The Krembil

July 2016

Introducing *The Krembil*: the official newsletter of the Krembil Research Institute (formerly the Toronto Western Research Institute). *The Krembil* 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
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News

Recap of Krembil Research Day 2016

Krembil trainees communicated their findings through 10 oral presentations and close to 80 poster presentations.

The 16th Annual Krembil Research Day was held on May 18, 2016 at the Chestnut Residence & Conference Centre. The event was commenced by Dr. Christopher Paige, UHN Executive VP, Science and Research; and Dr. Donald Weaver, Krembil Research Institute Director.

The event featured presentations by Drs. Eugenia Kumacheva and Aaron Wheeler from University of Toronto's Department of Chemistry. They described innovative single-cell culture technologies for use in cell biology and medicine.

Throughout the day, Krembil trainees shared their latest findings via a series of oral and poster presentations. Graduate student and postdoctoral fellow categories for the top three oral and poster presentations were judged and later awarded (view the results here).

The keynote speaker was Dr. Betty Diamond, Investigator and Head of the Center for Autoimmune & Musculoskeletal Diseases at The Feinstein Institute for Medical Research. She is a leading expert in the molecular and immunological factors that influence the pathogenicity of systemic lupus erythematosus (SLE). Her talk was titled "Antibodies and the Brain" and described her latest research on the role of anti-DNA antibodies in SLE and the potential mechanisms that lead to neurological symptoms of the disease.

Save the Date
Next year's Krembil Research Day will be held on **May 10, 2017** at the Chestnut Residence & Conference Centre (89 Chestnut Street in Toronto) and will feature a keynote address by Dr. Eve Marder (recipient of the 2016 Kavli Prize in Neuroscience).

For more information or to provide feedback about Krembil Research Day, contact the Krembil Administration office.

New Members of TGWHF

(L-R) Janet Turner and Jen Power.

Please join the Krembil Research Institute (Krembil) in welcoming two new additions to the Toronto General & Western Hospital Foundation (TGWHF): Janet Turner and Jen Power. Both of these individuals will play key roles in securing philanthropic gifts, which will be critical for building and improving the Krembil's research capacity.

In support of patient care and research, the TGWHF has launched a number of strategic campaigns. The TGWHF campaigns connected to the Krembil's research in the areas of brain and spine, bone and joints, and vision include The Brain Campaign, The Campaign to Cure Arthritis, The Vision Campaign and The Campaign for the UHN Centre for Mental Health. Find more information on all of TGWHF's campaigns on their website.

Janet Turner has been appointed as the new Director of The Brain Campaign. She has a notable fundraising track record with organizations including Sunnybrook, Holland Bloorview and London Health Sciences Foundations. Janet brings 20 years of experience in donor engagement and securing major gifts to the TGWHF.

Jen Power was recently hired as a TGWHF Principal Gift Manager. Prior to joining TGWHF, she spent over seven years with the CAMH (Centre for Addiction and Mental Health) Foundation. Jen is responsible for securing gifts that will be used to support the UHN Centre for Mental Health, Epilepsy and Core Research. Core funding is essential for maintaining the Krembil's infrastructure and day-to-day operations, as well as for supporting exciting trainee learning opportunities such as the annual Krembil Research Day and the Krembil Seminar Series.

Janet and Jen will no doubt contribute to the ongoing success of the Krembil, helping the institute to secure state-of-the-art research tools and achieve its vision of *a world without chronic, debilitating disorders*.

Research

Making Depression Less Debilitating

Poor workplace performance and sick days due to depression are major contributors to the $83 billion annual costs attributed to the disease.

Depression is one of the most common mental disorders in North America. Its symptoms include persistent feelings of sadness and hopelessness, low self-esteem and loss of interest or pleasure.

Depression can also impair a person's ability to think, concentrate, form memories and solve problems. These "cognitive deficits" can persist even after mood has improved and can interfere with social interactions and workplace performance. Presently, there are no treatments available that specifically target these deficits.

To address this, Krembil Clinician Investigator Dr. Roger McIntyre examined the effectiveness of two conventional antidepressants—vortioxetine and duloxetine—in treating the cognitive deficits associated with depression.

