout the day, Krembil trainees shared their latest findings through a series of oral and poster presentations. Graduate student and Postdoctoral fellow categories for the top oral and poster presentations were judged and later awarded. The overall category winners are summarized below (full results are available here).

This year marked the inaugural 'elevator pitch' session, where trainees presented a very brief, three-minute overview of their research findings. The audience voted on their choice for favourite elevator pitch: the people's choice went to Dr. Shabana Amanda Ali (Dr. M. Kapoor's lab), whose presentation focused on the process of biomarker discovery in osteoarthritis research.

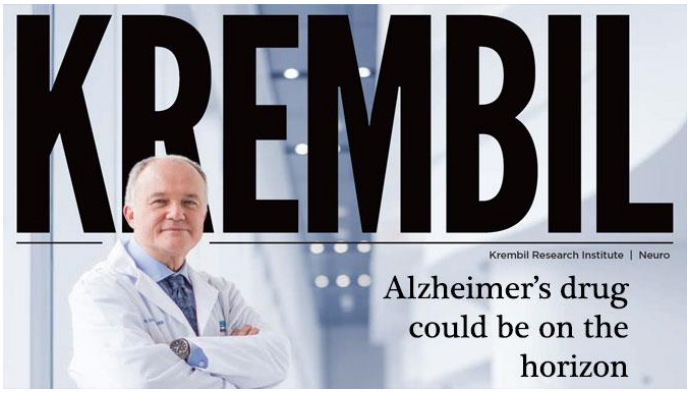
This year's keynote speaker was Dr. Eve Marder, Professor of Biology at Brandeis University and 2016 Kavli Prize in Neuroscience award recipient. She is a leading expert in how the intrinsic properties of neurons affects circuit function. Her talk was titled "Individual Variability and Resilience in Neurons and Neural Circuits" and described how developing a neural network model is necessary but not sufficient to understand circuit dynamics. She also shared insights about maintaining a long and successful career in science, including the importance of collaboration and learning from your peers.

The event would not have been possible without the hard work and dedication of the Trainee Affairs Committee led by Dr. Frances Skinner, the Krembil Administration team, morning and afternoon session Chairs Drs. Joan Wither and Mary Pat McAndrews, the presentation judges, and the leadership of Dr. Donald Weaver.

Save the Date

Next year's Krembil Research Day will be on May 18, 2018 and will feature a keynote address by world-leading vision scientist Dr. Samer Hattar from the National Institutes of Mental Health Laboratories. We hope to see you there!

Globe and Mail: Krembil Neuroscience



Two subsequent issues of The Globe and Mail's Krembil Magazine, scheduled for release in June and September, will cover stories relating to vision and arthritis research, respectively.

The Krembil Research Institute has partnered with The Globe and Mail to release a magazine series highlighting its researchers' tremendous scientific advancements. The first of three magazines in the series, distributed to Globe and Mail subscribers across Canada on April 26, 2017, focuses on success stories from Krembil's brain and spine program (you can read the full issue online).

"Researchers at Krembil are working relentlessly to understand and cure various neurological diseases," says Dr. Donald Weaver, Director of the Krembil Research Institute. The stories highlighted in The Globe and Mail 'Neuro' version are summarized below:

- Dr. Lyanne Schlichter is characterizing the role of immune cells, microglia and lymphocytes, in inflammation and inflammation-associated brain damage.
- Dr. James Eubanks is using genetic animal models to better understand and ultimately develop a cure for Rett Syndrome, a devastating neurological disorder that targets young girls.
- Dr. Michael Fehlings is studying whether combined surgical and pharmaceutical intervention can improve neurological function following spinal cord injury.
- Dr. Andres Lozano is using focused beams of ultrasound to surgically treat uncontrollable tremors.
- Dr. Jérémie Lefebvre is using mathematical models to find out how the brain works.
- Dr. Michael Tymianski is leveraging his fundamental neurobiology breakthroughs to develop new and innovative therapies to prevent and reverse stroke damage.
- Dr. Donald Weaver is using medicinal chemistry and computer-aided drug design to develop a pharmacological cure for neurodegenerative diseases, including Alzheimer's disease.
- Dr. Sidney Kennedy is part of a multidisciplinary team that is working together to find biological markers of depression, so that better and faster-working treatments can be developed.
- Dr. Charles Tator and colleagues are on a quest to find better ways to diagnose and treat concussions.
- Dr. Karen Davis is using advanced brain imaging techniques to understand how pain is processed in the brain, with the goal of developing highly effective pain management strategies.
- Dr. Anthony Lang is searching for biological markers of Parkinson's disease, which can be used to detect and treat the disease before damage occurs.
- Dr. Taufik Valiante is developing a medical device that, once implanted in the patient's brain, can safely detect and stop seizures before they happen.
- Mark Krembil, President of the Krembil Foundation, discusses why it has been a priority for his family to continue their commitment to funding medical research in Canada.

