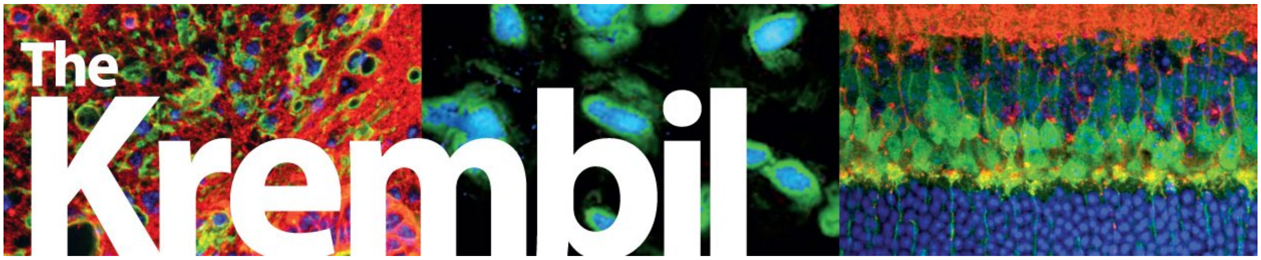


September 2023

The Krembil is the official newsletter of the Krembil Research Institute, highlighting recent news and awards, innovative research and exciting events happening at Krembil. For more information, visit www.discoverkrembil.ca.

Stories in this month's issue:

Jaideep Bains, PhD
Director, Krembil Research Institute
University Health Network

News

New to Krembil Business Office

Kim Perry joins the Krembil Research Institute as Business Manager.

Kim Perry, Business Manager, Krembil Research Institute.

The Krembil Research Institute is pleased to introduce its newest team member, Kim Perry, who is stepping into the role of Business Manager.

Kim has a wealth of institutional knowledge and experience conducting clinical and translational research at UHN. She joined the Division of Orthopedics in 2014 as a Biobank Technician and has since taken on progressive roles at the Schroeder Arthritis Institute.

As Biobank Manager and Laboratory Manager for Dr. Mohit Kapoor, she has developed standard operating procedures and research budgets, managed biospecimen collection and storage, and supported a wide range of research activities. In May 2020, she was redeployed to UHN's COVID Biobank and supported five COVID-related studies.

In her new role, Kim will work closely with Amy Ma in the Krembil Directorate office to ensure the efficient day-to-day operations of the Institute—supporting financial management, resource allocation and strategic planning.

"I am thrilled to take on this new role and contribute to Krembil's growth and success," says Kim. "To all our researchers, staff and trainees, if you don't already know me, reach out and introduce yourself. I look forward to working with you!"

Welcome Kim!

Kim obtained her Bachelor of Science from the University of Guelph and an Advanced Diploma in Biotechnology from Fleming College.

Deep Dive Into the Brain

Explore the intricacies of the human brain in a free Gairdner Global Perspectives Panel.

Join us on October 3, 2023 for the Gairdner Global Perspectives Panel event "*Mindsets: A Deep Dive Into the Brain*".

Event details
- Date: October 3, 2023
- Time: 5:15 - 7:00 PM
- Location: Li Ka Shing Knowledge Institute, 209 Victoria St, Toronto, ON, M5B 1T8
- Registration: https://bit.ly/Mindsets_Deep_Dive_Into_Brain

Hosted in partnership with the Krembil Brain Institute and the Ontario Brain Institute, and presented by TELUS Health, this event promises to be a thought-provoking journey into the intricacies of the human brain and some of the conditions that affect it, from cancer and multiple sclerosis to stress.

The free public lecture will feature talks from three distinguished Canadian neuroscientists:
- Dr. Gelareh Zadeh, Co-Director of Krembil Brain Institute and Senior Scientist at Princess Margaret Cancer Centre, will unravel the complexities of brain tumours;
- Dr. Jaideep Bains, Co-Director and Senior Scientist at Krembil Brain Institute, will discuss the impact of stress on brain cells and their connections; and

● Dr. Jiwon Oh, Medical Director of the Barlo Multiple Sclerosis Program at St. Michael's Hospital, will share her research into multiple sclerosis and how to treat it.

The event will culminate in a panel discussion moderated by Canadian broadcast journalist Mary Ito.

