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.

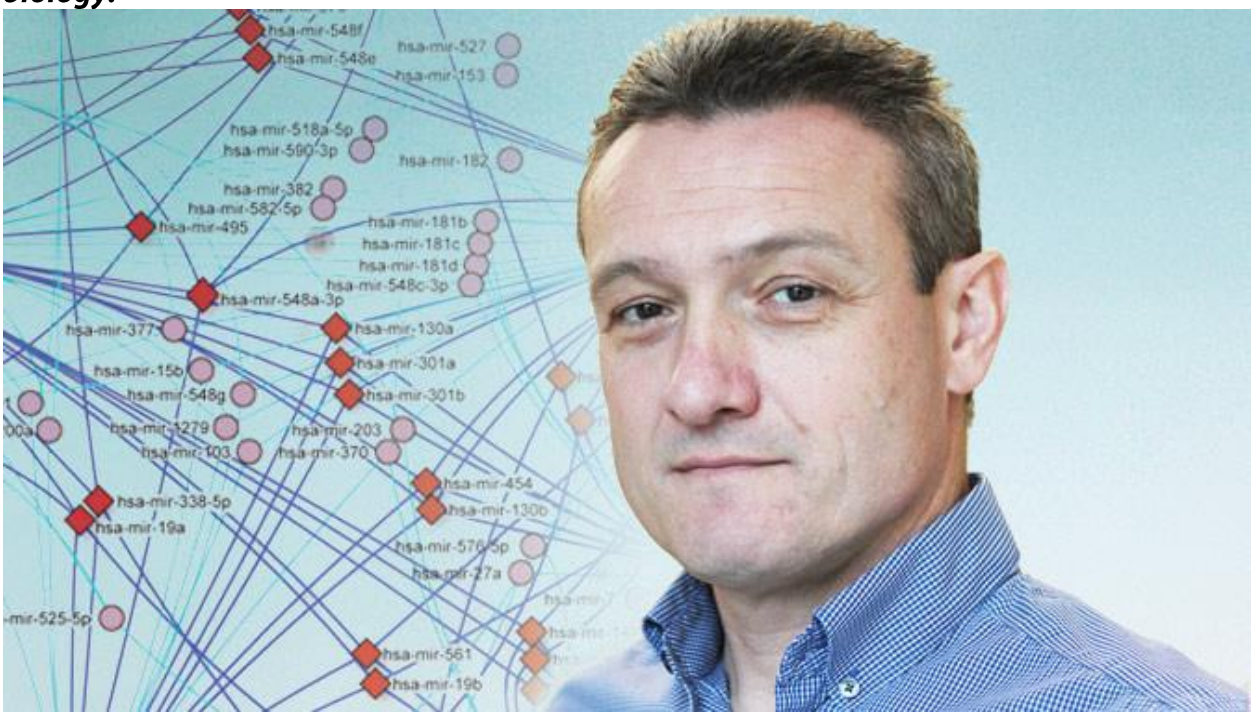
Stories in this month's issue:

Donald Weaver, PhD, MD, FRCPC, FCAHS
Director, Krembil Research Institute
University Health Network

News

Computational Power gets a Boost

Dr. Jurisica appointed at Krembil and brings with him key expertise in computational biology.



We are pleased to announce that Dr. **Igor Jurisica** has been appointed at the Krembil Research Institute as a Senior Scientist. Dr. Jurisica, who was formerly appointed at the Princess Margaret Cancer Centre, is an internationally acclaimed computational biologist. He has been recognized as one of the world's most influential researchers: his papers have been ranked among the top 1% most cited in his field by Thomson Reuters in 2014, 2015 and 2016.

Since 2015, he has served as Chief Scientist – Computational Biology at the Creative Destruction Lab, Rotman School of Management, University of Toronto. He has collaborated with IBM for 18 years—a partnership that has led to the creation of the IBM Life Sciences Discovery Centre at UHN, for which he serves as Director.

Another initiative that Dr. Jurisica is involved with is the World Community Grid (link is external), which uses volunteered computing power from across the globe to analyze large datasets in parallel using advanced machine learning. This project is enabling Dr. Jurisica to analyze millions of data points with the aim of identifying clinically relevant gene markers.