Dr. McIntyre and colleagues examined the outcomes of three clinical trials that enrolled a total of 1,652 participants diagnosed with depression. Each participant had received either vortioxetine, duloxetine or a placebo containing no drug for eight weeks. Their depressive symptoms and mental function were assessed before and after treatment. Dr. McIntyre and his colleagues' careful statistical analyses revealed that the study participants who received vortioxetine experienced significant and consistent improvements in cognitive function; however, those who received duloxetine did not.

"These findings suggest that vortioxetine could be a more effective treatment for depression—by improving mood and cognitive impairments," says Dr. McIntyre. "However, more research and longer-term clinical studies are needed before we can confirm this."

This work was supported by H. Lundbeck A/S, the Takeda Pharmaceutical Company Limited and the Toronto General & Western Hospital Foundation.

The effects of vortioxetine on cognitive function in patients with major depressive disorder (MDD): a meta-analysis of three randomized controlled trials. McIntyre RS, Harrison J, Loft H, Jacobson W, Olsen CK. International Journal of Neuropsychopharmacoly*. doi: 10.1093/ijnp/pyw055. 2016 June 15.* [Pubmed abstract]

Determining Degree of Knee Damage

Osteoarthritis affects approximately one in ten Canadians (The Arthritis Society). Exercise and physiotherapy can help alleviate the pain associated with the disease.

A joint is a connection between two bones. It contains cartilage and synovial fluid that act as a cushion and a lubricant, respectively, to protect bones from friction.

In osteoarthritis (OA), cartilage is destroyed and the composition of synovial fluid changes—causing joint stiffness, bone damage and pain. The disease progresses relatively unnoticed; by the time that it is diagnosed, the damage is often so severe that treatments are no longer effective.

Developing a molecular test that identifies early stages of OA could be used to predict damage before it happens, enabling earlier treatments. Small RNA molecules—called miRNAs—are found throughout the body and can turn on or off specific disease-related genes; therefore, they are often used in molecular tests as predictors of disease. A miRNA test that can distinguish between different stages of knee OA has not yet been developed.

Krembil Senior Scientist Dr. Mohit Kapoor initiated a study to address this issue. Dr. Yinghua Li from his team examined the levels of 752 different miRNAs in the synovial fluid of people with early-stage OA (those with little or no damage) or late-stage OA (those with moderate to severe damage). They found that the levels of seven miRNAs varied between the two stages, and that this set could be used to classify the stage of disease. Using complex computational models in collaboration with Dr. Igor Jurisica (Senior Scientist, Princess Margaret Cancer Centre), the team predicted that the set could collectively control two genes, RC3H1 and QKI.

“Our study is the first to report a set of miRNAs in the synovial fluid that can be used to distinguish between early- and late-stage knee OA,” says Dr. Kapoor. “Moreover, the roles of RC3H1 and QKI in knee OA are not known, representing new avenues of study on the path to finding effective new treatments for this chronic disease.”

This work was supported by the Arthritis Program at the University Health Network and the Toronto General &Western Hospital Foundation. I Jurisica is a Tier 1 Canada Research Chair in Integrative Cancer Informatics.

Identification of synovial fluid microRNA signature in knee osteoarthritis: differentiating early- and late-stage knee osteoarthritis. Li YH, Tavallaee G, Tokar T, Nakamura A, Sundararajan K, Weston A, Sharma A, Mahomed NN, Gandhi R, Jurisica I, Kapoor M. Osteoarthritis and Cartilage*. doi: 10.1016/j.joca.2016.04.019. 2016 Apr 30.* [Pubmed abstract]

Shaping Brain Waves

Abnormal electrical activity in the brain has been linked to neuropsychiatric disorders including epilepsy, Parkinson disease, schizophrenia and major depression.

Brain cells communicate with each other using pulses of electrical activity. Large groups of brain cells can synchronize their activity, causing large-scale rhythmic or repetitive electrical activity, similar to a heartbeat.

Large-scale brain activity fluctuates in specific rhythms—called “neural oscillations”—that can change frequency depending on arousal or attention. These neural oscillations play an important role in shaping our behaviour and have been linked to many actions, such as information processing, perception, motor control and memory.