"We are very excited to help host this event to share cutting-edge research with the public," says Dr. Jaideep Bains, Co-Director of the Krembil Brain Institute. "This is an excellent opportunity to showcase discoveries and the breadth of brain research that is being done in Canada."

For more information about this event, click here.

Research

A New Path to Diagnosis

Study uncovers markers of ankylosing spondylitis by studying cellular packages and their cargo.


(L-R) Dr. Robert Inman, senior author of the study, and Dr. Fataneh Tavasolian, first author of the study.

Researchers at the Schroeder Arthritis Institute have gained valuable insights into the biological basis of ankylosing spondylitis, a debilitating form of arthritis that causes chronic inflammation of the spine.

Ankylosing spondylitis is a challenging condition to manage, in part because the underlying disease processes are not well characterized and there is no definitive test for its diagnosis.

To improve patient care, efforts are under way to identify gene- and protein changes that contribute to the condition and could serve as disease signatures, called biomarkers.

One type of biomarker that is generating interest among researchers is microRNA (miRNA)—short strings of RNA that alter gene expression.

“Altered expression of microRNAs and proteins can play a key role in ankylosing spondylitis by triggering immune dysfunction and inflammation, but it’s unclear exactly how this occurs,” says Dr. Robert Inman, Co-Director and Senior Scientist at the Schroeder Arthritis Institute. “Clarifying the genetic and immunologic features of the condition is a critical step towards developing reliable diagnostic tests and targeted therapies.”

Dr. Inman and his team analyzed miRNAs and proteins that are present in exosomes—tiny vesicles that cells release to communicate with other cells.

“We studied exosomes because their role in intercellular communication implicates them in immune dysregulation,” explains Dr. Fataneh Tavasolian, a postdoctoral researcher in Dr. Inman’s lab. “By analyzing exosomes and their molecular contents, we can determine the messages that cells send to one another in ankylosing spondylitis and begin to unravel the molecular processes that underlie inflammation and other symptoms of this disease.”

The researchers isolated exosomes from the plasma of 40 men and women with and without ankylosing spondylitis and comprehensively analyzed their miRNAs and proteins, and effects on immune cells.

Exosomes from people with ankylosing spondylitis had elevated levels of two surface proteins that are linked to inflammation. When exposed to a type of immune cell—called T cells—these exosomes triggered the release of other proteins that promote inflammation.

The exosomes also decreased the activity of regulatory T cells—a specialized subpopulation of T cells that suppress runaway immune responses.

Collectively, these findings suggest that exosomes in people with ankylosing spondylitis have unique protein profiles, which could contribute to chronic immune activation and inflammation.

The team also identified 24 miRNAs that were differentially expressed in people with and without the condition—22 of which were consistently expressed at higher levels in people with the condition.

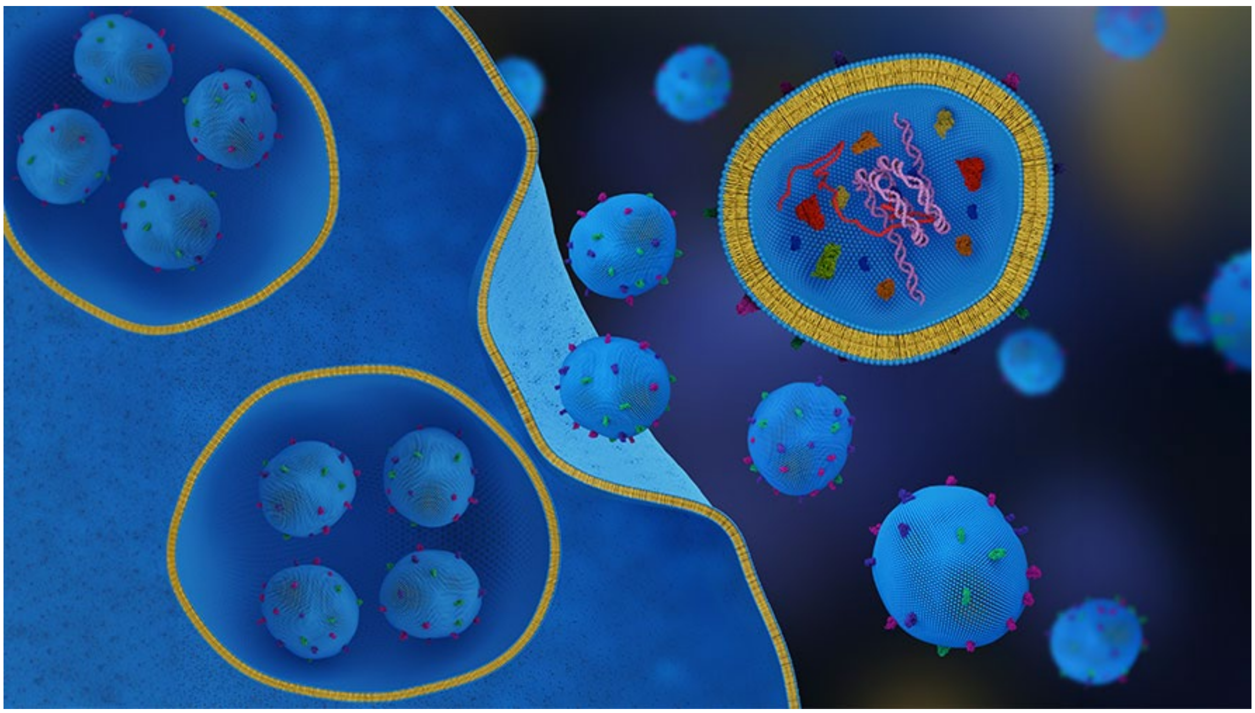
One miRNA—miR-30c-5p—stood out because of its role in regulating immune cell function.

