The Krembil

March 2024

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.

Dr. Jaideep Bains,
Director, Krembil Research Institute
University Health Network

Stories in this month's issue:

News

Women Changing the Game

Krembil highlights some of its talented women researchers and health care providers.

(L-R) Livestream host and moderator Dr. Chika Stacy Oriuwa and panelists Drs. Tina Felfeli, Nikita Looby and Nardin Samuel.

In celebration of the *International Day of Women and Girls in Science*, the Krembil Research Institute hosted a free educational livestream on Friday, February 9, 2024.

The event, which can be viewed here, attracted more than 4,500 people, including over 2,800 students from more than 100 classrooms, some as far as Ecuador, Columbia, Iceland and Australia!

The event was streamed live by middle and high school students from 14 Ontario school boards, including the Toronto District School Board and Durham District School Board, as well as students at international schools and universities.

Moderated by Dr. Chika Stacy Oriuwa, one of Time magazine's *2021 Next Generational Leaders* and an accomplished physician, spoken word poet and advocate, the livestream featured the following Krembil researchers and health care providers:

- Dr. Tina Felfeli, Donald K. Johnson Eye Institute
- Dr. Nikita Looby, Schroeder Arthritis Institute
- Dr. Nardin Samuel, Krembil Brain Institute

Each speaker gave a short, TED-style talk about what inspired them to pursue a career in science, how challenges and obstacles shaped their scientific journeys, and why they find their careers so rewarding.

The livestream also featured guest appearances from Canadian inventor Andini Makosinski and Canadian aerospace engineer Natalie Panek. These remarkable women shared inspiring messages about the importance of dreaming big and refusing to set limits for yourself.

Sharing her advice for young science-enthusiasts everywhere, Makosinski said, "Be bold in your passions and pursue them fearlessly."

The event concluded with a lively panel discussion in which the speakers answered questions submitted by participating classrooms.

"As we celebrate the International Day of Women and Girls in Science, we recognize the transformative power of diversity in research," says Krembil Research Institute Director Dr. Jaideep Bains. "We hope that hearing from some of the incredible women on our team inspires young people of all genders and backgrounds to break barriers and apply their unique perspectives to answering pressing scientific questions."

Want more inspiring stories about women researchers at UHN? Click here to read about some of the women who are advancing health research and innovation across the Institution.

According to the United Nations Educational, Scientific and Cultural Organization (UNESCO), women account for only one third of researchers worldwide, despite representing nearly half the population of undergraduate and graduate students. To address gender inequities in the fields of science, technology, engineering and math (STEM), the United Nations declared February 11 as the International Day of Women and Girls in Science.

Season 3: Your Complex Brain

Krembil Brain Institute launches a new season of its award-winning podcast Your Complex Brain.

(L-R, top to bottom) Season 3 features Krembil Brain Institute researchers and clinicians, Drs. Suganth Suppiah, Lorraine Kalia, Cathy Barr and Jaideep Bains.

UHN's Krembil Brain Institute is proud to announce the highly anticipated launch of Season 3 of its acclaimed podcast, *Your Complex Brain*.

Hosted by Heather Sherman, Manager of Communications at the Krembil Brain Institute, *Your Complex Brain* offers listeners a guided journey into the fascinating world of brain science and the unique perspectives and experiences of researchers, clinicians, patients and their loved ones.

With in-depth interviews, scientific discussions and powerful patient stories, the podcast aims to teach listeners about the complexities of the human brain and the importance of brain research.

Episodes in this season cover a wide range of topics, including:

- strategies for reducing one's risk of Alzheimer's disease
- the role of exercise in managing Parkinson's disease
- advancements in spinal cord injury research

● the impact of loneliness on the brain
● what women need to know about stroke prevention and recovery

This season will also take listeners to the frontline of AI-powered brain research, dive into the link between genetics and reading disabilities, and explore why getting a good night's sleep is crucial for brain health.

Your Complex Brain also shines a light on the collaborations between the Krembil Brain Institute and other leading research institutions, including the University of Toronto, The Hospital for Sick Children, the Centre for Addiction and Mental Health, and the University of Waterloo.

To learn more, watch the Season 3 trailer here.

