The Krembil

March 2019

The Krembil is the official newsletter of the Krembil 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 Talent Joins Media Team

Twayne Pereira will use his artistic skills and scientific knowledge to promote research.

Twayne Pereira, Public Affairs Associate, Krembil Research Institute.

We are pleased to introduce Twayne Pereira, Krembil's new Public Affairs Associate.

In this role, Twayne will manage Krembil's social media platform and create a variety of products—such as photos, graphics and short videos—to promote our research to the wider community. He will also work closely with Heather Sherman, our Senior Public Affairs Advisor, to support media requests and public outreach activities.

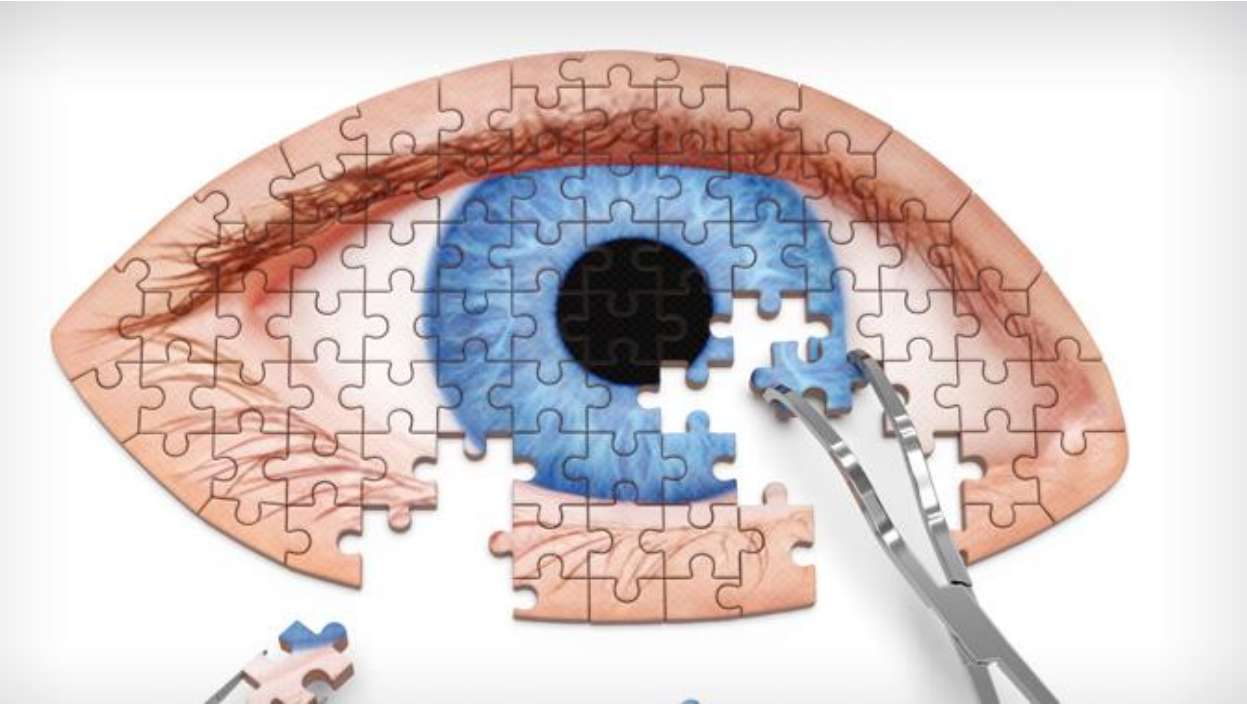
Twayne is equipped with an excellent combination of knowledge and skills for his new job. He holds an undergraduate degree in neuroscience and cell biology from the University of Toronto, and he spent a year working in Dr. Jonathan Downar's lab at Krembil. Notably, Twayne has an artistic eye and is passionate about photography, videography and graphic design. Over the past four years, he has worked as a freelance content creator for several publicity campaigns, and his work has been featured in 35mm Magazine and BlogTO. In addition, he filmed and developed daily summary videos for Boots and Hearts, Canada's largest country music festival.

