The Krembil

July 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

New Arthritis Research Director

Dr. Kapoor (above) has an accomplished research program aimed at understanding how osteoarthritis progresses, identifying new biological markers to support osteoarthritis diagnosis and disease tracking, and developing novel therapeutic strategies to counteract joint destruction.

The Krembil Research Institute has embarked on a mission to achieve operational excellence, and focus and augment research activity. As part of this endeavour, Krembil Senior Scientist Dr. Mohit Kapoor has been named as the inaugural Research Director for the arthritis research group.

The mission began with the merging of vision research and clinical programs into one institute, the Donald K. Johnson Eye Institute, under the combined leadership of Co-Directors, Drs. Valerie Wallace and Robert Devenyi. This collaborative effort has already resulted in renewed direction for the vision science research group at Krembil. The next step is to establish research priorities for the arthritis research group.

"It is essential that we establish research priorities that position us for the future," says Krembil Director Dr. Donald Weaver. "Building harmony between our fundamental and clinical science pursuits will foster collaboration amongst the various medical and surgical disciplines, leading to novel and important research questions, and facilitating the transfer of basic research advancements into clinical practice."

As part of his new role, Dr. Kapoor has been charged with the task of developing a harmonized strategic research plan (SRP) that will set the arthritis research group's direction for the next five years, while laying the groundwork for its continued success beyond the next five years. In addition, Dr. Kapoor will be working with the Toronto General & Western Hospital Foundation to help align fundraising priorities with the SRP.

In developing the SRP, Dr. Kapoor will begin an open consultation process with Division Heads, Drs. Aileen Davis (Healthcare Outcomes and Research) and James Eubanks (Genetics & Development); other members of the Krembil Research Council; arthritis research group members, who have active research programs in ankylosing spondylitis, osteoarthritis, pain, psoriatic arthritis, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, and other bone, muscle and joint diseases; and clinical leaders.

"The practice of building and implementing a new research plan is an important one," stresses Dr. Kapoor. "It provides a framework for what we are trying to build, a world leading biomedical research institute, and reinforces why we are building it—to discover cures and improve our patients' quality of life."

Globe and Mail: Krembil Eye Research

At the Donald K. Johnson Eye institute, clinicians work together with vision scientists, such as Co-Director Dr. Valerie Wallace (above), to advance discoveries from the lab to the clinic faster, improving patients' lives sooner.

The Krembil Research Institute has partnered with The Globe and Mail to release a magazine series highlighting Krembil research advancements. The second magazine in the series was distributed to Globe and Mail subscribers across Canada on June 27, 2017 and focuses on success stories from Krembil's Donald K. Johnson Eye Institute.

"In recent years, we've assembled a top-notch team of research scientists who are committed to finding answers to fundamental questions about the retina, the brain and disease function," says Dr. Valerie Wallace, Co-Director of Krembil's Donald K. Johnson Eye Institute with Dr. Robert Devenyi.

Stories within the Globe and Mail 'Vision' magazine highlight the significant advancements that Krembil researchers have made in recent years, and the new frontiers that they are exploring to better diagnose diseases of the eye and restore vision. These stories are summarized below:

- Dr. Philippe Monnier is developing therapies that can prevent cell death, reverse nerve damage and cure vision loss, as well as other diseases such as multiple sclerosis and stroke.
- Dr. Efrem Mandelcorn is adapting a simple eye test to facilitate the early diagnosis of neurodegenerative diseases, such as Alzheimer's and Parkinson's, before people have symptoms.
- Dr. Valerie Wallace is searching for a way to use transplanted cells to restore vision.
- Dr. Robert Devenyi is pioneering a new vision-saving method for people with retinal detachment—an emergency condition in which the tissue layer at the back of the eye is compromised.
- Dr. Jeremy Sivak is looking for ways to treat glaucoma, a group of conditions that are caused by damage to the optic nerve (ie, the major connection between the eye and the brain).
- Drs. David Rootman and Allan Slomovic are bringing back patients' vision by improving and implementing innovative surgical techniques.
- The late Dr. Martin Steinbach will be remembered for his leading contributions to vision research in Canada, including his most recent scientific endeavour: using virtual reality technology to detect the early signs of glaucoma, before eye damage occurs.
- Dr. Michael Brent is finding ways to break barriers and make it easier for people with diabetes to get regular eye exams.

Also in the magazine, vision research benefactor Donald K. Johnson explains the importance of private sector donations to "…help research organizations go from being good to being great."

"There are many exciting stories of progress and success emerging from our laboratories," explains Krembil Director 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."