“We are thrilled to be able to inform and engage the public through our podcast and introduce listeners to some of our key research teams, clinical leaders and patient partners,” says Heather Sherman. “There are countless amazing things to learn about the brain, and we couldn't be more excited to explore them with you.”

Following the success of previous seasons, which have garnered over 32,000 downloads and earned the podcast the 2024 People's Choice Award for Best Science & Medicine Podcast, the upcoming season promises to captivate, educate and inspire audiences once again.

“*Your Complex Brain* is a fantastic resource for anyone interested in understanding the brain and the latest advancements in neuroscience,” says Dr. Jaideep Bains, Krembil Director and Season 3 guest. “We invite everyone to tune in and join the growing community of supporters for the incredible work being done at UHN and our partnering institutions.”

Your Complex Brain is available on all major podcast platforms, including Apple Podcasts, Spotify and Google Podcasts. New episodes will air every other Tuesday. Subscribe so you don’t miss an episode!

Your Complex Brain is produced by Heather Sherman, Jessica Schmidt, Dr. Amy Ma, Kim Perry, Sara Yuan, Meagan Anderi, Liz Chapman and Lorna Gilfedder. For more information, visit https://www.uhn.ca/Krembil/Complex-Brain-Podcast.

Research

Classifying Parkinson's Disease

Scientists propose new, biologically based classification system for Parkinson disease.

Dr. Anthony Lang is a Senior Scientist at UHN's Krembil Brain Institute. He is also Director of the Edmond J. Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic and holds the Lily Safra Chair in Movement Disorders at UHN.

An international research team led by Krembil Brain Institute Senior Scientist Dr. Anthony Lang has proposed a new model for classifying Parkinson disease (PD).

In recent decades, researchers have uncovered several biological factors that underlie PD. Key factors include a build up of the protein α-synuclein in the brain, which leads to neuron degeneration, and genetic factors that increase one's risk of developing the disease. They have also begun to develop reliable methods to test for these factors—called disease biomarkers—in living patients.

Despite these advancements, doctors still diagnose the disease based on clinical features, such as the presence of tremors and other common motor symptoms.

According to Dr. Lang, a Professor of neurology, the Jack Clark Chair for Parkinson's Disease Research at the University of Toronto and the Lily Safra Chair in Movement Disorders at UHN, this traditional approach to diagnosing PD does not account for the complex biological processes at play.

“We need a radically different way of looking at this disease,” he says. “We have reached a point where our research must be driven by biological determinants of the disease, rather than limited clinical descriptions of its signs and symptoms.”

In a recent article published in *Lancet Neurology*, Dr. Lang’s team propose a new, biologically based model for classifying PD—called SynNeurGe (pronounced “synergy”).

The model emphasizes the important interactions between three biological factors that contribute to the disease:

1. the presence of pathologic α-synuclein in the brain (S)
2. evidence of neurodegeneration, which occurs as the disease progresses (N)
3. the presence of gene variants that cause or strongly predispose a person to the disease (G)

According to the team, this “S-N-G” classification system better accounts for the biological heterogeneity of PD and the many ways the condition can present in patients. Consequently, the system could help researchers identify subgroups of patients that have distinct disease processes and develop clinically meaningful disease-modifying therapies.

“We need to recognize that PD can differ dramatically between patients. We are not dealing with a single disorder,” explains Dr. Lang. “Our model provides a much broader, more holistic view of the disease and its causes.”

The team is confident that this new way of looking at PD will help researchers study its molecular basis, distinguish it from other neurodegenerative conditions that share common biological features and identify targets for new therapies.

Despite the model’s potential clinical applications, Dr. Lang cautions that it is intended for research purposes only and is not ready for immediate application to patient care. Although more research is needed before the classification system can be applied clinically, it is already spurring hope among patients and the medical community.