"There are many exciting stories of progress and success emerging from our laboratories," explains Dr. Weaver. "Some of these stories are told in this magazine. This is only a sampling of what we do and what we are capable of."

Research

When Good Things Happen

Engaging in life activities, including hobbies such as gardening, produces a multitude of benefits ranging from improved mental and physical health to life satisfaction and emotional well-being.

It is easy to take something as simple as walking for granted. But each year, approximately 35,000 Canadians require a hip replacement to keep them mobile.

The most common reason for needing total hip replacement (THR), the surgery where a damaged and painful hip is replaced with a new artificial joint, is advanced osteoarthritis. This condition causes joint degeneration, leading to stiffness and pain. Not only can THR alleviate pain, but it can also improve patients' hip function, mobility and quality of life—or so it was thought. Recent studies have begun to question this belief, and are beginning to show that THR may only slightly improve the ability of patients to engage in fulfilling life activities, such as exercising, volunteering or socializing with friends and family.

To understand why this is the case, Krembil Senior Scientist Dr. Aileen Davis and TRI postdoctoral fellow Dr. Crystal MacKay had 376 patients complete a battery of questionnaires before and one year after THR. As part of the questionnaires, patients were asked to indicate how often they participate in 16 life tasks on a scale of one (never) to five (very often). The results were used to calculate what is known as the Late Life Disability Index, which describes the degree to which individuals participate in life activities.

The researchers found that those who experienced more positive life events—such as enhanced social activities, or improved work and financial situations—in the year following surgery were also more likely to engage in life activities (e.g., complete errands, exercise, visit family and friends, and volunteer).

This suggests that positive life events are a better promoter of activity than improvements in hip pain or function. Unexpectedly, complications from surgery and other health-related issues had little impact on whether individuals participated in life activities after surgery.

"Our findings indicate that to improve engagement in life activities after total hip replacement, we need to embrace a more holistic approach to treatment, which supports the person within the context of their life circumstances and not just physical rehabilitation," says Dr. MacKay.

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

MacKay C, Webster F, Venkataramanan V, Bytautas J, Perruccio AV, Wong R, Carlesso L, Davis AM. A prospective cohort study examining medical and social factors associated with engagement in life activities following total hip replacement. Osteoarthritis Cartilage. 2017 Feb 11. doi: 10.1016/j.joca.2017.02.787.

Interval Training Your Brain

People with depression can have trouble eating, sleeping or finding the motivation to exercise. rTMS can help those patients that do not respond to standard antidepressant medications.

Our thoughts are built on electricity.

More accurately, brain cells known as neurons communicate with each other using electrical signals. When these signals are faulty, neurological disorders, including depression, schizophrenia and Parkinson disease, can arise.

Faulty signaling can manifest in a variety of ways: there can be excessive electrical signaling in and across brain regions (too much excitatory activity) or important signals can be wrongly blocked (too much inhibitory activity). To treat unbalanced activity, which can occur in conditions such as depression, an innovative therapy known as repetitive transcranial magnetic stimulation (rTMS) has been shown to help. The therapy does not require surgery: instead, electrical currents are applied to a patient's scalp, which help to restore balance in defective brain circuits.

During rTMS, patients receive a series of electrical impulses that are separated by rest intervals, called inter-trial intervals (ITIs). Changing the frequency of electrical impulses or the duration of ITIs can alter how brain circuits respond to rTMS treatment. However, the optimal ITI to elicit therapeutic effects remains unknown.