Research

No Pain, No Gain

Distant brain regions can be 'functionally connected' (ie, work together). The way that some of these connected regions interact at rest can provide clues as to how people process information when faced with distractors, such as pain.

Despite being hampered by painful injuries, many athletes continue to compete and win. For example, Toronto Maple Leafs Defenseman Bobby Baun played several playoff games with a broken ankle and helped his team win the Stanley Cup in 1964.

Why is it that some individuals can perform a task—and do it well—while experiencing pain?

Krembil Senior Scientist Dr. Karen Davis has shown that individuals can be classified as one of two types depending on how pain affects their performance. In P-type individuals, pain interferes with performing a task; whereas, in A-type individuals, such as Bobby Baun, pain enhances their performance.

To gain a better understanding of this divergent behaviour during pain and the factors that contribute to it, Dr. Davis and her PhD student Joshua Cheng conducted a study examining brain function in these two groups.

The study included 51 healthy participants who were asked to perform a challenging mental task (ie, counting the number of digits within three boxes on screen and reporting which box has the largest number of digits) as quickly and accurately as possible. All participants performed the task 96 times, half of which with the application of a painful electrical sensation on their skin and the other half without. They also underwent a functional Magnetic Resonance Imaging (fMRI) scan to record their spontaneous brain activity at rest (ie, when not performing the task).

The researchers found that pain reduced the speed and consistency of task performance in P-type individuals; whereas it enhanced the speed and consistency of performance in A-type individuals. By examining the fMRI scans, they also found that task performance was linked to participants' brain activity at rest. Specifically, activity between two major brain networks, the executive control network and the salience network, as well as within the salience network, was less sporadic (ie, less flexible) in P-type individuals. On the other hand, activity between/within these brain networks was more sporadic (ie, more flexible) in A-type individuals.

These findings suggest that increased flexibility in communication within the brain is important for prioritizing task performance over pain. Future research will examine how treatments for chronic pain—medications, meditation and cognitive-behavioural therapy—affect flexibility in communication within the brain, which may contribute to more personalized treatments for chronic pain.

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

Cheng JC, Bosma RL, Hemington KS, Kucyi A, Lindquist MA, Davis KD. Slow-5 dynamic functional connectivity reflects the capacity to sustain cognitive performance during pain. Neuroimage. 2017 Jun 3. doi: 10.1016/j.neuroimage.2017.06.005.

Timing is Everything

Recent studies suggest that early decompression surgery (ie, <24 hours following injury), to remove bone fragments or other tissues pressing on the spinal cord, can improve surgery success rates.

Your worst nightmares have come true. You have undergone surgery in an attempt to relieve your debilitating back pain. And, at first, things did get better. But now, your symptoms are back—and even worse than before.

Pain in the neck, back or lower back, along with numbness or weakness in the arms or legs, can result from damage caused by compression of the spinal cord, also called degenerative cervical myelopathy (DCM). A number of conditions can cause spine abnormalities that lead to spinal cord compression, including injury, spinal tumor, rheumatoid arthritis or infection.

Surgical decompression—surgery to relieve pressure and pinching of the spinal cord—is the mainstay treatment in patients with DCM, as it can minimize further damage, and improve patients' physical symptoms and quality of life. However, it has been shown that these improvements may vary significantly depending on a number of factors such as the severity of damage, duration of symptoms and age. Moreover, even after a flawless surgical procedure, patients' symptoms can worsen within the first 24 hours following surgery.

It is believed that the body's immune system may be responsible for this worsening of symptoms, due in large part to increased inflammation at the site of surgery. Novel strategies to prevent these "secondary" injury processes may lead to improved outcomes in patients who receive surgical treatment for DCM.

In an effort to uncover the factors that govern whether surgical decompression surgery is successful, Krembil Senior Scientist Dr. Michael Fehlings used an animal model of DCM. The model enabled the research team to compare the effects of surgical decompression surgeries done soon after injury with those done three months after injury.

In the early decompression group, reduced inflammation and improved function in the upper and lower limbs were observed within the first few weeks after surgery. However, when surgical decompression was delayed, there was prolonged activation of immune cells and increased inflammatory markers. Furthermore, delayed surgical decompression led to an increased incidence of complications and function did not return to the same extent in the upper and lower limbs.

Using existing clinical data, the research team confirmed these results in human patients with moderate to severe DCM. Of the 504 patients considered, when surgical decompression was performed within 6 months of symptom onset, patients recovered better than when the surgery was delayed for longer periods of time.