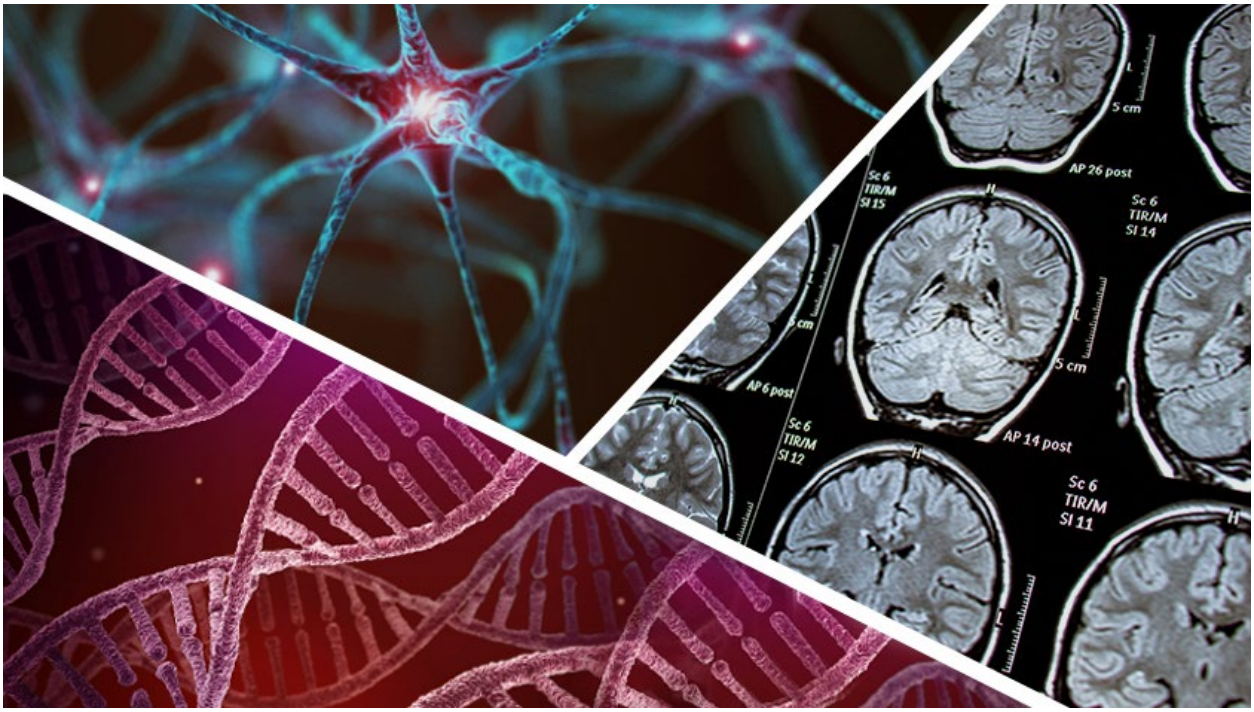
“The ability to tailor treatments improves when you can identify exactly what is going on in a specific patient like me,” says Hugh Johnston, Founding Chair of the Patient Advisory Board of the Movement Disorders Clinic at the Krembil Brain Institute. “This new way of thinking is what we have been waiting for. It’s a game changer.”

This work was supported by National Institutes of Health, Canadian Institutes of Health Research, Canada Foundation for Innovation, Michael J. Fox Foundation, Brain Canada, Ontario Brain Institute, Garfield Weston Foundation, Webster Foundation,

Edmond J Safra Philanthropic Foundation, Parkinson Foundation, Parkinson Canada, the State of Arizona, Mayo Clinic, Banner Health, Fonds de Recherche du Quebec – Sante´, Deutsche Forschungsgemeinschaft (German Research Foundation), German Federal Ministry of Education and Research, EU/EFPIA/Innovative Medicines Initiative, European Joint Programme on Rare Diseases, Niedersächsisches Ministerium für Wissenschaft und Kunst, Volkswagen Foundation, Petermax-Müller Foundation, German Parkinson Society, German Parkinson's Disease Association, Parkinson Fonds Deutschland gGmbH, Damp Foundation and UHN Foundation.

Dr. Lang is a Professor in the Department of Medicine and the Jack Clark Chair for Parkinson's Disease Research at the University of Toronto.

Höglinger GU, Adler CH, Berg D, Klein C, Outeiro TF, Poewe W, Postuma R, Stoessl AJ, Lang AE. A biological classification of Parkinson's disease: the SynNeurGe research diagnostic criteria. Lancet Neurol. 2024 Jan. doi: 10.1016/S1474-4422(23)00404-0.



The SynNeurGy model is based on a growing understanding that PD involves three key biological factors—a build up of α-synuclein, neuron loss and the presence of specific gene variants—and that the relative contribution of each of these factor often differs between patients.