“Traditional print media has its place, but telling a story through a short video or highlighting research with dynamic visuals can go a long way in engaging a broader audience. I hope that the videos and content that I create get everyone excited about the research that takes place at Krembil,” says Twayne.

Congratulations Twayne on your new role at Krembil!

Solving the Puzzle

New tool could provide insights to make cell therapy an effective treatment for vision loss.



The assay developed by Dr. Wallace's team could help researchers piece together the factors that have limited the use of cell-based treatments for vision loss.

A team of researchers at the University Health Network has developed a novel research tool that could help to advance new treatments to reverse vision loss caused by age-related macular degeneration (AMD).

AMD is a leading cause of vision loss in older adults. It is characterized by the loss and/or dysfunction of the cells that initiate vision. These cells—known as photoreceptors—detect light, transform it into electrical signals that are then relayed through nerve cells to the brain, where the signals are translated into images.

Researchers are currently exploring cell replacement therapy as a potential treatment for AMD. Cell replacement therapy involves the surgical transplantation of healthy photoreceptors from a donor into a host, replacing the lost or dysfunctional photoreceptors.

“Once transplanted, donor photoreceptors need to mature and establish functional connections to the host cells to be able to dispatch electrical signals to the brain. Presently, it appears that transplanted cells are not making these important connections, and we don’t know why,” says Dr. Valerie Wallace, a Senior Scientist at the Krembil Research Institute.

To address this, Dr. Wallace and her research team developed an efficient and inexpensive assay to identify and study the mechanisms that control the maturation of donor photoreceptors.

Using this assay, the researchers showed that the following three factors influence the initial stages of connectivity: the ROCK protein, which controls the growth of eye cells; Müller glia, which are cells that provide structural and functional support to nerve cells; and the CRX gene, which is important for the development of photoreceptors.

“We have established a novel assay to help us understand the mechanisms that regulate connections between donor and host cells. Our assay could reveal factors to promote these connections, which are crucial for cell replacement therapy to successfully restore vision in patients with AMD and other diseases that cause photoreceptor degeneration,” concludes Dr. Wallace.

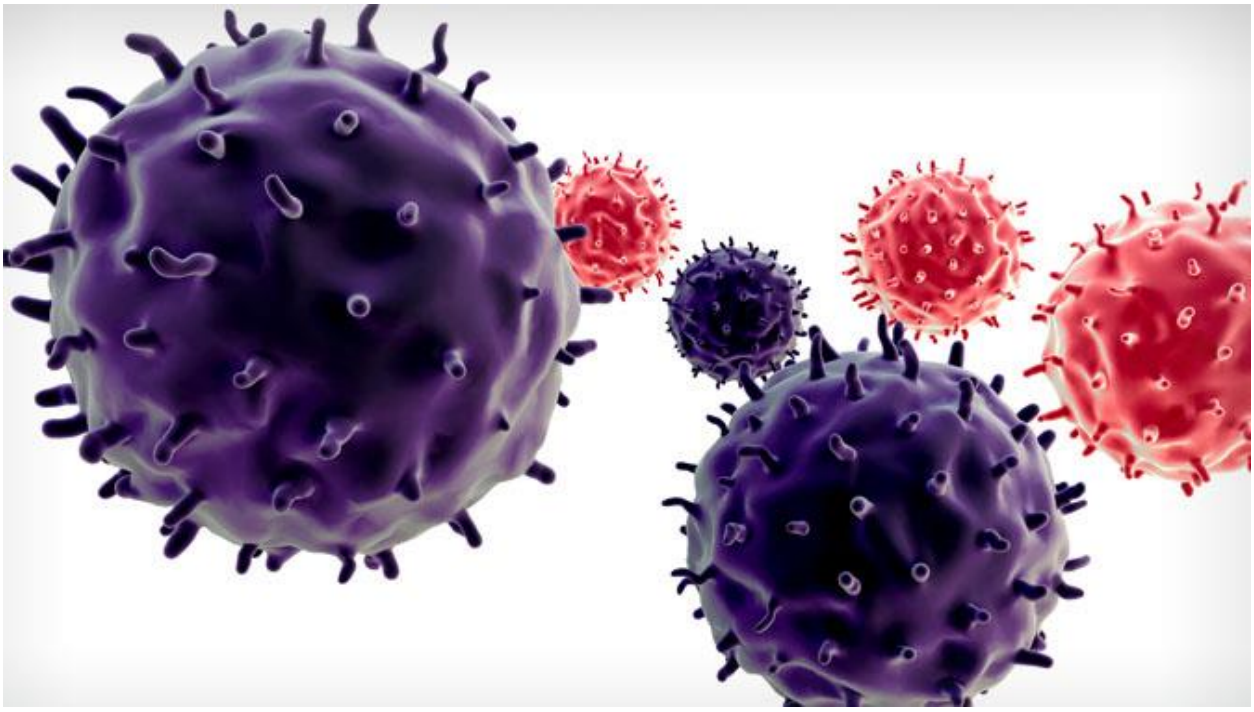
This work was supported by Brain Canada, the Foundation Fighting Blindness, the Ontario Institute for Regenerative Medicine, the Krembil Foundation, the Canada First Research Excellence Fund and the Toronto General & Western Hospital Foundation. MS Shoichet is a Tier I Canada Research Chair in Tissue Engineering.

