The Krembil

November 2016

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
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News

A Catalyst for Discovery

(L-R) The event featured a candid conversation between Krembil Director and Senior Scientist Dr. Donald Weaver, and science communicator Jay Ingram.

The first ever Discovery Ball took place on Saturday October 15, 2016, at the Liberty Grand. It is a new fundraising initiative spearheaded by the Toronto General & Western Hospital Foundation (TGWHF) that pairs people who are committed to advancing health care with dedicated researchers at the Krembil Research Institute (the "Krembil"). The ultimate goal of the event is to promote the Krembil's research success and to raise the capital required to support continued research advancements.

The Discovery Ball planning committee was co-chaired by Dr. Michael Baker and Ms. Stacey Krembil; Dr. Baker also hosted the event. Nearly 400 distinguished guests attended the event, including some of the world's top philanthropists, and Krembil affiliated researchers and physicians.

The night commenced with a reception that featured an artistic display of a variety of cell images from neuroscience, arthritis and vision labs across the Krembil. Next, there was a raffle draw for some remarkable prizes, including a handcrafted diamond rivière necklet. A video highlighting the work of Krembil Senior Scientists Drs. Mohit Kapoor, Valerie Wallace and Donald Weaver was then premiered. You can watch the full video by following the TGWHF Videostream on YouTube.

A live auction, hosted by broadcaster, award-winning writer and producer Husein Madhavji, capped the event. The highest bidders won the chance to become a scientist for a day—a rare opportunity to visit the labs of Drs. Kapoor and Weaver.

The event raised nearly $1 million to support research at the Krembil, and because it was such a great success, the Discovery Ball will now run on a bi-annual basis as a staple of TGWHF's fundraising efforts.

Seizing the Day

Visiting speaker Dr. Gregory A. Worrell (pictured above), an expert in the transition from normal brain activity to seizures, described new methods for predicting when an epileptic seizure is going to happen.

The Anne & Max Tanenbaum Symposium on the Frontiers of Science took place on Wednesday November 2, 2016, in the BMO Education & Conference Centre located within the Krembil Discovery Tower. The event was hosted by the Anne & Max Tanenbaum Chair in Cognitive Neuroscience and Krembil Senior Scientist Dr. Peter Carlen.

The theme of this year's symposium was 'listening and responding to the brain: neuroengineering and epilepsy', bridging the latest technological advances in seizure therapeutics and recent findings in basic epilepsy research. The event featured a series of intriguing talks given by leading experts in epilepsy research. The first talk was given by Dr. Carlen, who spoke about the brainstem's role in seizures and seizure-related death.

The Symposium's keynote speakers were Dr. Dominique M. Durand from Case Western Research University and Dr. Gregory A. Worrell from the Mayo Clinic. Dr. Durand spoke about harnessing the power of single brain cells to prevent seizures, while Dr. Worrell's talk focused on methods to forecast future epileptic seizures.

Other speakers included Krembil Scientist Dr. Taufik Valiante, and Drs. Roman Genov and Berj Bardakjian from the University of Toronto. Dr. Valiante talked about potential biological markers that can be used to find the precise brain region where seizures are initiated. Drs. Genov and Bardakjian discussed state-of-the-art electrical stimulation techniques to stop or prevent seizures and new ways to detect the epicenter of seizure activity in the brain, respectively.

“By bringing together leaders in neuroengineering and epilepsy biology to share and exchange their expertise, the Anne & Max Tanenbaum Symposium has helped to foster interdisciplinary collaboration, which will no doubt spark future scientific progress,” says Dr. Carlen.

Research

Small Particles with Big Impact

Approximately 4,300 new cases of traumatic spinal cord injury occur in Canada every year, most commonly in males between the ages of 20 and 29.

Immediately after spinal cord injury, healthy nerve cells self-destruct, toxic factors are released at the site of injury, and scars or cavities form. This cascade of events can lead to partial or complete paralysis depending upon the severity and location of the injury.

Neural precursor cells (NPC)—which are stem cells that give rise to nerve cells—have shown great promise at repairing spinal cord injury; however, their use as a treatment is limited because the hostile conditions at the site of injury causes them to die.

Krembil Senior Scientist Dr. Michael Fehlings has been exploring ways to promote NPC survival by using artificially created peptide building blocks that can self-assemble into three-dimensional structures. These structures promote NPC survival by acting as a supportive scaffold that bridges the cavity that can be formed after injury. As a result of enhanced survival, NPCs are able to grow into healthy neurons that replace the damaged ones.

