The Krembil

July 2020

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

Krembil Researcher Retires

Community says farewell to world-renowned arthritis researcher Dr. Aileen Davis.

After a remarkable career in research and patient care, Dr. Aileen Davis is retiring from her position as a Senior Scientist and Division Head at the Krembil Research Institute, effective June 30, 2020. Dr. Davis has been leading a prolific and impactful research program for more than 23 years, 15 of which were spent at Krembil and its predecessor, the Toronto Western Research Institute.

Dr. Davis is trained as a physiotherapist and clinical epidemiologist, giving her the expertise and experience needed to lead a research program that helped to improve the function in and quality of life of people living with musculoskeletal diseases, such as osteoarthritis and, earlier in her career, bone and soft tissue cancers. She designed and evaluated new models for delivering care to patients, and she developed several tools to measure patient outcomes in clinical care. Over the course of her career, Dr. Davis published more than 257 peer-reviewed scientific articles.

One of Dr. Davis's most notable research achievements is helping to bring the GLA:D program to Canada. GLA:D is an evidence-based program developed in Denmark for the treatment and management of osteoarthritic symptoms. In partnership with *Bone*

and Joint Canada, a national knowledge translation network, Dr. Davis led the evaluation of the program at 154 sites in seven provinces. As of December 2018, more than 1,600 Canadians had participated in the program and Dr. Davis's research study. Her findings revealed that deploying GLA:D in Canada helped to significantly reduce pain and improve function in Canadians living with hip and knee osteoarthritis. GLA:D is now being offered as routine evidence-based care to individuals with hip and knee osteoarthritis across the country.

Dr. Davis's greatest satisfaction is the success of her numerous trainees. Over the span of her career she was a primary supervisor and mentor to 25 graduate students and postdoctoral fellows. Many of her former trainees have become tenured faculty and productive researchers, as well as practicing physiotherapists and orthopedic surgeons.

In addition to her research and training activities, she has been (and continues to be) a highly active member of the scientific community. Presently, she is a board member of the Osteoarthritis Research Society International (OARSI), an Associate Editor for the academic journal *Osteoarthritis and Cartilage* and a member of the Editorial Board of *Arthritis Care & Research*.

Dr. Davis is a Professor Emeritus at the University of Toronto, in the Departments of Surgery; Physical Therapy; Rehabilitation Science Institute; Institute of Health Policy, Management and Evaluation at the Dalla Lana School of Public Health; and Institute of Medical Science.

The entire Krembil community would like to congratulate Dr. Davis on her research achievements, exceptional mentoring and contributions to improving care, as well as her valuable contributions to our community and institute."

Best wishes on your next adventure Dr. Davis.

Vision Researcher Recruited

Dr. Karun Singh, a neuroscientist and stem cell biologist, joins Krembil as a Senior Scientist.

In June 2020, the Krembil research community welcomed its newest member: Dr. Karun Singh, a mid-career researcher with extensive expertise in neuroscience and stem cell biology.

Dr. Singh's research has led to a better understanding of how genes affect neurological development by identifying those that put individuals at higher risk of developing neurodevelopmental disorders (NDDs). In his research, he uses a variety of experimental models of NDDs—including lab-engineered brain cells from patients—and cutting-edge techniques such as CRISPR gene editing.

He received the 2018 *Young Investigator Award* from the Canadian Association for Neuroscience for identifying two novel risk genes for NDDs: *TAOK2* in autism and *OTUD7A* in 15q13.3 microdeletion syndrome.

Dr. Singh's expertise and experience are highly complementary to those of Krembil's vision researchers. Through collaborations and scientific exchanges, he will help the vision researchers model disease in human and patient-derived material. Developing more humanized models of disease can lead to new insights into disease mechanisms.

"I am very excited to be part of Krembil's large neuroscience community, where basic and clinical science are so highly integrated. I look forward to establishing new projects

and collaborations—particularly with the vision and neurodegenerative disease groups—to mutually expand and enrich our research programs," says Dr. Singh.

Before joining Krembil, Dr. Singh was a Scientist in the Stem Cell and Cancer Research Institute and an Associate Professor in the Department of Biochemistry & Biomedical Sciences at McMaster University, where he held the endowed *David Braley Chair in Human Stem Cell Research*. He completed his PhD at the University of Toronto and his postdoctoral fellowship at the Massachusetts Institute of Technology in the United States.

Dr. Singh's recruitment was made possible by the generous support of Donald K. Johnson and Anna McCowan-Johnson through the Toronto General & Western Hospital Foundation.

Welcome to the Krembil Dr. Singh!

