The Krembil

March 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

Krembil Research Day Coming Soon

Graduate students, postdoctoral fellows and clinical fellows can submit an abstract for a poster presentation, 3-minute elevator pitch or 10-minute oral presentation.

The Krembil Research Institute is holding its 17th annual Research Day on Wednesday, May 10, 2017. The event will feature innovative methods and the latest research advances from Krembil's basic science, translational and clinical researchers. It will also be an opportunity to hear about trainees' research achievements, as they showcase their work via poster and oral presentations. This year's Research Day will be held at the Chestnut Residence and Conference Centre on 89 Chestnut Street.

The 2017 Research Day Keynote Speaker will be Dr. Eve Marder, Professor of Biology at Brandeis University. Dr. Marder's research is focused on how groups of brain cells interact and communicate with each other through networks known as neural circuits. These neural circuits allow signals to be passed between distant parts of the body, a critical component of the central nervous system. She is particularly interested in how some neural circuits maintain a similar function over time despite ongoing changes to the brain cells that make them up.

All Krembil researchers, trainees and staff are welcome to attend the event. There is no registration fee, but you must complete online registration if you are planning to attend.

The deadline for general registration is Monday, May 1, 2017 at 4 pm.

Additional information can be found on the Krembil Research Day website.

Celebrating New Appointments

Krembil Affiliate Scientist Dr. Clement Hamani's research focuses on the neurosurgical treatment of movement disorders, epilepsy, pain and psychiatric disorders such as major depression and schizophrenia.

Once per year, Krembil Director Dr. Donald Weaver hosts an event to recognize the Institute's new research appointments. This year's event took place on March 24th, at which Affiliate Scientist Dr. Clement Hamani and 33 newly appointed Clinician Investigators were welcomed to the Krembil family.

It is important to note that, although new to the Institute, many of the Clinician Investigators are not new to research; they have been performing research at UHN for many years.

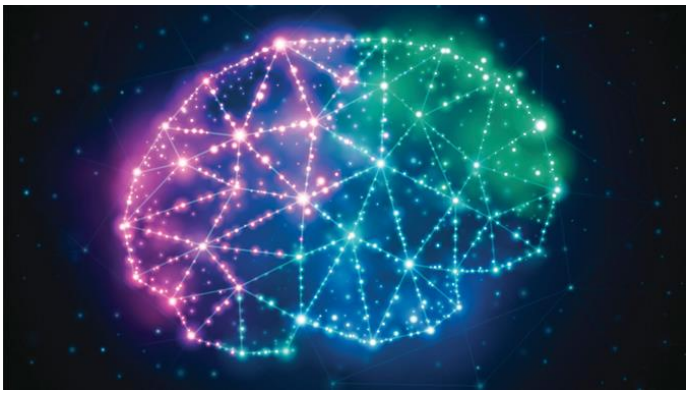
The Clinician Investigator appointment was launched in Fall 2015 to facilitate and advance clinical research at the Hospital. Once appointed as a member of the Institute, Clinician Investigators receive access to select resources. For example, they become eligible for internal small equipment and trainee support grant competitions. They also receive access to grant development and research dissemination services.

Most Clinician Investigators are physicians or surgeons who spend a majority of their time dedicated to clinical service, but they also lead significant research projects that span all three of Krembil's research pillars (ie, neuroscience, arthritis and vision). For example: Dr. Michael Brent studies vision loss and sight-restoring treatment, specifically related to age-related macular degeneration, diabetic retinopathy and vascular occlusive diseases; Dr. Christian Veillette collects patient outcomes data and uses predictive analytics to better inform clinical decision making; and Dr. Roger McIntyre studies the connection between mood disorders and cognitive impairment, with the aim of improving diagnostics and treatment.

Interested applicants must be actively performing clinical research and meet the criteria for research excellence, evaluated based on research funding; publication record; invited lectureships; engagement in teaching and mentorship roles; and participation on committees. Interested applicants should submit a letter of interest and a current CV to the Krembil administration office: krembil@uhnresearch.ca.