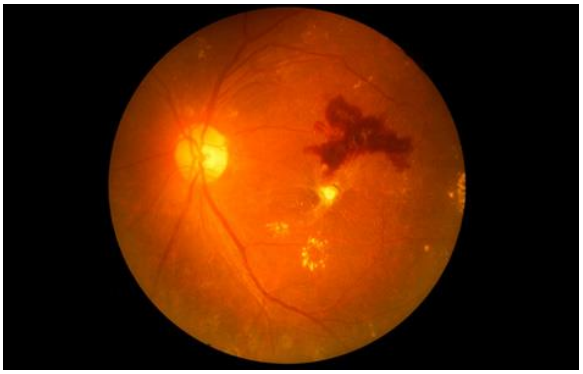
Dr. Fehlings and his team recently evaluated the potential of a novel self-assembling peptide (QL6) in further enhancing the effects of NPC therapy. His team found that injecting the peptide at sites of spinal cord injury not only increased transplanted NPC survival, but also led to improvements in limb function.

“We think that self-assembling QL6 peptides are an exciting strategy for promoting neural precursor survival,” explains Dr. Fehlings. “And we will be pursuing further research to evaluate their potential to support nerve cell regeneration and repair spinal cord injuries.”

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

Self-assembling peptides optimize the post-traumatic milieu and synergistically enhance the effects of neural stem cell therapy after cervical spinal cord injury. Zweckberger K, Ahuja CS, Liu Y, Wang J, Fehlings MG. Acta Biomaterials. *doi: 10.1016/j.actbio.2016.06.016. 2016 Sep 15.* [Pubmed abstract]

New Insights into Vision Loss



Virtually everyone who has had diabetes for at least 20 years will suffer from some form of vision impairment caused by damage to retinal blood vessels (pictured).

Diabetic retinopathy is the most common cause of blindness in working-age adults. It is a serious complication of diabetes in which the tissue layer at the back of the eye (retina) deteriorates.

Blood flow in the retina is altered in the early stages of diabetic retinopathy, suggesting that it could be a predictor of future vision loss; however, why blood flow alterations occur in people with the disease and how it contributes to degeneration of the retina is not known.

To address this issue, Krembil Senior Scientist Dr. Christopher Hudson and a team of graduate students and colleagues initiated a study to identify which proteins influence retinal blood flow in people with diabetic retinopathy. Using samples of eye fluid collected from study participants with early-stage diabetic retinopathy, his research team measured the levels of specific proteins that are thought to be disturbed in early diabetes. They found that people with diabetic retinopathy have increased levels of two proteins, TGF-β and PLGF, and decreased levels of the FGF-1 protein.

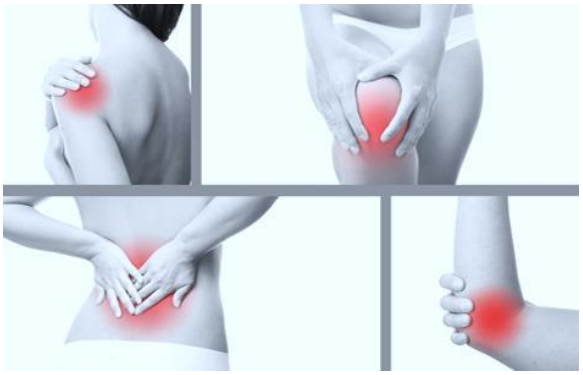
The team noted that it was the decreased levels of FGF-1 in particular that were associated with decreased retinal blood flow.

“Our study is the first to implicate FGF-1 as a factor associated with changes in retinal blood flow found in people with early diabetic retinopathy,” explains Dr. Hudson. “Although more research is needed, we are one step closer to developing a test that can help predict who is at risk of developing the disease—enabling earlier treatments to prevent or reverse vision loss.”

This work was supported by the Ontario Ministry of Research, Innovation and Science, the University of Toronto, the National Institutes of Health and the Toronto General & Western Hospital Foundation.

Aqueous humour concentrations of TGF-β, PLGF and FGF-1 and total retinal blood flow in patients with early non-proliferative diabetic retinopathy. Khuu LA, Tayyari F, Sivak JM, Flanagan JG, Singer S, Brent MH, Huang D, Tan O, Hudson C. Acta Ophthalmologica. *doi: 10.1111/aos.13230. 2016 Sep 28.* [Pubmed abstract]

Predicting Joint Pain in Women



Arthritis is a leading cause of disability among women in Canada; commonly affected joints include the shoulders, knees, spine and elbows.