Krembil Senior Scientist Dr. Robert Chen recently investigated how changing the ITI influenced brain activity: specifically, the balance between increased (excitatory) or reduced (inhibitory) activity. He found that rTMS has a greater influence on inhibitory brain circuity when the ITI duration was lessened; the proportion of patients whose inhibitory brain circuitry responded to rTMS went from 43 to 73% when ITI was reduced from 32 to 4 seconds. He also found that these inhibitory circuit changes occurred independently of excitatory circuit changes.

"This is the first study to demonstrate that it may be possible to substantially reduce treatment duration without affecting rTMS efficacy," says Dr. Chen. "If we can reduce the ITI, then we can deliver rTMS treatment in shorter sessions, reducing patient inconvenience and associated health care costs."

This work was supported by the Canadian Institutes of Health Research, Brain Canada, the National Institutes of Health, the Klarman Family Foundation, the Edgestone Foundation, the Ontario Brain Institute, and the Toronto General & Western Hospital Foundation.

Cash RF, Dar A, Hui J, De Ruiter L, Baarbé J, Fetters P, Peters S, Fitzgerald PB, Downar J, Chen R. Influence of inter-train interval on the plastic effects of rTMS. Brain Stimul. 2017 Mar 2. doi: 10.1016/j.brs.2017.02.012.

Arthritis Across the Ages

Arthritis does not only affect the obese or aged; extreme physical activity and injuries also increase the risk of arthritis.

Imagine if just walking around or getting up out of a chair was painful. This is the case for many people with arthritis—a family of joint diseases that cause pain and stiffness

By far the most common kind of arthritis is osteoarthritis, an age-related disease. This means that we can expect more people to suffer from the disease as Canada's population continues to get older.

While the number of people with arthritis is increasing, it is difficult to know exactly why. There are a number of risk factors for the disease beyond age. Thus, the odds of a millennial developing arthritis may not necessarily be the same as a baby boomer at the same age. Factors that

increase risk such as smoking and obesity, as well as factors that reduce risk such as income and education, change over generations.

To determine what risk factors are associated with arthritis prevalence across generations, Krembil Senior Scientist Dr. Elizabeth Badley and colleagues examined 16 years' worth of health data from the Canadian National Population Health Survey. They looked at arthritis prevalence and risk factors across four generations: the World War II "silent" generation (born 1935-1944), baby boomers (1945-1954 and 1955-1964) and Generation X (1965-1974).

The team found that arthritis is more prevalent in recent generations—and on average, recent generations are also getting the disease at a younger age. An important factor that predicted the increasing prevalence of arthritis was obesity. Even though recent generations are on average better educated, richer and smoking less than previous generations, which should be associated with less arthritis, they are also getting heavier which has largely cancelled out these advantages.

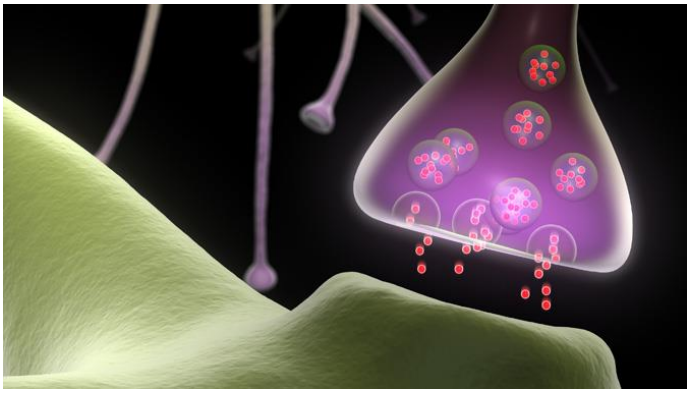
"Our understanding of the impact of weight on arthritis prevalence trends is likely to be an underestimate," comments Dr. Badley. "Arthritis prevalence may increase faster than previously believed as our population not only ages, but experiences increasing levels of obesity."