Research

Walking with Parkinson's



Lesion network mapping is a relatively new technique that has been used to identify brain regions implicated in pain, hallucinations and impaired decision making.

Imagine that while walking to the corner store, you freeze in mid-step and are unable to move your leg forward. This is something that nine out of ten people living with advanced Parkinson disease experience—a condition that is known as freezing of gait (FOG). Although FOG is a common cause of falls and severely compromises quality of life, the underlying disease mechanisms remain unclear.

To gain further insight into the causes of FOG, Krembil Clinician Investigator Dr. Alfonso Fasano co-led a new study examining the brains of 14 people who developed FOG as a consequence of various types of localized brain damage. The study was the result of international collaborations between UHN, the Berenson-Allen Center for Noninvasive Brain Stimulation, Harvard Medical School and Beth Israel Deaconess Medical Center.

The approach used by the researchers, known as 'lesion network mapping', was developed by Dr. Fasano's collaborators. He comments, "When the brain is damaged, due to stroke or cancer, scarring can develop in specific regions. Lesion network mapping works by pinpointing these scars, which are known as lesions, using magnetic resonance imaging to provide insight into brain function based on what symptoms are observed."

The researchers superimposed the locations of the lesions, as well as the connected brain regions (ie, brain networks), onto reference brains. By identifying the regions where most of the lesions and their networks overlapped, they discovered that 13 of the 14 lesions were connected to a specific region of the cerebellum—a part of the brain needed for producing precise and coordinated movements.

Dr. Fasano explains, "Our findings move us one step closer to helping those with the most severe forms of FOG in Parkinson disease—an achievement that is partly due to the patient population that we chose to focus on. By selecting 14 patients with medication-resistant FOG that did not have Parkinson disease, we were able to avoid other confounding symptoms that are often observed in patients with advanced Parkinson disease. Our next focus will be on defining the ideal target for deep brain stimulation as a potential therapeutic approach to help these patients."

This work was supported by the Sidney R Baer Jr Foundation, the National Institutes of Health, the Dystonia Medical Research Foundation and the National Parkinson Foundation, the National Center for Research Resources: Harvard Clinical and Translational Science Center and the Toronto General & Western Hospital Foundation.

Fasano A, Laganiere SE, Lam S, Fox MD. Lesions causing freezing of gait localize to a cerebellar functional network. Ann Neurol. 2017 Jan. doi: 10.1002/ana.24845.

Triggering Factors

Seizures occur when there is a sudden burst of electrical activity in the brain that disrupts normal activity and transmission of signals between brain cells.

Seizures can cause uncontrolled movements or a momentary loss of consciousness. These are symptoms that are frequently experienced by people with epilepsy—a common brain disorder characterized by recurring, unexpected seizures.

Researchers are not exactly sure how seizures are generated, but it is widely believed that potassium plays a role. Potassium is an electrically charged ion essential for healthy brain function. It moves across the cell membrane through specific channels, transmitting the electrical signals that regulate brain activity. However, brain activity can be disrupted when potassium levels are imbalanced, leading to a seizure.

To better understand the connection between potassium regulation and seizure onset, Krembil Senior Scientist, Dr. Peter Carlen, and his collaborators recently examined the role of a channel, known as the connexin-43 gap junction channel, that controls potassium distribution between brain cells called astrocytes.

Using measurements in the mouse brain, they discovered that blocking connexin-43 gap junctions significantly increased potassium levels outside of the cell; however, this imbalance was not enough to induce seizure activity.

When the researchers increased potassium levels using a compound that is known to induce seizure activity, they were able to cause spontaneously recurring seizures, in a part of the brain known as the cerebral neocortex, in association with raised potassium. In contrast, adding potassium directly to the system without using the compound did not generate seizures.

“We have shown that you can achieve high levels of potassium without triggering seizures by blocking connexon-43 gap junctions and in so doing demonstrated the powerful role that these channels play in controlling potassium levels in the brain,” explains Dr. Carlen. “To the best of our knowledge this is the first study to demonstrate that higher potassium levels do not cause seizures in the cerebral neocortex.”