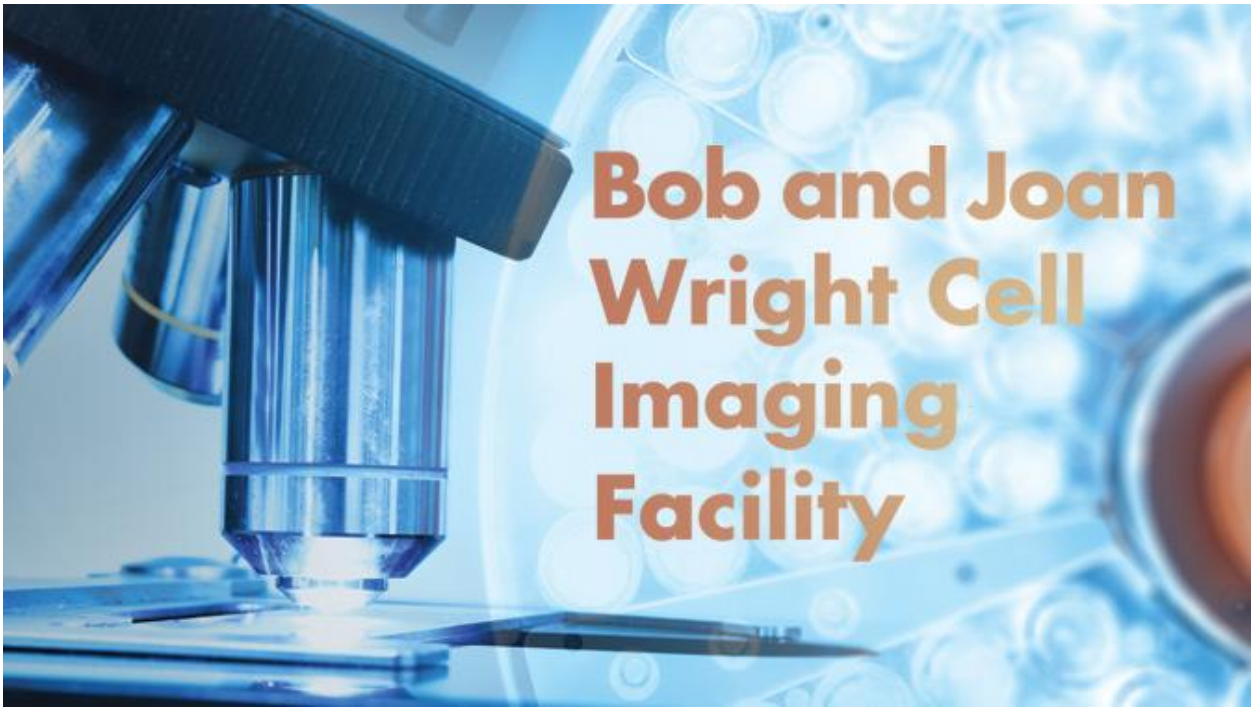
As a pioneer in his field, Dr. Jurisica brings immense computational expertise, including analysis, integration, visualization, and modelling of high dimensional data generated by high throughput biology to facilitate biomarker discovery. He has developed a large array of tools and databases to analyze signal transduction pathways, protein-protein interactions, and miRNA that will be instrumental to his proposed research at Krembil.

Dr. Jurisica will complement Krembil's growing computational biology section and will be focussing on arthritis as a chronic disease. He is a valued addition to our computational neuroscience research, and will support and advance a wide range of research initiatives across the institution.

We welcome Dr. Jurisica and lab to Krembil!

Imaging Facility Revitalized

Donation enables renovations and acquisition of cutting-edge imaging equipment at Krembil.



Recent funding from UHN research grants, the federal government and the Wright family, have enabled the transformation of the Bob and Joan Wright Cell Imaging Facility (WCIF), which is located at the Krembil Research Institute.

Since 2000, the WCIF has provided state-of-the-art microscopy capabilities to UHN and external researchers.