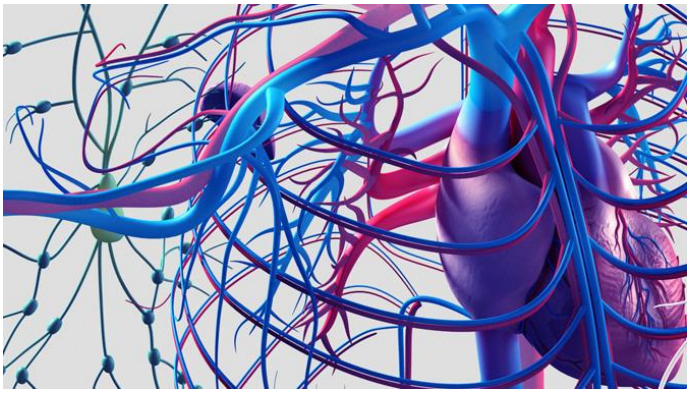
"To our knowledge, this is the first study that demonstrates the relationship between surgical intervention timing and immune system activation after surgery," said Dr. Fehlings. "Our results suggest that patients who have experienced symptoms for a longer period of time are more likely to achieve suboptimal surgical outcomes—and this is exactly what we see in the clinic."

This study underlines the importance of early diagnosis and surgery in DCM patients. Furthermore, reducing inflammation post-surgery may represent a novel therapeutic strategy to improve DCM patient recovery after surgical decompression.

This work was supported by the Cervical Spine Research Society, the Canadian Institutes of Health Research, and the Toronto General & Western Hospital Foundation. MG Fehlings is the Halbert Chair in Neural Repair and Regeneration.

Vidal PM, Karadimas SK, Ulndreaj A, Laliberte AM, Tetreault L, Forner S, Wang J, Foltz WD, Fehlings MG. Delayed decompression exacerbates ischemia-reperfusion injury in cervical compressive myelopathy. JCI Insight. 2017 Jun 2. doi: 10.1172/jci.insight.92512.

Betrayal in the Blood



Systemic lupus erythematosus, the most common form of lupus, can affect many parts of the body including the blood system, bones, brain, heart, joints, kidneys, and lungs.

In 2014, actress and singer Selena Gomez took some time out of the spotlight. While rumours swirled, it turned out that the hiatus was required so she could receive treatment for a disease known as lupus.

Millions of individuals worldwide, mostly women between the ages of 15 to 44, struggle with lupus. It is an autoimmune disease, meaning that the body's immune system goes into overdrive—attacking and causing extensive damage to healthy tissue.

B cells, named for their production in bone marrow, are one of the body's most important immune cells; they release specialized proteins (ie, antibodies) that protect the body from invaders such as viruses or bacteria. However, it is believed that they also play a critical role in initiating lupus by producing 'harmful' antibodies that tell the immune system to attack healthy cells.

Krembil Senior Scientist Dr. Joan Wither and her team have been using experimental models of lupus to uncover how and why B cells betray the body and incite the immune system to attack healthy cells.

In a recent study, the researchers tracked B cell antibody production using an experimental model in which B cells were forced to express a specific genetic code that induced lupus-like symptoms. The team discovered that this genetic code not only increased the proportion of antibody-producing B cells, but also the levels of antibody production.

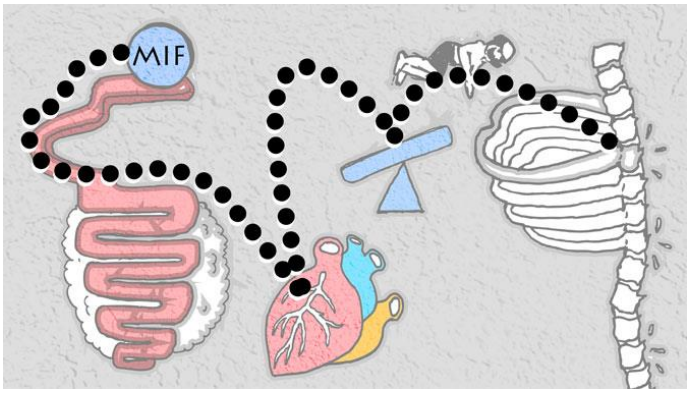
The code also increased the proportions of another type of immune cell (T follicular helper cell) that is known to enhance the growth of antibody-producing B cells. As the proportion of these T follicular helper cells increased, the proportion of B cells grew, and likewise, antibody production was augmented. These changes created an environment where the immune system was primed to attack healthy tissues.

"Although several studies have shown that defects in B and T cell populations contribute to antibody production, it still is not clear exactly how this occurs in the context of lupus," says Dr. Wither. "Our data reveal that changes in the proportion of T follicular helper cells may play a role in this process by enhancing the growth of the types of B cells that end up betraying the body and causing lupus."