Neural oscillations can also be shaped by applying electrical stimulation to a person’s scalp—a technique that is increasingly used to treat conditions that have become unresponsive to existing therapies (eg, treatment-resistant depression). Despite its utility in the clinic, little is known about how electrically stimulating a small number of neurons

at the brain's surface can influence whole-brain activity and behaviour.

To address this issue, Krembil Scientist Dr. Jérémie Lefebvre developed a computational model of how the brain might adapt to different electrical stimulation intensities and frequencies. His model revealed that, in addition to sustained and recurring stimulation, exposure to intense, high-frequency stimulation can cause ongoing brain waves to accelerate—a sign of improved information processing and awareness.

"These results open new perspectives on the manipulation of synchronous neural activity for basic and clinical research," says Dr. Lefebvre. "Information gleaned from our model lays the groundwork for future studies investigating how temporary treatment with brain stimulation can cause lasting effects in neuropsychiatric diseases with unbalanced brain activity, including major depression, Parkinson disease and schizophrenia."

This work was supported by the Natural Sciences and Engineering Research Council of Canada, the Swiss National Science Foundation, the European Research Council, the German Research Foundation and the Toronto General & Western Hospital Foundation.

Shaping intrinsic neural oscillations with periodic stimulation. Herrmann CS, Murray MM, Ionta S, Hutt A, Lefebvre J. The Journal of Neuroscience. *doi: 10.1523/JNEUROSCI.0236-16.2016. 2016 May 11.* [Pubmed abstract]

Tackling Brain Injury Head-On

At least 96% of all professional football players suffer from concussion-related brain damage at some point during their career.

Concussions are a widely underreported and debilitating sports injury. The effects of multiple concussions over time can result in lasting brain damage, memory loss and mood disorders such as depression and anxiety.

Professional football players are particularly vulnerable to the effects of multiple concussions: they receive on average about 900 to 1,500 blows to the head per season. Researchers are still unclear about how these repeated blows lead to the psychological symptoms that are seen in some retired football players.

To shed light on this issue, Krembil Clinician Investigator Dr. Carmela Tartaglia led a study to evaluate the effect of repetitive concussions in retired professional football players. The study team used sophisticated, novel imaging to evaluate the integrity of the fibers that connect the different parts of the brain—known as white matter—in order to gain a better understanding of how structural brain changes relate to psychological function.

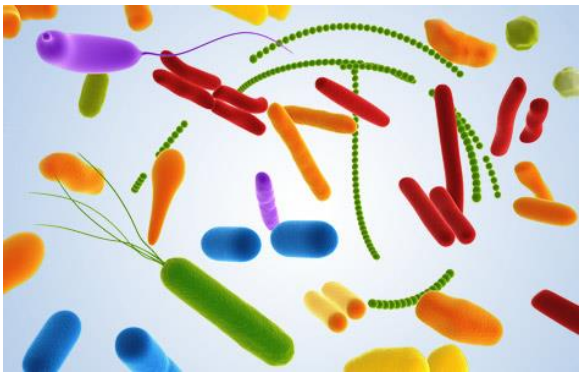
The researchers discovered that the former players, when compared to healthy subjects, had an area of the brain with decreased white matter integrity. As this area is important for visual memory, the team decided to investigate if the loss of white matter integrity had an effect on learning ability. They found reduced white matter integrity was linked to worse performance on a visual memory task.

Explains Dr. Tartaglia "Our study adds to the growing body of evidence linking multiple concussions to psychiatric and cognitive deficits in some athletes. The results explain some of the symptoms experienced by some of these athletes and suggests that brain imaging could complement existing psychological tests to identify neurological damage caused by sports-related concussion."

This work was supported by the PSI Foundation, the Canadian Sports Concussion Project, Krembil Neuroscience Centre and the Toronto General & Western Hospital Foundation.

The association between white-matter tract abnormalities, and neuropsychiatric and cognitive symptoms in retired professional football players with multiple concussions. Multani N, Goswami R, Khodadadi M, Ebraheem A, Davis KD, Tator CH, Wennberg R, Mikulis DJ, Ezerins L, Tartaglia MC. Journal of Neurology. *2016 May 3.* [Pubmed abstract]

Immune Cells from the Gut a Threat?