The recent funding has provided the facility with a new image analysis station as well as a fully equipped tissue culture processing area that allows live cell preparation on site. In addition, key equipment has been acquired to upgrade existing capabilities while providing new, advanced capabilities.

Equipment that was purchased through the support of Drs. Elise Stanley, Charles Tator and a recent donation from the Wright family, is listed below:

- **Zeiss LSM880** laser scanning confocal microscope with **Airyscan** enhanced resolution module
- **AxioObserver 7** widefield inverted microscope
- **AxioZoom** microscope

Funding from a Canada Foundation for Innovation (CFI) grant awarded to Drs. Philippe Monnier, Jeremy Sivak and Valerie Wallace has also provided the facility with a **Leica upright multiphoton** microscope.

As part of the revitalization, the team from UHN's Advanced Optical Microscopy Facility (AOMF) will be managing the WCIF. Management of the facility will be led by James Jonkman (Manager, AOMF) and user support and training will be provided by Kevin Conway, who will be on site on a part-time basis.

Please contact kevin.conway@uhnresearch.ca to discuss your microscopy requirements and to book training sessions on the new equipment.

Research

Light at the End of the Tunnel

UHN vision scientists discover potential neuroprotective treatment for glaucoma.

This Dr. Jeremy Sivak (pictured) leads a laboratory at Krembil Research Institute that is focused on studying the cellular responses to tissue damage and repair in the eye.

A research team led by Krembil Research Institute scientists has identified a new neuroprotective factor that has the potential to help people suffering from the common blinding disease glaucoma.

"This discovery provides hope that we can devise a new strategy for protecting the vision of glaucoma patients," said Krembil Scientist Dr. Jeremy Sivak, who holds the Glaucoma Research Chair at the Donald K. Johnson Eye Institute at UHN and is Associate Professor at the University of Toronto.

Dr. Sivak's research team was assisted by Dr. John Flanagan and Dr. Karsten Gronert of the University of California, Berkeley and the findings were published in the *Journal of Clinical Investigation.*

The team identified lipid molecule called LXB_4 that protects neurons against the harmful effects of glaucoma in preclinical models. "We found that this tiny lipid molecule is normally present in healthy eyes and acts as a neuroprotective signal," said Dr. Sivak. "Healthy eyes produce LXB_4, but in diseased eyes its levels are reduced. We showed that by restoring LXB_4 we can preserve injured nerve cells from dysfunction and death."

Glaucoma is a progressive neurodegenerative disease of the optic nerve that is irreversible and can eventually lead to blindness. It affects more than 400,000 Canadians and 70 million people worldwide. Although there is no known cure, a key strategy to develop new treatments for glaucoma, and for other neurodegenerative conditions, is to find ways to preserve the survival of nerve cells.

"A particularly exciting part of this discovery is that we don't think this effect is limited to glaucoma," said Dr. Sivak. "This neuroprotection extends to the central nervous system and could be applicable to a host of other neurodegenerative diseases."

Next steps for the research team include further investigation of the underlying mechanisms that control levels of the LXB_4 molecule, and designing a practical method to restore levels of the molecule to treat disease. Researchers also plan to explore the potential application of this discovery to other conditions, such as Alzheimer's Disease and Parkinson's Disease.

Source: UHN.ca (link is external)

Funding for this study was provided by the Canadian Institutes of Health Research, The Natural Sciences and Engineering Research Council of Canada, the National Institutes of Health and the Toronto General & Western Hospital Foundation.

Livne-Bar I, Wei J, Liu HH, Alqawlaq S, Won GJ, Tuccitto A, Gronert K, Flanagan JG, Sivak JM. Astrocyte-derived lipoxins A4 and B4 promote neuroprotection from acute and chronic injury (link is external). J Clin Invest. 2017 Nov 6. pii: 77398. doi: 10.1172/JCI77398.

Glaucoma is caused by pressure buildup in the eye that damages the optic nerve. An eye exam (pictured) can help diagnose glaucoma before the appearance of advanced symptoms, such as tunnel vision (loss of peripheral vision).