Tsai ELS, Ortin-Martinez A, Gurdita A, Comanita L, Yan N, Smiley S, Delplace V, Shoichet MS, Nickerson PEB, Wallace VA. Modeling of Photoreceptor Donor-Host Interaction Following Transplantation Reveals a Role for Crx, Müller Glia, and Rho/ROCK Signaling in Neurite Outgrowth. Stem Cells. 2019 Feb 4. doi:10.1002/stem.2985.

Dr. Valerie Wallace, Senior Scientist, Krembil Research Institute. Photo Courtesy of the Globe and Mail.

A Pain in the Knee

Severity of osteoarthritis symptoms is linked to predominant types of immune cells in joints.



Macrophages and monocytes are specialized immune cells examined in this study. Their primary role in the body is to attack and destroy foreign organisms.

Aging and ‘wear-and-tear’ can take a significant toll on the human body, especially our weight-bearing joints. Osteoarthritis—the most common form of arthritis—is a condition characterized by the progressive loss of cartilage in the joints of the hands, knees, hips and spine. Cartilage is an elastic tissue that covers and cushions bones in the joint, and as it degrades over time, joints become stiff and painful.

While we know that the immune system is involved in disease progression, it is unclear if and how different types of immune cells are linked to the severity of symptoms or quality of life.

To address this gap, a team led by Dr. Sowmya Viswanathan, an Affiliate Scientist at the Krembil Research Institute, analyzed several types of immune cells in the joint fluid of individuals diagnosed with knee osteoarthritis. As part of the study, these individuals completed questionnaires on their symptoms, daily living activity, quality of life, pain, stiffness and joint function prior to receiving treatment.

The researchers found that monocytes and macrophages were the most abundant types of immune cell present within the joint fluid of osteoarthritis patients. Further investigation revealed that particular subtypes of monocytes and macrophages were

linked to patient-reported outcomes, especially joint stiffness and function, as well as quality of life.

“Our findings suggest that certain populations of immune cells could serve as indicators of disease severity. They also provide new insights into the biology of osteoarthritis that could inform the development of therapies to slow or stop disease progression,” says Dr. Viswanathan.

This work was supported by the Arthritis Society and the Toronto General & Western Hospital Foundation.

Gómez-Aristizábal A, Gandhi R, Mahomed NN, Marshall KW, Viswanathan S. Synovial fluid monocyte/macrophage subsets and their correlation to patient reported outcomes in osteoarthritic patients: a cohort study. Arthritis Res Ther. 2019 Jan 18. doi: 10.1186/s13075-018-1798-2. Mov Disord. 2018 Nov 13. doi: 10.1002/mds.27506.

Dr. Sowmya Viswanathan, Affiliate Scientist, Krembil Research Institute.

Cause for Concern

Higher opioid use found in younger, depressed patients awaiting surgery for osteoarthritis.

This study reported a link between opioid use and depression, a serious mental illness that affects one in four Canadians at some point in their lives.

The opioid debate is complex: while opioid medications can be beneficial for pain management, in some cases they have been linked to worse outcomes and addiction.

