The Krembil

September 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

Arthritis Research in Focus

Third Globe and Mail magazine highlights Krembil arthritis research success stories.

The Krembil Research Institute has partnered with *The Globe and Mail* to release a magazine series highlighting Krembil research advancements. The third magazine in the series was distributed to Globe and Mail subscribers across Canada on September 7, 2017 and focuses on success stories in arthritis research.

"At Krembil, we've diligently built one of the top research programs in the world dedicated to finding [the cure for arthritis]," says Dr. Nizar Mahomed, Medical Director of the Arthritis Program at UHN. "We employ a collaborative, innovative team-first approach that's committed to stopping this disease in its tracks."

The current issue features a wide range of stories on Krembil researchers and arthritis research projects. These include a story on how Dr. Armand Keating is leading the first North American mesenchymal stem cell trial to treat patients with knee osteoarthritis at the source—an approach that Dr. Nizar Mahomed believes may one day make knee joint replacements obsolete.

Also featured are philanthropists Tony Fell and Bryce Douglas, who are the founding co-chairs of the Campaign to Cure Arthritis. As longtime supporters of the Arthritis Program at Toronto Western Hospital, they understand the devastating impact that arthritis can have on people's lives and the economy, and why private sector donations are critical to finding cures.

“There are many exciting stories of progress and success emerging from our laboratories,” explains Dr. Donald 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.”

Links to all three *Globe and Mail* magazines are available here.

Summer Student Research Day

Rapid fire talks highlighted Krembil advances in neuroscience, arthritis and vision research.

Twenty-two summer students conducting research in the areas of neuroscience, arthritis and vision presented their work at this year's event.

The 2017 Krembil Summer Student Research Day took place on August 23. The event, which was co-hosted by Drs. Frances Skinner and Joan Wither, offers summer students the opportunity to practice their presentation skills and to hear about different research performed by their peers over the summer.

After opening remarks from Dr. Donald Weaver, Director of the Krembil Research Institute, 22 summer students under the supervision of 18 different Krembil-appointed Principal Investigators presented their work. Through 5-minute 'rapid fire' talks, Krembil-led advances were highlighted in the fields of neuroscience, arthritis and vision research.

Examples included talks by: Afrin Bhattacharya from the lab of Dr. Cathy Barr on the effect of genetic variation in enhancers on risk for immune-mediated disorders; Prtha Kudesia from the lab of Dr. Rajiv Gandhi on the impact of osteoarthritis surgical outcomes on depressive symptoms; and Saba Samet from the lab of Drs. Martin Steinbach/Esther González on interhemispheric callosal dysfunction in early glaucoma.

Dr. Weaver closed the event by congratulating the students on their research achievements and their engaging presentations.

The event was co-organized by the Krembil Research Institute's Trainee Affairs Committee and its administration team. For more information or to provide feedback about the Summer Student Research Day, please contact the Krembil Administration office.

Facing the Strange Changes

Time and again, as new technologies hit mainstream, so do associated health concerns.

Bicycle face is a now discredited disorder that was first coined in 1897 to describe the 'dangers of bicycling', which included distorted facial expressions, wrinkles and bulging eyes.

Have you ever heard of a disorder known as *train brain*? How about *bicycle face*?

Both are bygone conditions that were, at one time, considered to be serious health problems. They also gained popularity when disruptive technologies (ie, train and bicycle travel, respectively) were first introduced on a grand scale.

The word 'disruptive' is used to describe technologies that reshape the world in which we live by creating new markets, changing how we do things or by impacting our core our values.

The connections between disruptive technologies and the rise of associated health concerns are discussed in a recent article by Krembil Director and Senior Scientist Dr. Donald Weaver. In the article, which was published in the journal *Neurology*, Dr. Weaver creates a new term to describe these disorders, known as disruptive technology disorders (DTDs).