MAIT cells form part of the body's non-specific immune response that responds to general threats such as bacteria (various types of bacteria illustrated above).

Ankylosing spondylitis (AS) is a form of arthritis that is characterized by painful swelling in the back and neck joints. While this swelling is the result of inflammation, which is mediated by the body's own immune system, the underlying cause of the disease is unknown.

Because most patients with AS also have inflammation of the gut, it has been suggested that there is a link between immune cells in the gut and the development of AS.

To explore this link, Krembil Senior Scientist Dr. Robert Inman and Eric Gracey, a graduate student in the Department of Immunology, tested whether a type of immune cell that develops in the gut—known as a mucosal-associated invariant T (MAIT) cell—is involved in AS. MAIT cells develop in response to bacteria in the gut and can be found in other parts of the body. The researchers chose to study MAIT cells because they have been implicated in other chronic diseases such as rheumatoid arthritis and lupus.

The results showed that people with AS had fewer MAIT cells circulating in their blood than healthy individuals; however, when looking at the fluid within joints, they found higher levels of MAIT cells. This suggests that the cells might be recruited to sites of inflammation (ie, inflamed joints).

Detailed analyses of the MAIT cells from joints revealed that many of them were 'activated' in a state that could promote harmful inflammation. Dr. Inman explains, "These cells displayed proteins on their surface that are known to promote inflammation—and one of these, known as interleukin-17, has been implicated in AS."

These results strengthen the possibility that immune cells originating in gut play a role in AS, while providing new molecular targets that could inform the development of new treatments.

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

IL-7 primes IL-17 in mucosal-associated invariant T (MAIT) cells, which contribute to the Th17-axis in ankylosing spondylitis. Gracey E, Qaiyum Z, Almaghlouth I, Lawson D, Karki S, Avvaru N, Zhang Z, Yao Y, Ranganathan V, Baglaenko Y, Inman RD. Annals of the Rheumatic Diseases. *doi:10.1136/annrheumdis-2015-208902. 2016 May 10.* [Pubmed abstract]

Memory to Measure Brain Function

While there is no cure for Parkinson disease, several studies suggest that physiotherapy and resistance training may improve motor symptoms, including balance, and reduce falls.

Some people with Parkinson disease (PD) will lose their ability to store and retrieve memories. This memory dysfunction occurs as a result of tissue loss in the hippocampus—a brain region that is intimately involved in learning, memory and emotion.

These memory problems may be a key warning sign for those with PD that are at greater risk of a rapid decline in cognition (ie, mental processes that include attention, action planning, problem solving and reasoning).

But the standardized clinical tests that are being used to evaluate memory are dependent on brain regions other than the hippocampus, which are often compromised in PD. Disruption in these other brain regions can account for at least part of the poor memory scores, making it difficult to know whether the true cause of poor performance

is hippocampal dysfunction. Therefore, a more accurate measure of hippocampal-dependent memory is needed.

To address this need, a research team led by Krembil Clinician Investigator Dr. Melanie Cohn and Krembil Senior Scientist Dr. Mary Pat McAndrews investigated the utility of an experimental memory task—Associative Reinstatement Memory (ARM)—in more accurately assessing hippocampal function. They tested whether ARM performance specifically taxed the hippocampus. They also used advanced imaging techniques to visualize the level of hippocampal activation while participants performed the task.

PD patients scored worse on ARM compared to healthy individuals and had less hippocampal activity while performing the task. The team also found that ARM was a sensitive measure of memory dysfunction in PD that was unaffected by other mental processes.

“Our results suggest that ARM specifically measures hippocampal dysfunction,” concludes Dr. Cohn. “Thus, it may be a useful tool for identifying individuals with PD who have an especially poor prognosis to better inform treatment plans.”

This work was supported by a Parkinson Society Canada pilot-project Grant and the Toronto General & Western Hospital Foundation.

Associative reinstatement memory measures hippocampal function in Parkinson’s disease. Cohn M, Giannoylis I, De Belder M, Saint-Cyr JA, McAndrews MP. Neuropsychologia. *doi: 10.1016/j.neuropsychologia.2016.04.026. 2016 Apr 29*. [Pubmed abstract]

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