This debate is particularly relevant to osteoarthritis—a condition that can cause persistent and often debilitating joint pain that worsens over time. Along with pain medication, surgery to replace affected joints is often a last resort.

“There exists a lot of unknowns regarding the use of opioid medication in this setting,” says Krembil Clinician Investigator Dr. Raja Rampersaud. “Few guidelines exist on the proper use of opioids for managing osteoarthritis-related pain, and recent evidence suggests that these medications are ineffective. As well, there is increasing evidence that opioid use in these patients may lead to worse surgery outcomes.”

To shed more light on this issue, Dr. Rampersaud and his collaborators initiated a study to explore the effect of opioid use and other factors—such as body mass index, age, level of education and health status—on the outcomes of patients with end-stage osteoarthritis having surgery.

“After analyzing data for over 1,125 patients, we found some concerning trends,” says Dr. Rampersaud. The study revealed that a large proportion of osteoarthritis patients—up to one third—are using opioids. Furthermore, opioid use was higher in younger individuals (those under 65 years of age) and those experiencing symptoms of depression.

“Our findings provide compelling evidence that more rigorous guidelines, and effective and timely alternatives are needed to protect individuals with osteoarthritis from the potential harms of opioid use. Also, given that recent studies have linked opioid use to worse surgical outcomes, carefully considering patient factors, such as age and mental health, could help to counteract these effects and improve the lives of those with osteoarthritis.”

This work was supported by University Health Network’s Arthritis Program and the Toronto General & Western Hospital Foundation.

Power JD, Perruccio AV, Gandhi R, Veillette C, Davey JR, Lewis SJ, Syed K, Mahomed NN, Rampersaud YR. Factors Associated With Opioid Use in Pre-surgical Knee, Hip and Spine Osteoarthritis Patients. Arthritis Care Res (Hoboken). 2019 Jan 10. doi: 10.1002/acr.23831.

Dr. Raja Rampersaud, Clinician Investigator, Krembil Research Institute. Photo courtesy of the Globe and Mail.

Comparing Memory Lanes

UHN researchers help to clarify how temporal lobe epilepsy accelerates forgetfulness.

Every year on March 26, people in countries around the world wear purple and host events to promote epilepsy awareness.

Imagine walking past a bakery with baguettes displayed in the window. Now imagine walking past the same bakery a week later and stopping to look at a display of croissants.

Healthy adults are typically able to recognize that the bakery's window display has changed. Individuals with temporal lobe epilepsy are much less likely to discern the change in the display.

To better understand why, Dr. Mary Pat McAndrews, Senior Scientist at the Krembil Research Institute, has been studying how memories are formed and recalled in those with temporal lobe epilepsy.

Temporal lobe epilepsy is the most common form of location-related epilepsy and often develops during adolescence. Those with the condition are able to learn and remember without difficulty for many hours, but forget those memories at an unusually fast rate in the following days. When medications do not work, surgery may be an alternative treatment.

"We asked some temporal lobe epilepsy patients who are considering surgery to look at photos of objects paired with photos of scenes—for example, a couch and an apartment

building," describes Samantha Audrain who co-led the study with Dr. McAndrews. "We then recorded how well they remembered these pairings at several timepoints in the following three days and compared the results to those from healthy volunteers."

"We found that individuals with temporal lobe epilepsy forgot about the object-scene pairings much more quickly than healthy individuals, starting after about six hours," adds Dr. McAndrews. "These findings agree with the theory that for those with the condition, the part of the brain that helps to process object information makes weaker connections with the part that helps store memories."

Further exploring why these connections are altered may reveal new strategies for identifying and treating patients who are more likely to experience long-term memory loss due to temporal lobe epilepsy.

This work was supported by the Natural Sciences and Engineering Research Council of Canada and the Toronto General & Western Hospital Foundation.
Audrain S, McAndrews MP. Cognitive and functional correlates of accelerated long-term forgetting in temporal lobe epilepsy. Cortex. 2019 Jan. doi: 10.1016/j.cortex.2018.03.022.

Dr. Mary Pat McAndrews, Senior Scientist, Krembil Research Institute.