In osteoarthritis (OA), the protective material at the ends of bones—called joint cartilage—breaks down. This results in bone-on-bone friction, leading to joint damage, swelling and pain. Inflammation in the affected joints is recognized as a contributing factor to these symptoms.

Studies have consistently identified differences between men and women with OA: women are more commonly affected, have a higher burden of disease and report greater joint pain associated with OA than men. Moreover, women may have a heightened inflammatory response, placing them at increased risk for OA-related joint pain.

To shed light on these differences, a team of investigators led by Krembil Scientist Dr. Anthony Perruccio examined how the link between inflammation and joint pain differed in men versus women. The research team measured the levels of C-reactive protein (CRP), a widely used marker of inflammation, in the blood of 189 men and women with OA. They also asked each participant to indicate how many of their joints caused them pain. The team found that the number of reported painful joints increased proportionally with levels of CRP in women with OA; however, there was no relationship between the two factors in men with OA.

Dr. Perruccio explains, “Our study findings create a potential avenue to better risk-stratify women and men with OA pain. This information can be used to tailor assessment and treatment plans to reduce disease symptom burden and improve outcomes for individuals living with OA.”

This work was in part supported by the Canadian Institutes of Health Research, the Arthritis Research Foundation and the Toronto General &Western Hospital Foundation through a University Health Network Arthritis Program Pilot Grant.

Systemic inflammation and painful joint burden in osteoarthritis: a matter of sex? Perruccio AV, Chandran V, Power JD, Kapoor M, Mahomed NN and Gandhi R. Osteoarthritis and Cartilage. *doi 10.1016/j.joca.2016.08.001. 2016 Aug 19.* [Pubmed abstract]

Good Intentions, Bad Reactions

Reactive gliosis occurs following injuries to the brain, spine and eye. This response can help protect the site of injury, but can also produce damaging inflammatory signals that prevent recovery.

Unlike with other parts of the body, damage to the brain, spine and eye (ie, the central nervous system) leads to a specialized inflammatory response. The inflammatory response in the central nervous system is termed ‘reactive gliosis’ and involves helper cells, known as astrocytes.

During reactive gliosis, astrocytes become activated and produce proteins called type III intermediate filaments—a process that occurs in nearly all neurodegenerative diseases including Alzheimer disease, Parkinson disease, stroke, diabetic retinopathy and glaucoma. Despite the common involvement of these intermediate filaments in the damage response, the specific role of these proteins in the balance between health and disease remains unclear.

The basic working unit within the central nervous system is known as a neuron; thus, promoting neuron survival is vital. Using the neurons within the retina of the eye as a model system to study neurological damage, Krembil Scientist Dr. Jeremy Sivak and his team studied the effect of blocking the production of type III intermediate filaments on neuronal survival. The team injected a specific inhibitor of type III intermediate filaments, known as withaferin (WFA), into injured eyes that were actively undergoing reactive gliosis. They found that WFA injection prevented reactive gliosis and blocked production of inflammatory signals leading to neuron death.

“To our knowledge, this is the first study to demonstrate that injecting small molecule drugs, such as WFA, into a living system can inhibit intermediate filament dynamics and protect neurons from the negative effects of reactive gliosis,” says Dr. Sivak. “Knowing how to control the body’s own responses to injury could enable scientists to create new treatments that prevent cell death or promote recovery in chronic disease.”

This work was supported by the Canadian Institutes of Health Research, the Glaucoma Research Society of Canada, the National Science and Engineering Research Council, and the Toronto General & Western Hospital Foundation. J Sivak is the Toronto General and Western Hospital Foundation Glaucoma Research Chair.

Pharmacologic inhibition of reactive gliosis blocks TNF-α-mediated neuronal apoptosis. Livne-Bar I, Lam S, Chan D, Guo X, Askar I, Nahirnyj A, Flanagan JG, Sivak JM. Cell Death and Disease. *doi:10.1038/cddis.2016.277. 2016 Sep 29.* [Pubmed abstract]

Towards Promoting Brain Repair

Two types of strokes can damage brain cells: ischemic strokes, which occur when blood vessels become blocked; and hemorrhagic strokes, which occur when blood vessels burst.