Pinpointing the miRNAs that differ between people with and without ankylosing spondylitis could ultimately resolve the genetic basis of the disease and inform the development of therapies aimed at restoring immune balance.

“The insights that we have gained from this study could open doors to disease biomarkers that support early diagnosis and intervention, as well as new treatments that target underlying disease processes,” concludes Dr. Tavasolian.

This work was supported by Spondyloarthritis Research Consortium of Canada, the Schroeder Arthritis Institute, the Krembil Foundation, the Arthritis Society and the UHN Foundation. Dr. Robert D. Inman is a Professor in the Departments of Medicine and Immunology at the University of Toronto. Dr. Fataneh Tavasolian is a postdoctoral researcher at the Schroeder Arthritis Institute.

Tavasolian F, Lively S, Pastrello C, Tang M, Lim M, Pacheco A, Qaiyum Z, Yau E, Baskurt Z, Jurisica I, Kapoor M, Inman RD. Proteomic and genomic profiling of plasma exosomes from patients with ankylosing spondylitis. Ann Rheum Dis. 2023 Aug 2:ard-2022-223791. doi: 10.1136/ard-2022-223791.



Exosomes (illustrated above) are created by cells and secreted to facilitate intercellular communication. Once released, they enter the bloodstream and deliver their contents—including miRNAs and proteins—to other cells throughout the body.

Diversity Builds Resilience

Krembil researchers uncover a protective role of diversity among brain cells.

(L-R) Dr. Jérémie Lefebvre, an Affiliate Scientist at the Krembil Brain Institute, Dr. Taufik Valiante, a Senior Scientist at the Krembil Brain Institute, and Dr. Axel Hutt, Research Director of the National Institute for Research in Digital Science and Technology in France.

Diversity is a hallmark of life. Variation among species and cell types within a single organism is key for supporting the myriad functions and adaptations needed to survive. A new study from the Krembil Brain Institute has explored the importance of brain cell diversity for brain function and health.

“In previous studies, we found that individuals with epilepsy have lower cell diversity in a brain region that is responsible for the generation of seizures,” says Dr. Taufik Valiante, co-senior author of the study. “We also demonstrated that when neurons behave too much like one another, neuronal networks become unstable.”

“We wanted to expand on this work and understand more generally why there are so many distinct neurons within the same regions of the healthy human brain,” explains co-senior author Dr. Jérémie Lefebvre. “While scientists have previously suggested that brain cell diversity is just noise, our research into epilepsy suggested that it protects against the development of seizures.”

To explore this possibility, the team applied computational tools to model neuronal networks—complex webs of interconnected neurons.

“We applied mathematical tools that were developed in the field of ecology and have been traditionally used to study ecosystems, but rather than using them to study food webs, we used them to study neuronal networks,” explains Dr. Hutt, first author of the study. “The specific type of diversity that we explored was that related to neuron excitability—how easily a neuron will send a signal after receiving a stimulus.”