Blueprinting Lupus Flares

Researchers identify immune profiles associated with changes in disease activity in lupus.

(L-R) Drs. Kieran Manion, former postdoctoral researcher at the Schroeder Arthritis Institute, and Joan Wither, Senior Scientist at the Schroeder Arthritis Institute.

Researchers at UHN's Schroeder Arthritis Institute have deciphered the immunological signature of flares in systemic lupus erythematosus (SLE), paving the way for improved prognosis and treatment.

SLE is a chronic autoimmune disease that affects many body systems. SLE can be a complex puzzle for clinicians because it can present very differently in patients. Additionally, in approximately 80% of patients, SLE is marked by intermittent flares in disease activity, interspersed with symptom-free periods.

"Managing SLE can be quite challenging due to the unpredictable nature of the condition. Pre-empting flares is important for preventing tissue damage, but we have a limited arsenal of tools to predict whether a given patient will experience a flare and when it will happen," explains Dr. Joan Wither, a Senior Scientist at the Schroeder Arthritis Institute and senior author of the study.

"A major goal for researchers today is to determine the immune processes that drive changes in SLE activity to allow clinicians to closely monitor high-risk patients and offer pre-emptive treatments."

To accomplish this, Dr. Wither's team examined the immune cells present in blood samples from men and women with or without SLE. The team grouped people with similar immunological profiles and tracked immune changes at six-month and 12-month follow-up visits.

The team studied 47 distinct cell populations in samples from 46 patients experiencing flares, 25 patients not experiencing flares and 16 healthy controls.

The study revealed a spectrum of immunologic profiles linked to SLE activity. Based on their profiles, participants fit into five clusters, each characterized by unique clinical phenotypes—or observable disease features.

Levels of certain immune cells, such as age-associated B cells and T peripheral helper cells, predicted SLE activity one year later. For example, patients with higher levels of B cell activity were more likely to experience flares at their initial clinic visit and, if B cell activation continued or subsequently developed, have sustained or recurrent high disease activity over the subsequent year.

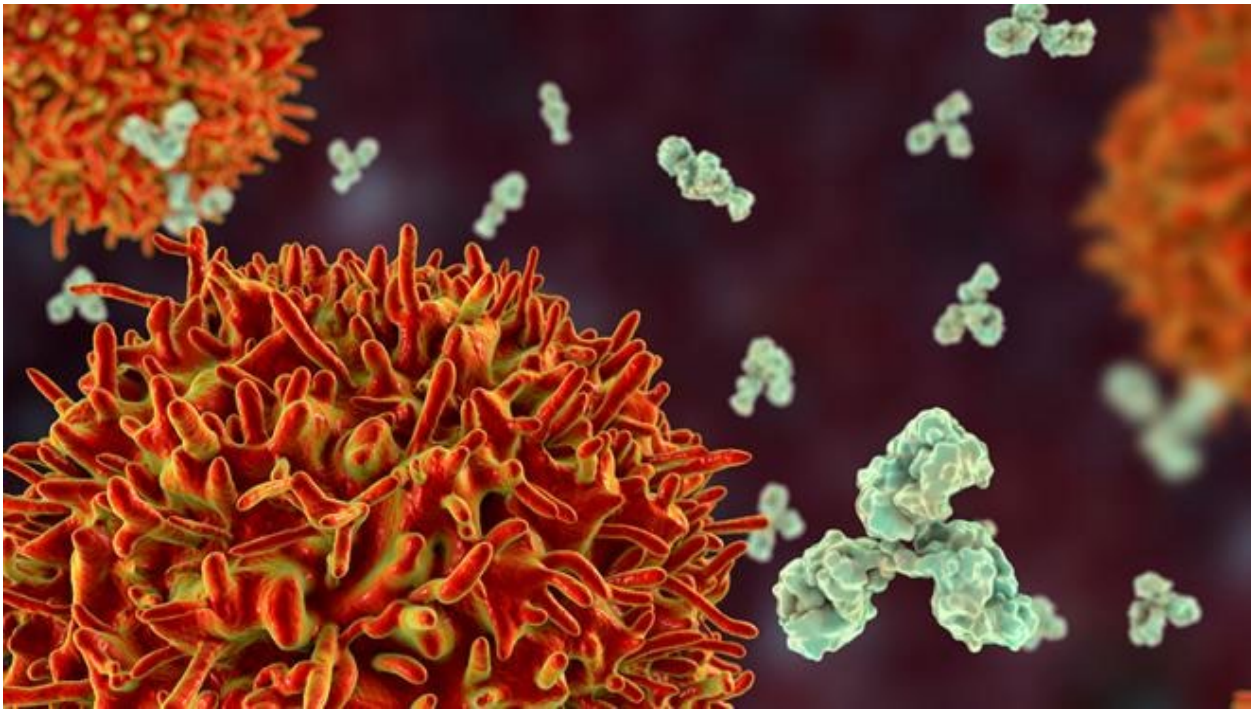
Conversely, patients who had elevated levels of T helper cells in the absence of changes in B cell activity, or those with elevated levels of type 1 helper cells and innate immune cells, typically transitioned to a symptom-free state during the follow-up period.