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

Bazzigaluppi P, Weisspapir I, Stefanovic B, Leybaert L, Carlen PL. Astrocytic gap junction blockade markedly increases extracellular potassium without causing seizures in the mouse neocortex. Neurobiol Dis. 2017 May. doi:10.1016/j.nbd.2016.12.017.

Mind Over Mirror

Anorexia nervosa leads to life-threatening conditions such as malnutrition and heart failure, and it remains the psychiatric disorder with the highest mortality rate.

Imagine if every time you looked in the mirror you did not like what you saw. This is the case for people with anorexia nervosa—a disorder characterized by a fear of gaining weight and preoccupation with body image.

To achieve a low body weight, people with anorexia nervosa exhibit behaviours such as restricting calories or over-exercising. And they often have mood disorders such as depression and anxiety, and are frequently in denial about their illness. Of those that do seek psychological therapy or other conventional treatments, up to half do not get better. For these people, there are few effective and long-lasting alternative treatments.

To address this issue, Krembil Senior Scientist Dr. Andres Lozano and a team of researchers that included Dr. Blake Woodside (TGHRI Affiliate Scientist) started using a surgical procedure called deep brain stimulation (DBS) as an experimental therapy for anorexia nervosa—a world first—in 2013. DBS involves implanting electrodes into specific parts of the brain and delivering electrical stimulation to modulate brain activity in these regions. Dr. Lozano targeted the subcallosal cingulate region with DBS, as this part of the brain is implicated in mood disturbances.

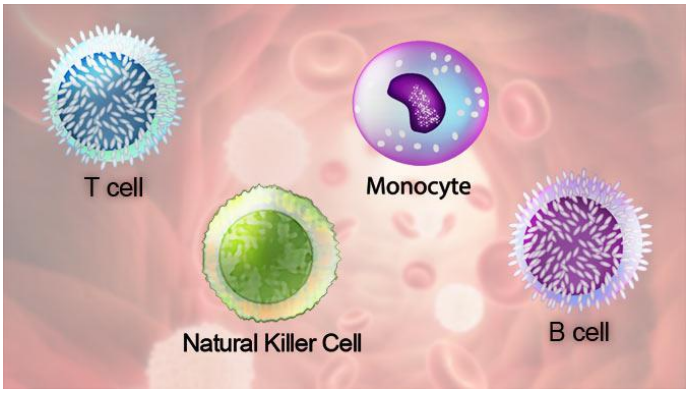
Building on these preliminary trials, which demonstrated promising results, the group of researchers initiated the largest and most comprehensive study to date investigating DBS for people with treatment-unresponsive anorexia nervosa. The results of the study demonstrated that the treatment is associated with increased body mass index (an indicator of body fat based on height/weight), as well as improved mood, including reduced depression and anxiety. Importantly, these effects were long-lasting, and the treatment was safe and well-tolerated.

“Our study emphasizes the need for continued research into our understanding of how the brain works—not only for anorexia nervosa, but also for other psychiatric disorders,” explains Dr. Lozano.

This work was supported by the Klarman Family Foundation Grants Program in Eating Disorders Research, the Canadian Institutes of Health Research and the Toronto General & Western Hospital Foundation. A Lozano is a Tier 1 Canada Research Chair in Neuroscience.

Lipsman N, Lam E, Volpini M, Sutandar K, Twose R, Giacobbe P, Sodums DJ, Smith GS, Woodside DB, Lozano AM. Deep brain stimulation of the subcallosal cingulate for treatment-refractory anorexia nervosa: 1 year follow-up of an open-label trial. Lancet Psychiatry. 2017 Feb 23. doi: 10.1016/S2215-0366(17)30076-7.

Finding the Root Cause



Certain immune cells, known as mononuclear cells (a selection of which are pictured), accumulate at the site of persistent inflammation.

Too much of a good thing can be harmful.