The researchers exposed their neural networks to a slowly changing signal that mimics what a neuron might experience in the environment. They found that the networks were less stable when their neurons were not diverse. This instability manifested as sudden shifts in neuron activity levels.

“Our models revealed that cellular diversity bolsters the brain’s resiliency, making it better able to maintain functions in the face of ageing, disease and injury,” says Dr. Valiante.

The team suggests that a deeper understanding of the diversity among brain cells could improve our understanding of various neuropsychiatric disorders and how to treat them.

“Our findings may explain why drugs that are used to treat epilepsy fail in so many patients. By shedding light on the underlying mechanisms of the disease, this research could pave the way for improved therapies,” says Dr. Valiante. “Importantly, changes in cell diversity are likely not limited to epilepsy, but also play a role in various neurodevelopmental and neurodegenerative conditions.”

These findings serve as a striking reminder of the fundamental role that diversity plays in the resilience of natural systems in the face of change. This truth applies not only to neural circuits but also to humans, communities and other complex systems.

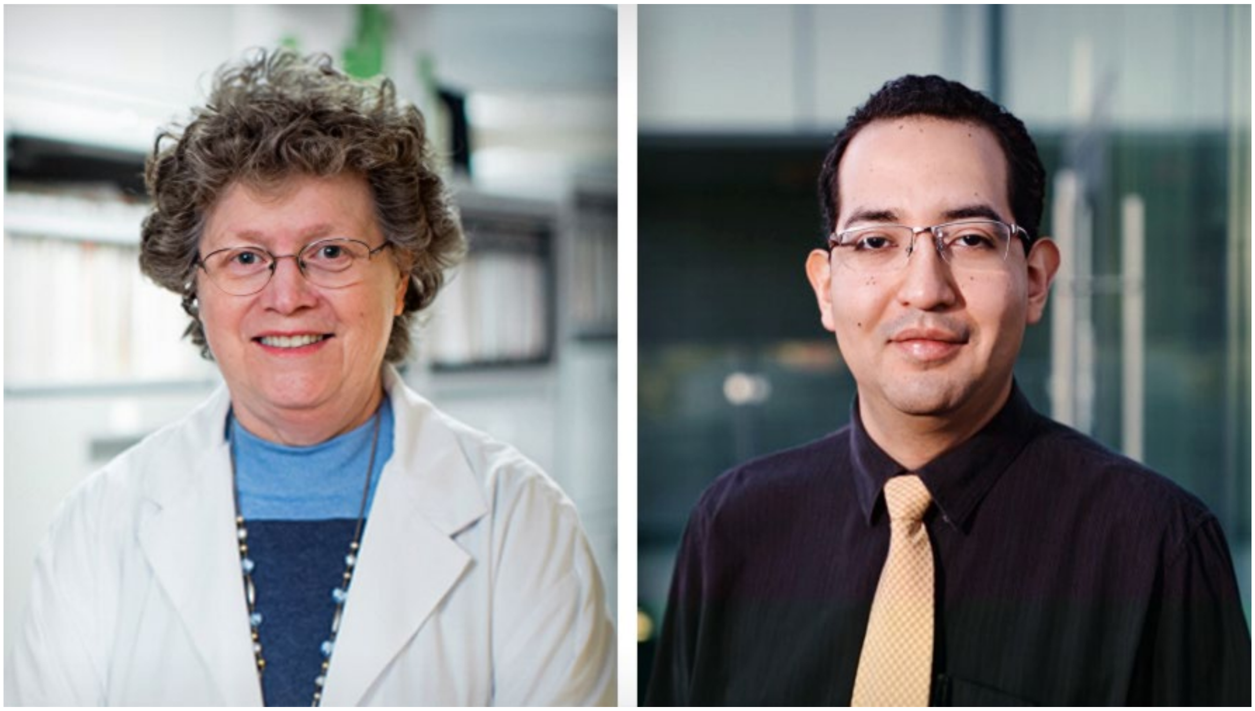
This work was supported by the National Sciences and Engineering Research Council of Canada, the Krembil Foundation and the UHN Foundation. Dr. Valiante is an Associate Professor in the Department of Surgery at the University of Toronto. Dr. Jérémie Lefebvre is an Associate Professor in the Department Mathematics at the University of Toronto and an Associate Professor of Biology at the University of Ottawa. Dr. Axel Hutt is Research Director at the National Institute for Research in Digital Science and Technology in France.