These findings underscore the role of dysregulated immune responses in driving SLE flares and suggest that age-associated B and T peripheral helper cells could serve as biomarkers for ongoing or recurrent flares.

Dr. Kieran Manion, a former postdoctoral researcher in Dr. Wither's lab and the first author of the study, emphasizes the clinical significance of the team's findings: "Our study uncovered distinct immunological profiles in SLE patients that are associated with different ways the disease can manifest. By using these profiles to stratify patients, we can improve their prognosis and offer more personalized therapies to mitigate flares and improve their long-term outcomes."

This work was supported by the Canadian Institutes of Health Research, the Pfizer Chair Research Award, the Arthritis Centre of Excellence, the Schroeder Arthritis Institute and UHN Foundation. Dr. Wither is a Professor in the Department of Immunology at the University of Toronto.

Manion K, Muñoz-Grajales C, Kim M, Atenafu E, Faheem Z, Gladman DD, Urowitz M, Touma Z, Wither JE. Different Immunologic Profiles Are Associated With Distinct Clinical Phenotypes in Longitudinally Observed Patients With Systemic Lupus Erythematosus. Arthritis Rheumatol. 2023 Dec 10. doi: 10.1002/art.42776.



When the immune system is activated by a pathogen, distinct cell populations interact to mount a response. In SLE and other autoimmune diseases, immune cells mistakenly attack the body's own tissues.

Resolving Inflammation

UHN researchers uncover potential therapeutic targets for treating neuroinflammation.

(L-R) Dr. Izhar Livne-Bar, a Research Associate in Dr. Jeremy Sivak's lab, and Dr. Jeremy Sivak, a Senior Scientist at UHN's Donald K. Johnson Eye Institute. Photo credit: The Globe and Mail.

Researchers at UHN's Donald K. Johnson Eye Institute (DKJEI) have shed light on the molecular processes underlying the neuroprotective effects of lipoxins, paving the way for novel therapies for neurodegenerative diseases.

Lipoxins are small lipid molecules that are known to protect the nervous system from damage caused by inflammation.

DKJEI Senior Scientist Dr. Jeremy Sivak previously discovered that these molecules are produced in the retina—the neural tissue that lines the back of the eye—and showed that they protect neurons in an experimental model of retinal degeneration.

"An important step towards using lipoxins as targeted treatments for neurodegenerative diseases is determining how they protect against excessive inflammation," explains Dr. Sivak, the senior author of the study.

Dr. Sivak's team set out to determine the mechanisms by which two lipoxins dampen inflammation using an experimental model of posterior uveitis—retinal inflammation which can cause vision loss.

"We were particularly interested in how lipoxins interact with glial cells, which are critical for maintaining the immune response in the nervous system," explains Dr. Izhar Livne-Bar, a research associate in Dr. Sivak's lab and the first author of the study.

The team discovered that the lipoxins act on glial cells—namely astrocytes and microglia—to interrupt a cascade of cellular events that drive inflammation.

The lipoxins reduced retinal cells' production of key signalling proteins called chemokines and cytokines, which typically initiate inflammatory processes.

Interestingly, the glial cell changes initiated by lipoxins depended on when they were administered—before or after the onset of inflammation. When lipoxins were delivered before the onset of inflammation, they primarily reduced the activity of astrocytes and initiated anti-inflammatory processes. In contrast, when they were delivered after inflammation began, they primarily reduced microglia activation and initiated processes that resolved the inflammation.