The differences between generations also highlight the need for arthritis management and education programs aimed at reducing obesity and other risk factors in young and middle-aged adults. These programs would help counter the earlier onset and increasing rates of arthritis experienced by those in Generation X and future generations.

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

Badley EM, Canizares M, Perruccio AV. A population-based study of changes in arthritis prevalence and arthritis risk factors over time: Generational differences and the role of obesity. Arthritis Care Res (Hoboken). 2017 Mar 8 doi: 10.1002/acr.23213

The Neuron's Outbox



Vesicles are small, bubble-like structures that store and release neurotransmitters (depicted in pink)—enabling cells to communicate with one another.

Have you ever touched a hot surface? Almost instantly, your brain not only receives messages about heat and pain, but also sends a message to pull your hand away from the surface.

These messages are transmitted across a complex network of specialized cells, called neurons, in a matter of milliseconds. This rapid method of communication is accomplished using small chemical messengers called neurotransmitters: the neuron sending the message releases neurotransmitters that are received by the next neuron, which continues to pass the message along in the same way.

Inside the sending neuron, neurotransmitters (ie, the message) are stored within "synaptic vesicles" (ie, the envelope). Synaptic vesicles fuse to the inner wall of the neuron nerve fiber terminal and rapidly release the neurotransmitters enclosed within, passing them on to the target neuron; however, it remains unclear how this function is accomplished.

It is for this reason that Krembil Senior Scientist Dr. Elise Stanley and her research team recently initiated a study to determine the exact interactions between synaptic vesicles and the sending neuron's inner wall. It is known that proteins embedded in the neuron's wall, called voltage-gated calcium channels (CaVs), enable synaptic vesicles to fuse. Thus, the team used sophisticated techniques to label synaptic vesicles and CaVs; they then visualized these labelled structures with state-of-the-art electron microscopes. The team found that CaV proteins anchor synaptic vesicles in place, right next to the neuron's inner wall. This CaV-synaptic vesicle binding could be the critical first step in triggering neurotransmitter release: the CaV may grab synaptic vesicles floating within the cell—bringing them close to the cell membrane such that they are ready to release their neurotransmitter contents.

“The results of this study contribute to our fundamental understanding of how cells in the nervous system communicate with one another,” says Dr. Stanley. “By building a more complete picture, we can identify molecules or processes that could be exploited for therapeutic purposes in cases where communication between neurons goes awry, as it does in degenerative or functional brain disorders such as Alzheimer disease or epilepsy.”

This work was supported by the Canadian Institutes of Health Research and the Toronto General & Western Hospital Foundation. E Stanley is a Tier 1 Canada Research Chair in Molecular Brain Science.

Chen RHC, Li Q, Snidal CA, Gardezi SR, Stanley EF. The calcium channel C-terminal and synaptic vesicle tethering: analysis by immuno-nanogold localization. Front Cell Neurosci. 2017 Mar 30. doi: 10.3389/fncel.2017.00085.

Making a Mental Map

An important role of the hippocampus is to facilitate spatial memory, including navigation. One study found that London cab drivers who served longer had larger hippocampus volumes.

Have you ever had trouble remembering where you parked your car in a busy parking lot? The part of the brain that enables us to learn and remember this type of information is known as the hippocampus. The same region also processes emotion—not surprising given that memories often hold powerful emotional weight.

When something goes wrong in the hippocampus, we have trouble remembering. The challenge for researchers is figuring out exactly what went wrong. This is because the brain is a huge electrical network: specialized cells known as neurons communicate with each other by transmitting electrical signals. Proteins on the surface of neurons, known as ion channels, enable this transfer of information by controlling the flow of charged particles (ions) in and out of the cell.

One way to tackle this challenge is to develop and use computer models to simulate brain function—these models can be programmed to mimic the activity of individual cells or entire brain networks.

Krembil Senior Scientist Dr. Frances Skinner and her PhD student, Vladislav Sekulić, recently took this approach to figure out how ion channels in the hippocampus affects brain function.

Their models focused on the distribution of ion channels on a particular type of neuron called O-LM cells, which are important for gating information flow into the hippocampus. O-LM cells fire together (ie, in synchrony) with other cells in the hippocampus. When these cells fire 4-7 times per second, they are believed to contribute to processing emotions. In contrast, when they fire 7-12 times per second, they are believed to be helping to form a mental map of your surroundings.