Research

Tracing the Paths to Disease

New study reveals neuropathological patterns in progressive supranuclear palsy.

The current study maps the regions of the brain where pathological tau proteins arise in individuals with various sub-types of progressive supranuclear palsy. These sub-types include Richardson syndrome and Parkinsonism.

Progressive supranuclear palsy (PSP) is a rare brain disorder with no known cure. As it worsens, the disease can cause serious problems with walking, balance, eye movements, swallowing, as well as changes in mood and thinking.

A recent large-scale international study led by Krembil Senior Scientist Dr. Gabor Kovacs identified the underlying stages of disease, which are key to better managing symptoms and developing targets for therapy. “This is the first study that attempts to define stages of PSP,” says Dr. Kovacs. “By knowing where to look, we can better monitor patients and better predict prognoses.”

The research project included international collaborators, including Dr. John Trojanowski from the University of Pennsylvania and Dr. Günter Höglinger from the German Centre for Neurodegenerative Disease. Together, the research team evaluated more than 200 brains affected by PSP and defined six stages of disease progression.

An abnormal protein, known as the pathological tau protein, is seen in the brains of individuals with PSP. The researchers traced how this protein spreads through the brain in distinct paths for each clinical sub-type. The findings showed that irrespective of the disease's clinical sub-type the first stage of PSP develops in the same brain region.

"Knowing where the pathological accumulation of the tau protein starts in the brain, means that we can now focus on researching this area specifically," says Dr. Kovacs. "Because this region comprises unique cell populations with different receptors or metabolic activity—we will get a better idea of which brain cells to target with therapy in the early stages of PSP."

The study was also able to show that the major difference between clinical sub-types of PSP relates not only to the involvement of nerve cells but also to the supporting cells called astroglia and oligodendroglia.

"We've provided a conceptual framework for the spread of tau to understand the mechanisms of how pathological tau jumps from one neuron to the next neuron and how the supporting tissue plays a role," says Dr. Kovacs. "With this understanding, we hope to provide a foundation for basic research to develop blocking agents or therapies to stop the spread of the tau protein."

Krembil Senior Scientist, Dr. Gabor Kovacs.

Dr. Kovacs is Co-Director of the Rossy Program for PSP research, which is led by Dr. Anthony Lang, Director of the Movement Disorders Clinic at Toronto Western Hospital. Funding for the study was obtained by Dr. Lang. Under the directorship of Dr. Lang and a team of world-leading researchers in movement disorders, it is the only program in Canada dedicated to PSP research and care. The research was also supported by Open Access funding from Projekt DEAL, the National Institutes of Health, the Penn Institute on Aging, Fundació Marató de TV3, the Rossy Foundation, the Edmond J. Safra Foundation, the Bishop Dr. Karl Golser Foundation, the German Research Foundation (DFG), the German Federal Ministry of Education and Research (BMBF), the NOMIS Foundation and the Toronto General & Western Hospital Foundation.

Gabor G. Kovacs, et al. Distribution patterns of tau pathology in progressive supranuclear palsy (link is external). Acta Neuropathol. 2020 Aug;140(2):99-119. doi: 10.1007/s00401-020-02158-2 (link is external). Epub 2020 May 7.

Stronger Together

Partnership between UHN and company reveals a new putative treatment for spinal arthritis.

The spine contains 33 adjacent bones known as vertebrae. Neighbouring vertebrae are connected by facet joints, which can become inflamed and damaged in ankylosing spondylitis.

A UHN study suggests that a novel drug could potentially prevent bone fusion in ankylosing spondylitis (AS), a form of arthritis that affects the spine.

AS is an autoimmune disease characterized by chronic inflammation and damage in the spine joints, which can lead to pain and stiffness in the back. As the disease progresses, AS can cause the bones in spine to fuse, thereby reducing a person's mobility and quality of life.

"Although there are treatments that can lessen symptoms in AS, none of these treatments have been conclusively shown to prevent spine fusion," says Dr. Robert Inman, a Senior Scientist at the Krembil Research Institute (UHN).

In the study, a team of researchers led by Dr. Inman characterized NDI-031407, a new drug developed by the company Nimbus Therapeutics. This drug inhibits the activity of TYK2, which is a protein that modulates type III immunity, a branch of the immune system responsible for protecting the body against disease-causing bacteria and fungi. Dysregulation of type III immunity is believed to underpin AS, and genetic studies suggest that TYK2 is also involved.