This definitely holds true when it comes to the immune system. As the body’s primary weapon against bacterial and viral intruders, the immune system is vital for maintaining health. But an overactive immune response can also be detrimental and can lead to a prolonged immune response (ie, chronic inflammation) that can damage healthy tissue.

When the immune system attacks the joints of the spine, spinal arthritis can result. Also known as ankylosing spondylitis (AS), this condition can cause the spine’s vertebrae to fuse. While there are medications that can slow disease progression or offer pain relief, there is currently no

cure for AS. Moreover, the exact causes of the disease remain a mystery.

However, it is known that genetics—the genes that you inherit from your parents—play a key role in AS. In total, over 60 genes have been linked to the disease.

Recent findings from Krembil Scientist Dr. Nigil Haroon reveal that the function of a gene, known as endoplasmic reticulum aminopeptidase 2 (ERAP-2), is abnormal in individuals with AS. Now his research team is digging deeper into how exactly abnormal ERAP-2 function may contribute to disease.

The researchers used experimental models and patient immune cells, known as peripheral mononuclear cells, to explore the role of ERAP-2 in AS. “When ERAP-2 was missing or decreased, we saw increased levels of particular immune proteins, known as MHC-I free heavy chains, that are associated with disease risk. This is particularly relevant because one type of MHC-I free heavy chain molecule—known as HLA-B27–is found in 80-90% of AS patients. We also saw increased levels of cellular stress known as the unfolded protein response. And it is known that overstimulation of this response can lead to chronic inflammation—a key factor in the development of ankylosing spondylitis,” says Dr. Haroon.

By uncovering the role of this gene in AS, Dr. Haroon has laid a foundation for the design and identification of new curative treatments that could one day address the underlying causes of this disease.

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

Zhang Z, Ciccia F, Zeng F, Guggino G, Yee K, Abdullah H, Silverberg MS, Alessandro R, Triolo G, Haroon N. Functional interaction of ERAP2 and HLA-B27 activates the unfolded protein response. Arthritis Rheumatol. 2016 Dec 28. doi:10.1002/art.40033.

All in the Family

Frontotemporal dementia affects men and women equally and is the second most common early onset dementia after Alzheimer disease.

Neurological diseases can be a major challenge to treat. Part of this challenge is that the same neurological disease can cause different symptoms and respond differently to therapies depending on the patient. Identifying defective genes associated with disease can aid in creating better, more customized therapeutics; however, as more genes are considered, another level of complexity can arise.

This is the case for a gene known as C9orf72, which is commonly mutated in individuals with amyotrophic lateral sclerosis (ALS) and/or a type of dementia known as frontotemporal dementia (FTD).

These diseases represent two different types of disorders: ALS affects nerve function, while FTD affects brain function. Thus, to help differentiate whether the C9orf72 mutation causes ALS or FTD, researchers have identified additional mutated genes that act as ‘modifiers’ to shift outcomes.

One such ‘modifier’ gene is ATXN2. This gene is present as one of three sizes based on the number of ‘CAG-repeats’ present within it: a normal form (22-23 repeats), an intermediate form (27-33 repeats) and a long form (>35 repeats).

In individuals with C9orf72 mutations, the intermediate form of ATXN2 predisposes individuals to ALS, but not FTD. On the other hand, it remains unclear whether the long form plays a role in disease onset in either of these patient groups.

To shed light on this, Krembil Clinician Investigator Dr. Carmela Tartaglia identified, for the first time, two patients with C9orf72 mutations who also had the long form of ATXN2 mutation. In contrast to people who have the intermediate length mutation of ATXN2, these two patients had FTD, but not ALS.

Dr. Carmela Tartaglia explains, “We were lucky to identify these two mutations as they are not often screened for at the same time. We first screened for the ATXN2 mutation because the patients had coordination problems, at which point we

found the long form of the mutation. Then, because the patients had atypical symptoms, including significant behavioral and cognitive changes in addition to coordination problems, we screened for and found mutations in the C9orf72 gene."