Easing the Pain

New therapy found to provide relief from painful symptoms of debilitating joint disease.

Tofacitinib is a tablet that can be taken orally unlike many of the drugs prescribed for psoriatic arthritis, which are given by injection and thus likely to cause more joint pain.

Imagine being plagued by constant but unpredictable pain in your joints. You feel fine some days but experience excruciating pain and stiffness much of the time. Sometimes the pain is particularly severe in the morning but at other times it seems to never end.

Such is the case for patients with psoriatic arthritis, a type of arthritis that often develops in individuals with a skin condition known as psoriasis. The condition occurs when the body's immune system goes rogue and begins to attack healthy tissues causing skin and joint inflammation.

Patients who have a severe form of the disease receive special drugs, known as tumor necrosis factor (TNF) inhibitors, to suppress their immune system's activity. But only half of psoriatic patients who take TNF inhibitors feel better, which is why there are ongoing efforts to develop more effective treatments for the disease.

A team led by Krembil Senior Scientist Dr. Dafna Gladman recently published a report in *The New England Journal of Medicine* that examined whether a drug known as tofacitinib, which is an oral agent, is effective for those who do not respond to TNF inhibitors.

The study involved over 350 patients from fourteen countries who randomly received two different doses of tofacitinib or two different doses of a drug with no active ingredients (placebo).

The researchers found that tofacitinib reduced symptoms associated with psoriatic arthritis in around half of patients, and was about twice as effective as the placebo. It not only reduced joint inflammation but also improved physical function in patients and in certain cases, effectively treated the skin disease.

Explains Dr. Gladman "We did note that a few of the patients who received tofacitinib experienced serious infections. This sometimes occurs when drugs that suppress the body's immune system are prescribed. These side effects will need to be considered when prescribing the medication. However, for many patients who have no other options, tofacitinib is a promising treatment for control of the arthritis."

This work was supported by Pfizer.

Gladman D, Rigby W, Azevedo VF, Behrens F, Blanco R, Kaszuba A, Kudlacz E, Wang C, Menon S, Hendrikx T, Kanik KS. Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors (link is external). N Engl J Med. 2017 Oct 19;377(16):1525-1536. doi: 10.1056/NEJMoa1615977.

Too Much of a Good Thing

Researchers uncover a pathway that promotes excessive tissue repair and organ malfunction.

When fibrosis affects the lung, the tissue stiffens and prevents oxygen uptake into the body; as a result, those affected often require oxygen therapy (pictured).

Maintaining work-life balance. Eating a healthy diet. Balance is something that our minds and bodies are constantly striving for.

For example, when the lungs are damaged by cigarette smoke or infections, the body sets to work, trying to repair the damage. Underlying this process is a type of cell known as the myofibroblast, which are recruited to the site of injury to orchestrate would-healing responses, including scar formation.

The problem is that, just as we sometimes fail at balancing our lifestyles, the body can get it wrong. In the case of repeated injury to the lung, myofibroblasts can become over-active; this promotes the formation of excessive scar tissue—so much so that the organ becomes inflexible, resulting in a serious condition known as pulmonary fibrosis. As fibrosis worsens, individuals with pulmonary fibrosis find it harder and harder to breathe and the transport of oxygen into the bloodstream becomes insufficient—causing respiratory failure and death.

It is not exactly known how myofibroblasts are activated to promote organ scarring. To address this issue, a team led by Krembil Senior Scientist Dr. Mohit Kapoor and co-lead investigators Dr. David Lagares and the late Dr. Andrew Tager (both from Harvard University)

initiated a study to explore the molecular signals that activate myofibroblasts in people with pulmonary fibrosis.

In the study, the researchers compared lung myofibroblasts isolated from people with or without pulmonary fibrosis, and found that the level of Ephrin-B2, a protein on the surface of cells, was higher in myofibroblasts from fibrotic lungs. Using a series of experimental models, they discovered that an enzyme called ADAM10 causes part of Ephrin-B2 to be cleaved from the surface of the cell. The released piece, called sEphrin-B2, instructs myofibroblasts to migrate to the site of injury, generate scar tissue and promote fibrosis.