The researchers showed that NDI-031407 prevented disease progression, by stopping inflammation and joint damage, in two different experimental models of AS. The drug achieved this by dampening the activity of two types of immune cells, Th17 and gamma delta T cells, both of which are key players in type III immunity and are implicated in AS.

“Our study provides compelling evidence that TYK2 modulates the type III immune response and that targeting TYK2 maybe be an effective disease-modifying therapeutic for AS with the potential to not only relieve symptoms but also to prevent bone fusion in the spine,” adds Dr. Inman.

The majority of this work was performed by Dr. Eric Gracey, a former PhD student under Dr. Inman’s supervision. Dr. Gracey is now completing a postdoctoral fellowship in Gent, Belgium, where he is continuing to examine arthritis and help develop new treatments for it.

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

Gracey E, Hromadová D, Lim M, Qaiyum Z, Zeng M, Yao Y, Srinath A, Baglaenko Y, Yeremenko N, Westlin W, Masse C, Müller M, Strobl B, Miao W, Inman RD. TYK2 inhibition reduces type 3 immunity and modifies disease progression in murine spondyloarthritis (link is external). J Clin Invest. 2020 Apr 1. doi: 10.1172/JCI126567.

Targeting Cancer at Its Roots

Protein in cancer stem cells could represent a new target to treat aggressive brain cancer.

Cancer stem cells, which enable some tumours to return after treatment, are like the bulbs of perennial plants. As long as the bulb is present, the plant will grow back.

A UHN study has revealed a new therapeutic approach that could help to treat glioblastoma, the most common and most aggressive form of brain cancer in adults. In 2017, glioblastoma claimed the life of Gord Downie, the former frontman of Canada's iconic rock band, The Tragically Hip.

Glioblastoma is a deadly cancer diagnosed in approximately a thousand Canadians every year. Less than 5% of these individuals survive more than five years. The rates of survival are dismal because most of these brain tumours do not respond to current treatments. New and more effective treatments are therefore urgently needed for this disease.

In the study, Dr. Valerie Wallace, a Senior Scientist at the Krembil Research Institute (UHN), and her trainee Dr. Ahmed El-Sehemy discovered that the protein Norrin plays an important role—albeit a complicated one—in the growth and proliferation of glioblastoma tumours.

"Norrin has been implicated in blood vessel formation in the brain, eye and inner ear, and the regulation of brain cell behaviour. Our findings indicate that Norrin is present in

a wide range of brain tumours and that higher levels of the protein are linked to better patient survival," says Dr. Wallace.

Glioblastoma tumours contain a small number of specialized cells known as cancer stem cells, which can give rise to new tumour cells. These stem cells are widely believed to be responsible for the cancer's resistance to treatment and its recurrence. Accordingly, targeting these cells could be the key to treating glioblastoma.

The researchers found that Norrin affects the growth and proliferation of a tumour's cancer stem cells. In stem cells with high levels of the ASCL1 protein, Norrin promoted cell growth, whereas in cells with low ASCL1 levels, Norrin inhibited growth. Although ASCL1's role in brain cancer is not entirely clear yet, the protein is known to be involved in the generation of brain cells during development.

Dr. Wallace comments, "Our study reveals an unanticipated role of Norrin in brain cancer progression. Norrin could be a potential therapeutic target for glioblastoma tumours and may inform the design of patient-specific treatments."