Hutt A, Rich S, Valiante TA, Lefebvre J. Intrinsic neural diversity quenches the dynamic volatility of neural networks. Proc Natl Acad Sci U S A. 2023 Jul 11;120(28):e2218841120.

Neurons communicate with each other to form complex networks. Researchers can assess diversity within neural networks by measuring how individual cells respond to excitatory and inhibitory inputs.

Getting Ahead of Arthritis

Subtle changes in DNA could predict the transition from psoriasis to psoriatic arthritis.



(L-R) Drs. Dafna Gladman, a Senior Scientist at the Schroeder Arthritis Institute and a Professor of Medicine at the University of Toronto, and Omar Cruz-Correa, a Research Associate in Dr. Gladman's lab.

Scientists at the Schroeder Arthritis Institute have identified genetic markers that can accurately predict whether a person will develop psoriatic arthritis (PsA). These findings could help to prevent permanent joint damage and disability by enabling early disease detection and treatment.

PsA is a type of arthritis that is common in people who have psoriasis, an autoimmune condition that affects the skin. The condition occurs when the body's immune system mistakenly attacks the joints, leading to inflammation, pain and reduced mobility.

Approximately 30% of people with psoriasis will develop PsA. Unfortunately, there are no early warning signs for the transition to PsA, so patients are often unaware of underlying disease changes until they experience significant and lasting joint damage.

"This is a major challenge for timely intervention, and it underscores the need for predictive tools to help us manage this condition," explains Dr. Dafna Gladman, a Senior Scientist at the Schroeder Arthritis Institute and the lead author of the study.

To identify biomarkers that can predict PsA development, Dr. Gladman and her team studied genetic features in 700 men and women who had psoriasis without musculoskeletal symptoms.

The team specifically looked at DNA methylation—the process by which DNA gathers tiny chemical tags that serve as genetic switchboards, influencing cellular functions by turning particular genes on or off.

“We focused on DNA methylation because it is relatively easy to measure and plays a role in regulating gene expression in response to external factors, such as stress and diet," says Dr. Omar Cruz-Correa, a postdoctoral researcher in Dr. Gladman's lab and the first author of the study.

The team studied DNA methylation patterns in blood samples from people with psoriasis who went on to develop arthritis—called converters—and those who did not. Both groups were matched for age, sex, disease stage and duration of follow-up.

"We saw significant methylation differences between converters and nonconverters,” says Dr. Gladman, who is also Director of the Psoriatic Arthritis Program and Deputy Director of the Centre for Prognosis Studies in Rheumatic Diseases at UHN. “We identified 36 locations related to 15 genes that had increased methylation. These regions can predict with high accuracy which individuals with psoriasis will develop PsA."

Although measuring 36 individual DNA markers is not feasible for a diagnostic test applied in clinical settings, Dr. Gladman explains that these results point us towards interesting metabolic pathways that might be involved in PsA and require further study.

"A variety of molecular processes affect gene expression—DNA methylation is just one of them," concludes Dr. Cruz-Correa. "We need to investigate how these mechanisms work together to regulate gene expression in order to paint a clearer picture of the pathogenesis of psoriatic disease."

In the future, dermatologists and other clinicians could assess DNA methylations and other predictive markers to identify individuals with psoriasis who are at a heightened risk of developing PsA. This proactive approach would enable health care professionals and patients to rapidly detect musculoskeletal symptoms and initiate treatment early to delay or prevent permanent joint damage.

This work was supported by the National Psoriasis Foundation, the Arthritis Society, the Canadian Institutes of Health Research, the Krembil Foundation and the UHN Foundation.

Cruz-Correa OF, Pollock RA, Machhar R, Gladman DD. Prediction of psoriatic arthritis in patients with psoriasis using DNA methylation profiles. Arthritis Rheumatol. 2023 Jul 18. doi: 10.1002/art.42654.

PsA is often associated with psoriasis, a skin condition that is characterized by red, scaly patches; however, not everyone with psoriasis develops PsA.

Keeping Cancer at Bay

Study identifies meningeal macrophages as key mediators of anti-cancer signalling in the brain.

Dr. Valerie Wallace (left) is Co-Director and Senior Scientist at the Donald K. Johnson Eye Institute. Dr. Nenad Pokrajac (right) is a postdoctoral researcher in Dr. Wallace's lab.