The team also found that administering sEphrin-B2 protein under the skin caused skin fibrosis, further implicating this molecule as a key player in the formation of excessive scar tissue. Moreover, by blocking the activity of ADAM10, they found that less sEphrin-B2 was released, resulting in reduced activation of myofibroblast cells and reduced fibrosis.

"Our study provides the first proof of concept that the ADAM10-sEphrin-B2 pathway drives organ fibrosis," explains Dr. Lagares. Dr. Kapoor adds, "These results provide new targets for the development of therapies to prevent organ failure by preventing fibrosis—not only in the lungs and skin, but also in other tissues affected by fibrosis such as joints, the heart, the liver and the kidney."

This work was supported by Université de Montréal, the American Thoracic Society Foundation, the Pulmonary Fibrosis Foundation, the Scleroderma Foundation, the National Institutes of Health, the Scleroderma Research Foundation and the Toronto General & Western Hospital Foundation.

Lagares D, Ghassemi-Kakroodi P, Tremblay C, Santos A, Probst CK, Franklin A, Santos DM, Grasberger P, Ahluwalia N, Montesi SB, Shea BS, Black KE, Knipe R, Blati M, Baron M, Wu B, Fahmi H, Gandhi R, Pardo A, Selman M, Wu J, Pelletier JP, Martel-Pelletier J, Tager AM, Kapoor M. [*ADAM10-mediated ephrin-B2 shedding promotes myofibroblast activation and organ fibrosis.*](#) [(link is external)](#) *Nat Med. 2017 Oct 23. doi: 10.1038/nm.4419.*

Dr. Mohit Kapoor (pictured), Director of Arthritis Research at Krembil Research Institute, led this multi-centre study with Dr. David Lagares and the late Dr. Andrew Tager, both from Harvard University and Massachusetts General Hospital.

Parkinson State of Mind

Krembil researchers discover a novel brain state that sheds new light on Parkinson disease.

Like streets in a city, brain cells called neurons physically connect with each other to create 'neural pathways' capable of transmitting information between distinct regions of the brain.

More than one billion people around the world use the web mapping service Google Maps. Among its most popular features is the trip planner, which suggests the most optimal route to travel from one destination to another.

Similarly, the healthy brain depends on many networks of optimally connected routes to efficiently send and receive information. A new study by Krembil Senior Scientist Dr. Antonio Strafella reveals that the disruption of these networks may result in Parkinson disease—a neurodegenerative disorder causing changes in movement, behaviour and cognitive ability.

In the study, Dr. Strafella and his research team used a highly sophisticated imaging analysis technique called dynamic functional connectivity to visualize the brains of people with or without Parkinson disease. They found that brains switch back and forth between two states: in the first state, the brain has sparse connections, but these connections function very efficiently in transmitting information; however, in the second state, the connections are unstable despite the fact that they are highly connected.

In comparing the brain states of those with or without Parkinson disease, the researchers found that people with Parkinson disease were more likely to be in the second state. A shift in

brain states from the first to the second was associated with the severity of Parkinson disease symptoms, such as tremor, slowness of movement and impaired speech.

"We are the first to identify this second brain state," says Dr. Strafella. "Our results indicate that the brain of a patient with Parkinson disease is not very efficient and is not taking the fastest and shortest route between two points to perform a task. Our next step is to figure out what role this process plays in the evolution of the disease and how treatments to influence this brain state might help improve patients' quality of life."

This work was supported by the Canadian Institutes of Health Research and the Toronto General & Western Hospital Foundation. A Strafella is a Tier 2 Canada Research Chair in Movement Disorders and Neuroimaging.

Kim J, Criaud M, Cho SS, Dı´ez-Cirarda M, Mihaescu A, Coakeley S, Ghadery C, Valli M, Jacobs MF, Houle S, Strafella AP. Abnormal intrinsic brain functional network dynamics in Parkinson's disease (link is external). Brain. 2017 Oct 5. doi: 10.1093/brain/awx233.

The study was led by Krembil Senior Scientist Dr. Antonio Strafella (pictured).