Dr. Weaver also defines four predictable and step-wise stages through which the popularity of DTDs rise and fall. These include the introduction of the new technology in the 'preliminary phase'; the first description of the DTD, known as the 'initial moderate phase'; to an 'extreme phase' during which the number of purported sufferers quickly increases; and, finally, a 'second moderate phase' in which the pandemonium of the 'extreme phase' subsides.

One example of this, already alluded to above, is *train brain* (or *railway spine*). The term was first used in 1866 by British surgeon John Erichsen, during a time when commercial rail travel was gaining popularity, to describe posttraumatic back pain and headaches that were believed to be caused by the frequent accidents of early rail travel. Despite improvements that made rail travel safer, *train brain* continued to be diagnosed, such that even minor accidents were implicated. By the early 1900s, close to the peak of rail use, and after various studies failed to identify physical injury associated with the condition, diagnosis of *train brain* subsided.

Other DTDs include *elevator sickness*, *automobile-induced neurasthenia* and *phonograph-induced musicophobia*. One commonality between these disorders is that they often involve neurologic symptoms, such as headaches, dizziness and feelings of weakness.

The most recent DTD included in the article is *cell phone sickness*. In 1998, at the peak of cell phone-related health concerns, a Royal Society of Canada panel investigated the condition, which was characterized by headaches, dizziness and the fear of brain cancer. Since then, as cell phone use has increased immensely, the number people suffering from the disorder has sharply declined, suggesting that this DTD has progressed beyond the 'extreme phase' and has entered the final, and more moderate phase of the DTD lifecycle.

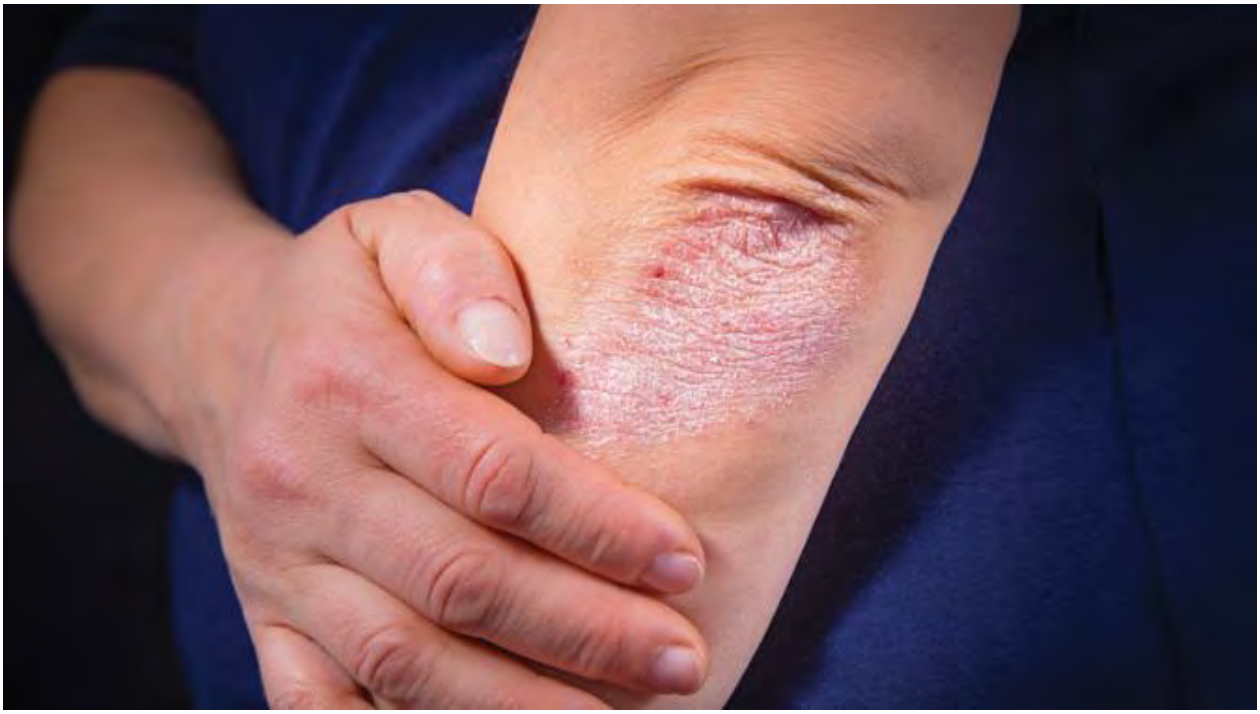
With the advent of smart phones and social media, a new condition is emerging known as *net-brain* (also *iDisorder*) which is characterized by 'narcissism, poor attention span and fear of missing out.' While you may think that you know someone with this disorder, only time will tell whether *net-brain* is the next DTD.