Researchers at UHN's Donald K. Johnson Eye Institute (DKJEI) have discovered a pivotal role of macrophages—a type of immune cell that destroys invading microorganisms—within the membranes that envelop and protect the brain in anti-cancer cell signalling.

It is commonly believed that gene mutations within precancerous cells are sufficient to trigger uncontrollable tumour growth and metastasis—but this is not the case.

It fact, it is quite difficult for tumours to form and grow. This challenge results from biological roadblocks that either exist within precancerous cells (e.g., molecular pathways that turn off cell division) or come from nearby healthy cells, such as immune cells.

For cancer cells to flourish, they need to co-operate with healthy cells in their environment. This process is a constant push-pull, with tumours continually receiving chemical signals that promote or inhibit their growth.

In a recent study published in *Developmental Cell*, a team of UHN scientists has brought to light a key cell population and chemical signalling pathway that inhibit the development of brain tumours.

According to Dr. Valerie Wallace, Co-Director and Senior Scientist at DKJEI and the lead author of the study, we can think of a developing cancer like a smoldering fire. “Early stage tumours are akin to embers that fail to cause fires because they are smothered by factors in their environment,” she explains. “This smothering often succeeds in extinguishing the embers, but they can burst into flames if sufficient fuel becomes available.”

The cells and processes that smother early tumours are clinically relevant for cancer screening and treatment. Screening tests such as colonoscopies are aimed at detecting precancerous lesions so they can be removed before they progress, and drugs that mimic or bolster natural anti-tumour processes can help prevent or treat cancers.

“Because we cannot biopsy brains to screen for early stage cancers the way we do elsewhere in the body, there are a lot of unknowns related to anti-cancer cell signalling in this tissue,” says Dr. Nenad Pokrajac, a postdoctoral researcher in Dr. Wallace’s lab and the first author of the study.

To overcome this limitation, the team used an experimental model of medulloblastoma—the most common type of cancerous brain tumour in children—to study how non-tumour cells affect tumour formation in a particular brain region called the cerebellum.

“From previous studies, we knew that blood vessels in the cerebellum can have anti-tumour effects, but these vessels interact with many partners,” says Dr. Pokrajac. “Our goal was to pinpoint the cells that work with blood vessels to inhibit tumour growth.”

The sophisticated experimental model enabled the team to track the division of cancer cells in response to changes in cell signalling.

The team discovered that the meninges—the tissues that line the surface of the brain and spinal cord—are powerful cancer fighters.

Of the many cell types present in the meninges, macrophages stood out as key players in the fight against tumour development. When the researchers removed these cells or inhibited their activity, tumours grew faster.

“We also discovered that macrophages attack early tumours by releasing a protein called CXCL4, which inhibits a powerful growth-promoting protein called CXCL12,” explains Dr. Pokrajac. “Based on these findings, blood vessels instruct macrophages that reside in the meninges to release CXCL4 to smother tumours by depriving them of fuel.”

Importantly, because macrophages can be found throughout the meninges, their protective role is likely not specific to the cerebellum, or even to a particular type of tumour.

More research is needed to confirm whether this is the case, but the team’s findings raise the possibility that these cells play a general, widespread role in the development of brain tumours.

“This is an exciting step forward for understanding how brain tumours form and how we can leverage the body’s natural cancer-fighting processes to treat them,” concludes Dr.

Wallace. “In many tissues, it can take years for tumours to develop. If we can identify the processes that keep tumours at bay, and how they can go awry, we can intervene early and improve patient outcomes.”

The work was supported by the Cancer Research Society, the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, the Ontario Institute for Regenerative Medicine, the Government of Ontario, the University of Toronto-UHN Vision Science Research Program, Medicine by Design-University of Toronto, Foundation Fighting Blindness and the UHN Foundation. Dr. Valerie Wallace is DKJEI Co-Director and Senior Scientist and a Professor in the Department of Ophthalmology & Vision Science at the University of Toronto. She holds the Donald K. Johnson Chair in Vision Research at UHN and a Tier 1 Canada Research in Retina Regeneration at the University of Toronto.

Pokrajac NT, Tokarew NJA, Gurdita A, Martinez AO, Wallace VA. Meningeal macrophages inhibit chemokine signalling in pre-tumour cells to suppress mouse 1 medulloblastoma initiation. Developmental Cell. 2023 Sept 28. doi: 10.1016/j.devcel.2023.08.033.