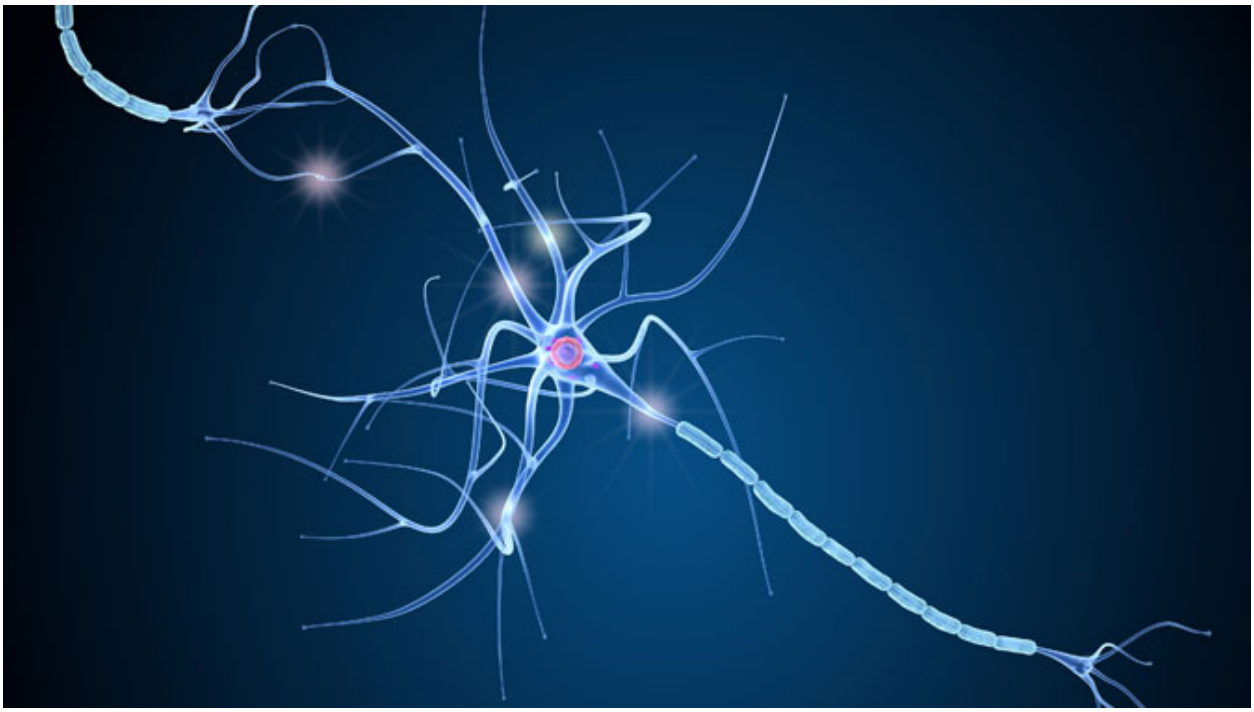
This work was supported by the Cancer Research Society, the Canadian Institutes of Health Research and the Toronto General & Western Hospital Foundation. VA Wallace holds a Tier 1 Canada Research Chair in Retina Regeneration.

El-Sehemy A, Selvadurai HJ, Ortin-Martinez A, Pokrajac NT, Mamatjan Y, Tachibana N, Rowland KJ, Lee L, Park NI, Aldape KD, Dirks P, Wallace VA. Norrin mediates tumor-promoting and -suppressive effects in glioblastoma via Notch and WNT. (link is external) J Clin Invest. 2020 Mar 17. doi: 10.1172/JCI128994.

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

Investing in Infrastructure

The brain adjusts communication speed between its different regions to increase resilience.



Nerve fibres are covered by a fatty insulation layer called myelin. The formation of myelin associated with white matter begins in the second trimester and continues into adulthood.

Dr. Jeremie Lefebvre, Affiliate Scientist at Krembil Research Institute and Associate Professor of Biology at the University of Ottawa, recently used mathematical models to show that brain cells can adjust how fast they communicate with each other to increase their collective efficiency.

When we think, learn and remember, different parts of the brain must communicate with each other and work together to process, store and retrieve information. This communication takes the form of electrical signals, which are passed along bundles of nerve fibres in an extensive tissue network collectively known as white matter.

“Like electrical cables which have a layer of insulation on the outside, nerve fibres also have insulation around them,” says Dr. Lefebvre.

“And instead of remaining unchanged after the brain becomes developed, this insulation layer is increased within white matter to make communication between brain regions faster when needed, such as when we learn something new.”

Using available data on the conduction of brain signals in macaques and the anatomy of the human brain, Dr. Lefebvre and his colleagues constructed a mathematical model of the human brain's communication network.

Analysis of the model showed that by enabling parts of the network to transmit signals faster—that is, by adding insulation to nerve fibres where and when needed—the brain's internal communication network becomes more stable and more efficient.

"This adaptive insulation of nerve fibres makes the brain more resilient as well," adds Dr. Lefebvre. "If a part of the network is damaged from trauma, the rest is able to compensate over time to help maintain stable communication between brain regions."

Much of the physiology of these dynamic processes within the brain remains poorly understood. By using mathematical models, researchers can simplify the brain's complexity and shed light on an aspect of its function. This study shows that the brain's constant investment in its infrastructure plays a major role in how we learn and adapt to change.

This work was supported by the Natural Sciences and Engineering Research Council of Canada, the Canadian Institutes of Health Research and the Toronto General & Western Hospital Foundation. P Frankland holds a Tier 1 Canada Research Chair in Mental and Behavioural Disorders.

Noori R, Park D, Griffiths JD, et al. Activity-dependent myelination: A glial mechanism of oscillatory self-organization in large-scale brain networks (link is external). Proc Natl Acad Sci U S A. 2020 Jun 26. doi:10.1073/pnas.1916646117.