To learn more about the interplay between disruptive technology and health, read more at UHN.ca.

Supported by the Toronto General & Western Hospital Foundation. DF Weaver holds a Tier 1 Canada Research Chair in Clinical Neuroscience. Disruptive technology disorder: A past, present, and future neurologic syndrome. Weaver DF. Neurology. 2017 Jul 25;89(4):395-398. doi: 10.1212/WNL.0000000000004095.

Variations on a Gene

Researchers identify gene variants that are associated with psoriatic disease.



Psoriasis is a disease in which the body's immune system attacks skin cells, resulting in skin patches that are red, scaly and itchy.

Your genetic makeup is more than 99 percent similar to that of every other person. So, if we share so much similarity in our genes, what makes us different?

Part of the reason for our differences is that we inherit gene variants—called alleles—from our parents. While many alleles can exist for any given gene, each of us only has two per gene: one allele comes from our father and the other allele comes from our mother.

The different allele combinations for each of our tens of thousands of genes result in different observable traits, such as height or eye colour.

A new study by Krembil Senior Scientist Dr. Dafna Gladman shows that allele variation may also explain why some people are more susceptible to psoriasis, a common immune-mediated skin disease, and its related arthritis, psoriatic arthritis.

To demonstrate this, Dr. Gladman and her research team focused on the *KIR3DL1* gene, which encodes a protein that is known to play a key role in activating the immune system. The team developed a genetic method to identify different *KIR3DL1* alleles and classify them into four categories based on the corresponding state of the protein: high levels of protein, low levels of protein, null (undetectable) protein, and a shortened form of the protein.

Using this novel approach, the team identified and categorized *KIR3DL1* alleles from 652 people with psoriatic disease (including 260 patients with psoriasis only and 392 patients with psoriatic arthritis) and 371 people without the disease. They found that the null protein category was more frequent in those without psoriatic disease. There was no difference between those with psoriasis alone and those with psoriatic arthritis.

"Our results suggest that when alleles fall within the 'null' category, they may confer some type of protection against psoriasis," explains Dr. Gladman. "Our work lays the foundation for the development of clinical tools that may help clinicians better predict who is at risk for developing the disease, enabling earlier treatments and preventing long-term consequences."

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

Berinstein J, Pollock R, Pellett F, Thavaneswaran A, Chandran V, Gladman DD. Association of variably expressed KIR3dl1 alleles with psoriatic disease. Clin Rheumatol. 2017 Aug 11. doi: 10.1007/s10067-017-3784-5.

Breaking Epilepsy's Genetic Code

Genetic tests could improve diagnosis and treatment in patients with unexplained epilepsy.

Most cases of epilepsy are believed to be the result of a variety of genetic alterations combined with environmental factors.

Our bodies depend on electricity. Electrical signals are crucial for your heart to beat, and the electrical activity in your brain enables you to read and understand this sentence. When the electrical signaling goes awry, major health issues can arise.

Epilepsy is a neurological disorder characterized by recurrent surges of abnormal electrical activity in the brain that produce seizures. The cause of the surges is not well understood; however, researchers have shown that it can involve genetics, head trauma, developmental disorders, prenatal brain damage and infections.

Accurately diagnosing the cause of seizures is necessary for prescribing the best treatments. Despite this, in almost half of those affected by epilepsy, the cause of seizures is unknown.