Stroke is a leading cause of long-term disability. People who suffer a stroke often experience neurological problems, such as difficulty using or understanding language, and problems with learning and memory.

The first few hours to days after a stroke are critical for preventing further brain damage. This is because, almost immediately after a stroke, the brain undergoes a potentially toxic inflammatory response. This response involves the release of various proteins in the 'interleukin' family. Some interleukins are helpful in the repair process, whereas others can exacerbate damage; thus, one potential therapeutic strategy is to stimulate the release of the interleukins that promote brain repair. However, no such treatments currently exist.

One protein in particular, called interleukin-4 (IL-4), has been shown to induce an anti-inflammatory state that is thought to reduce damage and promote repair. To explore the therapeutic potential of IL-4, Krembil Senior Scientist Dr. Lyanne Schlichter and her team tested whether supplementing the brain with additional IL-4 would lessen stroke-associated damage.

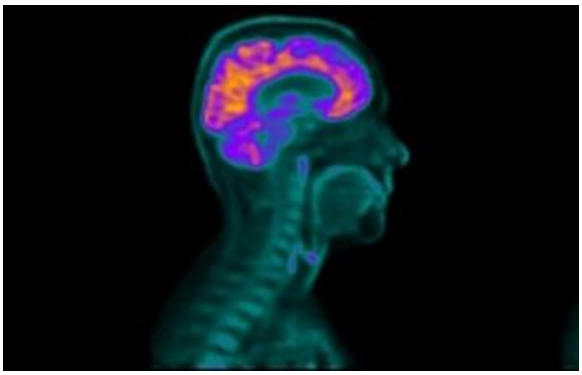
Using experimental models, the researchers artificially raised IL-4 levels and measured markers of inflammation. In this "proof-of-principle" study, a single, early IL-4 treatment increased the levels of several anti-inflammatory markers and immune cells involved in clearing cellular damage—and these levels remained elevated for seven days post-treatment.

"While raising IL-4 levels did not lessen the acute damage to neurons, the heightened and sustained effects on the immune response that we observed are promising," says Dr. Schlichter. "Future studies are needed to explore whether these long-term reductions in inflammation translate into improved clinical outcomes."

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

Molecular and cellular responses to interleukin-4 treatment in a rat model of transient ischemia. Lively S, Hutchings S, Schlichter LC. Journal of Neuropathology & Experimental Neurology. *2016 Sep 15.* [Pubmed abstract]

Finding the Fountain of Fatigue



Brain regions that are more active during a positron emission tomography (PET) scan show up as brighter in the resulting brain image (pictured above).

Parkinson disease (PD) is the second most common neurodegenerative disorder after Alzheimer disease. It is characterized by tremors, rigid muscles, slow movements and problems with posture and balance. In addition to these symptoms, up to 70% of people living with PD will experience an unexplainable and debilitating fatigue, for which no treatment is available.

Krembil Senior Scientist Dr. Antonio Strafella launched a study to find out why so many people with PD feel an overwhelming lack of energy. He used a positron emission tomography scanner to obtain brain images from 23 PD patients with and without fatigue. Positron emission tomography is an advanced imaging technique that can be used to examine the metabolic activity (ie, energy use) of tissues comprising an organ such as the brain. Study participants also completed questionnaires to assess their fatigue level and sleep quality.

By comparing the brain images, the research team discovered that two groups of brain regions in particular—the salience network and the default mode network—display different levels of activity between PD patients with and without fatigue. The salience network was less active and the default mode network was more active in PD patients with fatigue than in those without fatigue. The salience network is involved in preparing the brain for action, so its reduced activity may be a contributing factor in causing fatigue in PD.

“According to the patients in my clinical practice, fatigue is one of the more devastating symptoms of PD,” says Dr. Strafella. “However, we must work to better understand the physiological mechanisms that contribute to fatigue in PD before we can develop a way to treat it.”

This work was supported by Parkinson Society Canada, and the Toronto General & Western Hospital Foundation. AP Strafella holds a Tier 2 Canada Research Chair in Movement Disorders and Neuroimaging.

Fatigue in Parkinson's disease: The contribution of cerebral metabolic changes. Cho SS, Aminian K, Li C, Lang AE, Houle S, Strafella AP. Human Brain Mapping. *doi: 10.1002/hbm.23360. 2016 August 29.* [PubMed abstract]

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