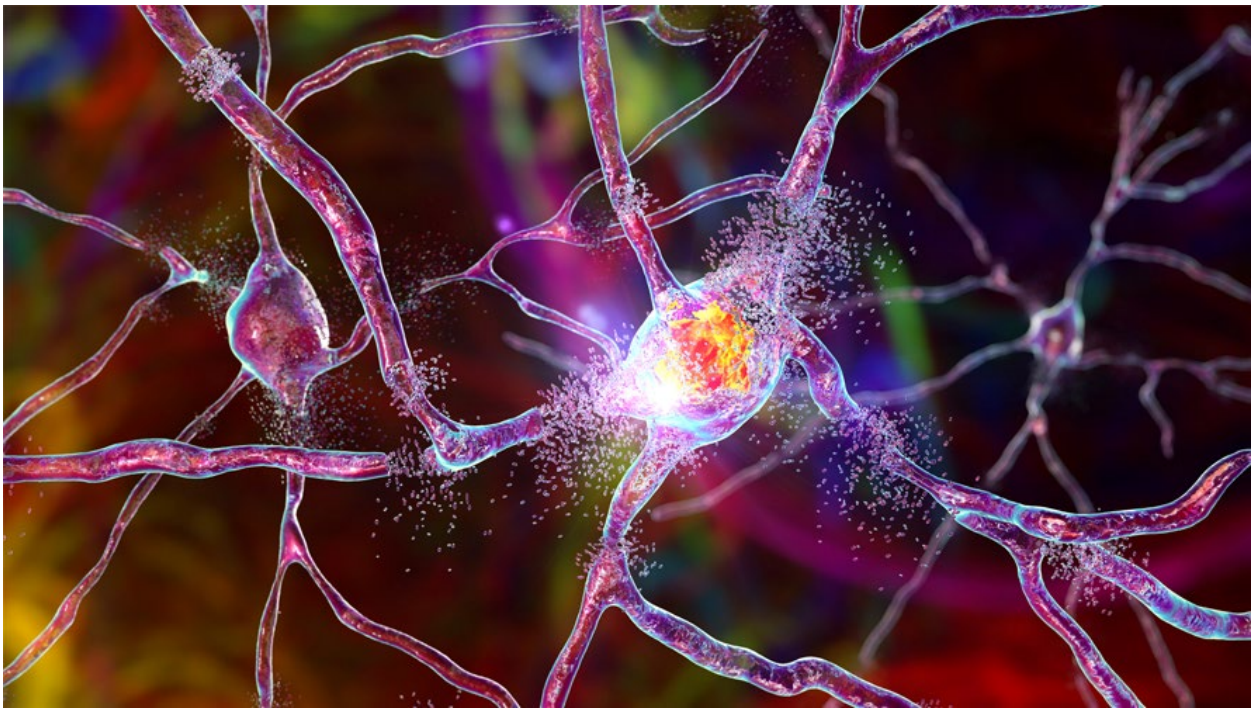
This finding prompts further investigations, as it has implications for developing lipoxin-based treatments for neurodegeneration.

"Discovering how lipoxins are involved in distinct processes that prevent and resolve inflammation brings us a step closer to determining how we can translate the actions of these molecules as treatments for a wide range of neurodegenerative diseases," concludes Dr. Livne-Bar.

This work was supported by the Canadian Institutes of Health Research, the National Institutes of Health, and UHN Foundation. Dr. Jeremy Sivak holds the Graham Trope Chair in Glaucoma Research and is an Associate Professor in the Department of Ophthalmology and Vision Sciences at the University of Toronto.

Drs. Izhar Livne-Bar and Jeremy Sivak hold a US patent for the use of lipoxins to treat neurodegeneration.

Livne-Bar I, Maurya S, Gronert K, Sivak JM. Lipoxins A4 and B4 inhibit glial cell activation via CXCR3 signaling in acute retinal neuroinflammation. J Neuroinflammation. 2024 Jan 11. doi: 10.1186/s12974-024-03010-0.



Inflammation is a critical part of our body's innate immune response; however, excessive inflammation can cause cell degeneration and lasting tissue damage. Inflammation is a common feature of many neurodegenerative diseases, including glaucoma, Alzheimer disease and multiple sclerosis.