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

Chang NH, Manion KP, Loh C, Pau E, Baglaenko Y, Wither JE. Multiple tolerance defects contribute to the breach of B cell tolerance in New Zealand Black chromosome 1 congenic mice. PLoS One. 2017 Jun 19;12(6):e0179506. doi:10.1371/journal.pone.0179506.

Following your Gut



This study reveals that MIF released from cells in the intestine can travel through the blood stream to the spine, where it transforms soft tissue into bone and leads rigidity and pain.

Anyone who has played the 80s board game Mouse Trap will remember how a chain reaction that starts with a small ball rolling side-to-side down a hill ends with a mouse being trapped under a plastic net.

Just like how different events in the game come together to set the trap, different and sometimes unlikely parts of the body can conspire in the development of disease.

Recent findings from Krembil Scientist Dr. Nigil Haroon have identified a molecule, known as macrophage migration inhibitory factor (MIF), which may link inflammation in the gut and a type of spinal arthritis known as ankylosing spondylitis (AS).

The link between the gut and AS is well known, as over half of those with AS also have bowel inflammation; however, it is still unknown how the gut might contribute to the disease, if at all.

Dr. Haroon's team focused on MIF, because it is elevated in the blood of patients with AS and other inflammatory diseases, such as psoriasis and inflammatory bowel diseases.

By analyzing clinical data, the researchers revealed that elevated MIF levels could be used to predict the progression of AS. Specifically, they found that MIF can promote inflammation and bone formation in the spine—two hallmarks of AS. Dr. Haroon comments, "We found that MIF can directly mediate bone formation in experimental models involving bone-forming cells known as osteoblasts, and that MIF does this by modulating a cell signalling pathway known as Wnt."

Another question that the research team explored was: where does MIF originate from in the body?

It was this question that led them to the gut. Initially the researchers looked to circulating immune cells—obvious culprits, as they are involved in inflammation—however, they were unable to find heightened MIF stores in these cells.

Next, they explored whether tissues in the large intestine might be the source. The results revealed, for the first time, that cells of the small intestine known as Paneth cells, as well as 'resident' immune cells in the same tissue, known as CD68+ macrophages, produce MIF.

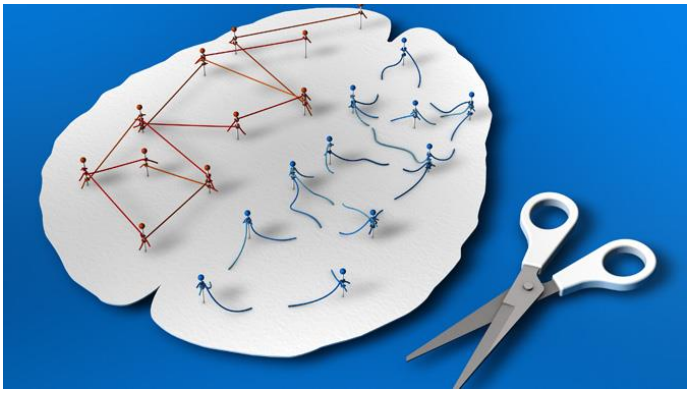
"These results led us to propose a new hypothesis: inflamed cells of the gut secrete MIF, perhaps as a response to altered gut microbes, which then travels to the spine where it contributes to the inflammation and irregular bone formation in the joints of the back, ultimately leading to the debilitating pain and stiffness experienced by individuals with ankylosing spondylitis," says Dr. Haroon.

Future studies will be focused on advancing the use of MIF to predict AS progression, as well as the development of future therapeutics that target MIF to slow or stop progression of the disease.

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

Ranganathan V, Ciccia F, Zeng F, Sari I, Guggino G, Muralitharan J, Gracey E, Haroon N. Macrophage Migration Inhibitory Factor induces inflammation and predicts spinal progression in Ankylosing Spondylitis. Arthritis Rheumatol. 2017 Jun 8.

Fixing Network Connectivity Issues



Depending on the location, nerve damage in the brain and spinal cord can have functional consequences such as paralysis, muscle twitches or vision loss.

Few situations can be as frustrating as realizing that your mobile phone is not receiving a signal. When this happens, many of us have developed relatively easy strategies to re-establish a solid connection, such as moving closer to a cellular tower or changing cell phone providers.