By artificially adjusting the distribution of ion channels in their models, the researchers found that specific combinations and distributions of ion channels predispose, or “tune”, the cells to fire at either low or high firing rates. Thus, their models suggest that OL-M cells contribute to emotional or spatial learning in the hippocampus by virtue of having different and particular ion channel distributions.

“It is exciting to consider that our modeling approach has been able to make predictions about the roles of specific cell properties in memory processing,” says Dr. Skinner. “As O-LM cell activity can be measured using implanted electrodes, the next step will be to test our models’ predictions in freely behaving animals. By working together, computer modellers and experimentalists can develop an understanding of how memory systems work, and by extension, help discover new treatments for memory disorders.”

This work was supported by the Natural Sciences and Engineering Research Council of Canada, the SciNet HPC Consortium and the Toronto General & Western Hospital Foundation.

Sekulić V, Skinner F. Computational models of O-LM cells are recruited by low or high theta frequency inputs depending on h-channel distribution. Elife. 2017 Mar 20. Doi: 10.7554/eLife.22962.

Healthy Fear of Heights

Blood oxygen levels can be lowered for prolonged periods of time during respiratory failure (as in ICU patient, pictured right), and also at high altitudes (pictured left).

For mountaineers who push themselves too far, too fast, a particular type of chronic mountain sickness, known as high-altitude cerebral edema, can develop.

A recent study, led by Krembil Clinician Investigator Dr. Daniel Mandell, revealed an unlikely link between mountaineers suffering from this condition and patients in the intensive care unit (ICU).

Dr. Mandell comments, “Our study showed that critically ill patients displayed extremely small, yet extensive points of bleeding in the brain known as microbleeds—a phenomenon that is also experienced by those suffering from this type of altitude sickness.”

The impetus for the study was to help explore unexplained intellectual decline experienced by some ICU patients. While the ICU provides a vital lifeline to those recovering from conditions such as major surgery, serious infections or organ failure, these patients often experience lingering memory problems and trouble concentrating.

In the study, the research team used magnetic resonance imaging (MRI) to look at the brains of 12 ICU patients. Discussing the approach, Dr. Mandell comments, “We used a type of MRI called ‘susceptibility weighted imaging’, which provides exquisite detail of blood flow in the brain.”

The cause of the microbleeds observed in ICU patients is still unknown. “While microbleeds are known to result from prolonged exposure to high altitudes, chronic high blood pressure or diseases of the blood vessels, the majority of our study participants did not have any of these conditions. This suggests that the microbleeds that we observed are a new phenomenon—one that warrants further study,” says Dr. Mandell.

One potential explanation for the observed microbleeds could be that they are caused by low blood oxygen levels. This is a particularly attractive idea because, similar to mountaineers at high altitudes, low blood oxygen levels are experienced by ICU patients with respiratory failure. In fact, in the study, most of the 12 ICU patients exhibited respiratory failure and all but one of them required mechanical ventilation.

While it is still not clear whether microbleeds account for the unexplained intellectual symptoms experienced by ICU patients, these findings lay the groundwork for future studies that will explore this link and develop approaches to prevent microbleeds.

This work was supported by Remmert Adriaan Laan Fonds (Dr. Coutinho) and the Toronto General & Western Hospital Foundation.

Fanou EM, Coutinho JM, Shannon P, Kiehl TR, Levi MM, Wilcox ME, Aviv RI, Mandell DM. Critical Illness-Associated Cerebral Microbleeds. Stroke. 2017 Apr;48(4):1085-1087. doi: 10.1161/STROKEAHA.116.016289. Epub 2017 Feb 24.

Krembil Relentless.

UHN Toronto Western Hospital

@KrembilRI

@KrembilRI

For more information about upcoming events, please contact the Krembil administration team: **krembil@uhnresearch.ca**

If you have any feedback about the newsletter, please contact Nick Dery: **ndery@uhnresearch.ca**

To access previous issues, visit the **The Krembil archives** at www.uhnresearch.ca/krembil_newsletters.