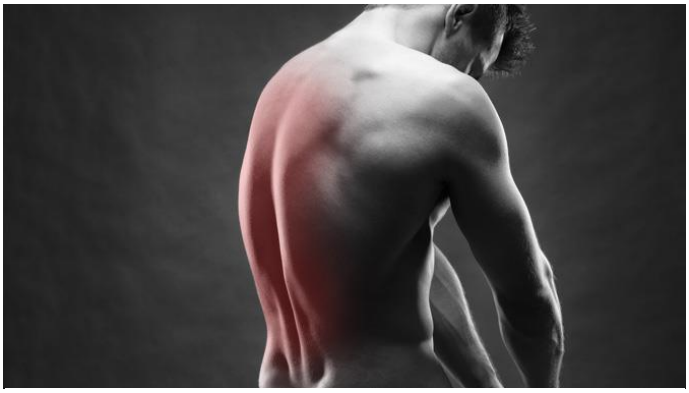
"Because the patients do not show signs of ALS, this study suggests that the long form of ATXN2 may modulate the pathologic mechanism of C9orf72 mutations differently than the intermediate length mutation."

Taken together, these findings show that much more remains to be discovered about the interplay between genetics and symptoms in this disorder—findings that will inform improved diagnostics and the creation of better, more customized therapies."

This work was supported by the Canadian Consortium on Neurodegeneration in Aging, the Weston Brain Institute and the Toronto General & Western Hospital Foundation.

Zhang M, Xi Z, Misquitta K, Sato C, Moreno D, Liang Y, Slow E, Rogaeva E, Tartaglia MC. C9orf72 and ATXN2 repeat expansions coexist in a family with ataxia, dementia, and parkinsonism. Mov Disord. 2017 Jan. doi: 10.1002/mds.26841.

Back to the Basics



Ankylosing spondylitis affects twice as many men as it does women and symptoms typically begin to appear in late adolescence or early adulthood.

The worst-case scenario for people with ankylosing spondylitis (AS) is complete fusion of the spine.

AS is a form of arthritis that primarily affects the joints of the spine for which there is currently no cure. It is characterized by pain, swelling and inflammation. The body adapts to the inflammation by calcifying the soft tissues around the affected joints (ie, turning them into bone). Over time, this process leaves the spine as stiff as a tree trunk, severely limiting mobility.

A particular gene, called the human leukocyte antigen B27 subtype (HLA-B27), is associated with the disease: over 90% of AS patients have HLA-B27. But fewer than 1 in 20 people with the HLA-B27 gene develop AS. Thus, there must be another mechanism involved in disease onset.

HLA-B27 delivers specific molecules, called antigens, to T-cells. T-cells activate the immune system when presented with antigens. Thus, a popular theory is that both HLA-B27 and disease-specific antigens are needed to initiate the chronic immune response observed in AS. But this theory has remained unproven.

A research team led by Krembil Senior Scientist Dr. Robert Inman and Dr. Malek Faham from Adaptive Biotechnologies Corporation recently investigated the possible link between HLA-B27 and the immune system by collecting T-cells from people with and without AS. In studying the cells, the team found 21 features that were unique to T-cells from AS patients with HLA-B27. These results suggest that the T-cells in people with AS are able to receive certain antigens from HLA-B27 that the T-cells in healthy people are not.

These findings advance our understanding of the complex relationship between HLA-B27, the body's immune system and AS. They suggest that the immune system, triggered by a particular antigen that specifically interacts with HLA-B27, influences the development of AS—findings that may be the first step towards preventing the disease.

This work was supported by Adaptive Biotechnologies Corp., the W. M. Keck Foundation Medical Research Program and the Toronto General & Western Hospital Foundation.

Faham M, Carlton V, Moorhead M, Zheng J, Klinger M, Pepin F, Asbury T, Vignali M, Emerson RO, Robins HS, Ireland J, Baechler-Gillespie E, Inman RD. Discovery of T-cell receptor beta motifs specific to HLA-B27+ ankylosing spondylitis by deep repertoire sequence analysis. Arthritis Rheumatol. 2016 Dec 21. doi: 10.1002/art.40028.

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

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