Unlike getting better phone reception, however, it is not as easy to re-establish lost connections between the brain and organs of the body. This is because damage to the complex network of fibres that transmit and receive signals within the brain is often irreversible. Even if nerve fibres begin to regrow after damage, certain inhibitory signals in the surrounding environment prevent new fibres from re-establishing connections.

A study by Krembil Senior Scientist Dr. Philippe Monnier reveals a new strategy that may help overcome these inhibitory signals to promote the repair of damaged nerve fibres in the eye. Dr. Monnier and his research team focused on the regenerative properties of exosomes, encapsulated particles that are released from one cell type and taken up by another—an important form of cell-to-cell communication.

The team found that when exosomes from fibroblast cells (cells that are responsible for generating scar tissue) are taken up by nerve cells, a nerve fibre repair switch is turned on, promoting nerve fibre growth. This repair happens despite the presence of inhibitory signals in the surrounding environment, and is unique to exosomes from fibroblast cells, but not those of other cell types.

Using major connections between the eye and brain as an experimental model of nerve injury, the researchers demonstrated that treating the area of damage with fibroblast exosomes enhanced repair and prevented cell death.

“Our study is the first to show that fibroblast exosomes trigger a regeneration pathway in nerve cells,” explains Dr. Monnier. “It also reinforces the notion that exosomes derived from different cell types have different functions—setting the stage for the development of precise regenerative therapies that can be used to repair the damaged nervous system.”

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

Tassew NG, Charish J, Shabanzadeh AP, Luga V, Harada H, Farhani N, D’Onofrio P, Choi B, Ellabban A, Nickerson PEB, Wallace VA, Koeberle PD, Wrana JL, Monnier PP. *Exosomes mediate mobilization of autocrine Wnt10b to promote axonal regeneration in the injured CNS*. Cell Rep. 2017 Jul 5. doi: 10.1016/j.celrep.2017.06.009.

Genetic Disorder Provokes Seizures

Seizures are brief periods of abnormal electrical activity in the brain, with many potential causes such as genetic abnormalities, low calcium or drug side effects.

We are all walking around with genetic variations. In most cases, these variations are completely harmless. In other cases, they can lead to serious conditions, including an increased likelihood of experiencing seizures. This is the case for people living with 22q11.2 deletion syndrome (DS). The name 22q11.2 deletion syndrome covers terms once thought to be separate conditions, such as DiGeorge syndrome and velocardiofacial syndrome.

22q11.2 deletion syndrome is the second-most common genetic disorder after Down syndrome, affecting about one in 4,000 births. It is caused by the deletion of a section of chromosome 22. In turn, this deletion can affect the production of more than 40 different proteins.

People with this syndrome can experience a wide range of symptoms, including heart defects, poor immune function, low calcium levels, as well as neuropsychiatric conditions such as developmental delay, intellectual disability and schizophrenia. However, some neuropsychiatric symptoms remain poorly understood. In particular, while there has been evidence that children with DS are at a higher risk of having seizures, there has been very little research conducted on adults with the syndrome.

To address this issue, Krembil Clinical Researcher Dr. Danielle Andrade and her team reviewed the medical records of 202 adult patients with 22q11.2 deletion syndrome. They found that nearly 16% of patients had a confirmed history of provoked seizures, and 5% had a history of epilepsy (recurrent, non-provoked seizures) which is significantly greater than the occurrence in the general population.

Many factors can provoke a seizure, such as a high fever, low calcium levels in the blood or the effects of drugs. Low calcium levels are common in people with DS and could explain some of their increased risk for seizures. An even more important factor may be drug use—particularly antipsychotics and antidepressants—with 66% of DS patients documented as taking these medications during one or more of their seizures. Half of the patients in the study had their first seizure while starting or increasing their dose of these medications, many times in order to lessen the severity of other neuropsychiatric symptoms associated with the syndrome.

“Our finding should alert clinicians to the heightened risk of seizures not only in children, but also in adults with 22q11.2 deletion syndrome,” says Dr. Andrade, “especially those with neuropsychiatric symptoms who are in need of antipsychotic and antidepressant medications, which was the majority of patients in our study.”

This work was supported by the Brain and Behaviour Foundation, Canadian Institutes of Health Research, Brain Canada, unrestricted educational grant from UCB, and the Toronto General & Western Hospital Foundation. AS Bassett holds a Tier 1 Canada Research Chair in Mental and Behavioural Disorders.

Wither RG, Borlot F, MacDonald A, Butcher NJ, Chow EWC, Bassett AS, Andrade DM. 22q11.2 deletion syndrome lowers seizure threshold in adult patients without epilepsy. Epilepsia. 2017 Jun. doi: 10.1111/epi.13748.

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