Healthy Liver, Healthy Brain

Molecules secreted by the liver help maintain blood vessels in the brain.

(L-R) Dr. Philippe Monnier, Senior Scientist at the Donald K. Johnson Eye Institute, and Michelle Syonov, PhD student in Dr. Monnier's lab and first author of this study.

Clinical observations have long hinted that the liver plays an important role in brain function. Individuals diagnosed with liver disease often experience neurological symptoms, including impaired cognition, mood changes and disruptions in sleep patterns.

Despite these observations, the connection between the liver and brain has remained elusive—until now. A new study from UHN's Donald K. Johnson Eye Institute (DKJEI) offers valuable insights into the molecular processes that link these two organs.

At the heart of this connection is the blood-central nervous system barrier (BCB)—a layer of tightly connected cells encircling the blood vessels within and around the brain and spinal cord. This barrier protects the nervous system by permitting the passage of important chemicals and nutrients from our blood and blocking harmful substances and pathogens.

In a recent study published in *Nature Communications*, researchers led by DKJEI Senior Scientist Dr. Philippe Monnier tested the possibility that the liver releases molecules that help maintain the integrity of the BCB.

“We wanted to determine whether molecules secreted by the liver act on the BCB, how this process occurs and what happens when it is disrupted, as in the case of liver disease,” explains Dr. Monnier.

The researchers discovered that HFE2, a protein secreted by liver cells, significantly contributes to the maintenance of intercellular connections between specialized cells lining blood vessels, crucial for the integrity of the BCB. When liver cells stop producing HFE2, these connections weaken, causing the BCB to become leaky.

The leaky BCB allows the entry and accumulation of fibrinogen—a blood-derived protein—in the brain, where it kills neurons.

Digging deeper, the team discovered that HFE2 maintains the brain’s protective barrier by blocking the actions of another protein—called RGMa. In the absence of HFE2, this protein damages vessel-lining cells, causing the barrier to break down.

“Our findings indicate that these two proteins have opposing effects—HFE2 helps keep the BCB closed, whereas RGMa tends to open it up,” explains Michelle Syonov, a doctoral candidate at the University of Toronto and first author of the study.

“We also learned that these proteins compete for the same receptor in the brain, so when one is in abundance, there is less opportunity for the other to exert its effects,” adds Dr. Xue Fan Wang, a former graduate student in Dr. Monnier's lab and co-first author of the study. “If we can balance the activity of these proteins, we could prevent neuron death in diseases characterized by BCB damage, such as multiple sclerosis.”

To test this idea, the researchers manipulated the levels of HFE2 in an experimental model of multiple sclerosis. They found that higher levels of HFE2 were associated with less RGMa activity, less neuron death and less severe disease.

These findings have important clinical implications, as HFE2 and RGMa could serve as targets for new drugs to treat diseases that involve BCB dysfunction.

Interestingly, these findings could also pave the way for developing strategies to improve our ability to administer existing drugs.

“The BCB is a critical defence mechanism for the nervous system, but it also makes it challenging to deliver drugs directly into the brain where they can have the greatest effects,” explains Robin Vigouroux, a former graduate student in Dr. Monnier's lab and co-first author of this study. “If we can temporarily disrupt the BCB, we can improve treatments for conditions ranging from brain tumours to Alzheimer disease.”

This work was supported by Heart & Stroke, the Canadian Foundation for Innovation, the Canadian Institutes for Health Research, an anonymous donor, the Vision Research Science Program at the University of Toronto, the Krembil Foundation and UHN Foundation.

Wang XF, Vigouroux R, Syonov M, Baglaenko Y, Nikolakopoulou AM, Ringuette D, Rus H, DiStefano PV, Dufour S, Shabanzadeh AP, Lee S, Mueller BK, Charish J, Harada H, Fish JE, Wither J, Wälchli T, Cloutier JF, Zlokovic BV, Carlen PL, Monnier PP. The liver and muscle secreted HFE2-protein maintains central nervous system blood vessel integrity. Nat Commun. 2024 Feb 3. doi: 10.1038/s41467-024-45303-1.

Michelle Syonov (L) and Dr. Philippe Monnier (R) running experiments in the Monnier lab at the Donald K. Johnson Eye Institute.