Krembil Clinician Investigator Dr. Danielle Andrade recently examined the utility of a genetic test to help determine the cause of unexplained epilepsy in adults with intellectual disability (ID). The test detects a type of genetic alteration known as copy number variation (CNV), which has been linked to other diseases.

Dr. Andrade and her colleagues performed the genetic test on 143 adults and interpreted the

results in the context of each patient's clinical features. They found that a high proportion (16%) of these patients carried rare CNVs that contributed to their epilepsy. Of the CNVs identified, eight were found to affect genes previously implicated in ID, autism and/or epilepsy. Moreover, the researchers pinpointed five altered genes that most likely contributed to patients' clinical features.

"This study shows that genetic testing could provide clinicians with important information that may improve the diagnosis and treatment of epilepsy. Adults with epilepsy of unknown cause should be re-investigated with the modern DNA technologies available today", says Dr. Andrade.

This work was supported by the Ontario Brain Institute, the Government of Ontario and the Toronto General & Western Hospital Foundation. A Bassett holds a Tier 1 Canada Research Chair in Schizophrenia Genetics and Genomic Disorders.

Borlot F, Regan BM, Bassett AS, Stavropoulos DJ, Andrade DM. Prevalence of Pathogenic Copy Number Variation in Adults With Pediatric-Onset Epilepsy and Intellectual Disability. JAMA Neurol. 2017 August 28. doi:10.1001/jamaneurol.2017.1775

Predicting Osteoarthritis Severity

High-fat diets cause lasting changes in metabolism that may predict osteoarthritis severity.

High-fat diets can cause lasting changes in metabolism that can be detected in the blood months after returning to a normal diet.

“Obese people suffer from osteoarthritis worse than non-obese people” sounds like non-news. After all, it’s common sense that carrying more weight on your joints will lead to more pain and wear-and-tear. However, the truth is more complex than that: non-weight-bearing joints (such as the hands) also see increased rates of osteoarthritis associated with obesity, suggesting that another factor is at work.

A team of researchers, including Krembil Senior Scientist Dr. Mohit Kapoor, Drs. Poulami Datta, Yue Zhang and Jason Rockel, identified this as an important gap in understanding: "We know that there is something circulating in the blood of those on a high-fat diet that causes the process to accelerate. This is what we decided to investigate."

The researchers used an experimental model to answer important questions about the relationship between obesity and osteoarthritis. This form of arthritis is the most common, with more than three million Canadians affected. Obese individuals have an increased incidence of the disease and are 33% more likely to require joint replacement surgery.

Dr. Kapoor’s team found that the consumption of a high fat diet (leading to obesity) could speed up the effects of osteoarthritis on cartilage degradation. They then identified a set of three molecules in the blood that could be used to predict the risk of developing

osteoarthritis and the risk of increased severity. These molecules, called metabolites, are related to how fat is used by the body.

While eight metabolites are known to be associated with osteoarthritis, the new findings revealed that just three were needed to predict an increased risk of osteoarthritis severity. The research team also found that a hormone known to influence hunger, fat stores, metabolite levels and more—called leptin—was increased after the high fat diet. While blood levels of leptin returned to normal after switching back to a leaner diet, leptin levels in cartilage remained high for months. "The heightened levels of leptin in the joints that we observed may be key to understanding why the risk of osteoarthritis remains high for obese individuals, even after these individuals make positive lifestyle changes and lose weight," says Dr. Kapoor.

The team is now taking these results to the clinic: they will be collecting and analysing blood samples obtained from actual patients at Toronto Western Hospital to investigate the interplay between obesity, the metabolites that they identified and leptin in osteoarthritis.

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

Datta P, Zhang Y, Parousis A, Sharma A, Rossomacha E, Endisha H, Wu B, Kacprzak I, Mahomed NN, Gandhi R, Rockel JS, Kapoor M. High-fat diet-induced acceleration of osteoarthritis is associated with a distinct and sustained plasma metabolite signature*. Sci Rep. 2017 Aug 15;7(1):8205. doi: 10.1038/s41598-017-07963-6.*