# The Krembil

July 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:

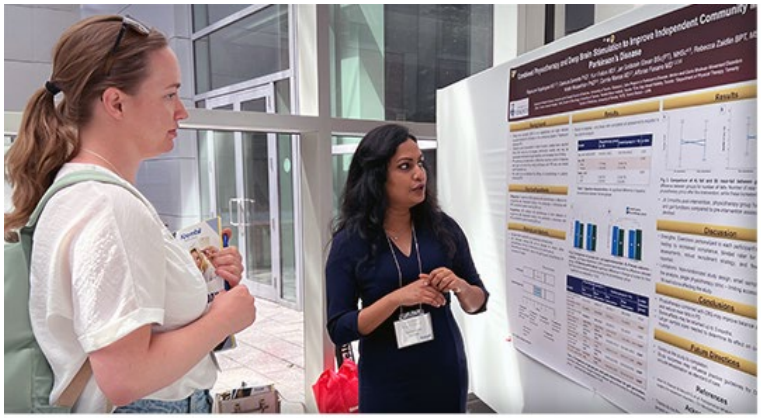


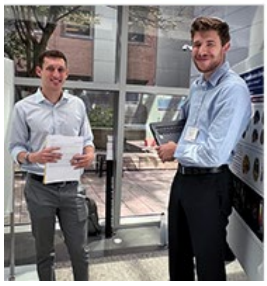
Jaideep Bains, PhD
*Director, Krembil Research Institute*
*University Health Network*

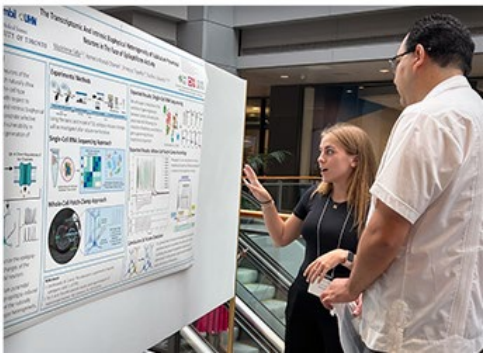
# News

# Krembil Research Day 2023

***Krembil Research Day showcases the exceptional talent and innovation of trainee researchers.***





*This year's Research Day hosted approximately 225 trainees, faculty and staff, and featured 72 posters and 9 oral presentations.*

Krembil's annual Research Day is a unique opportunity for trainees, investigators and staff to come together to network and celebrate research achievements.

This year's in-person event took place on June 22, 2023, at the MaRS Centre, and hosted approximately 225 trainee researchers, faculty and staff from various disciplines.

The event kicked off with a video welcome message and opening remarks from Dr. Jaideep Bains, Director of the Krembil Research Institute. Dr. Bains praised trainees for their dedication and exceptional contributions to the Institute and expressed his excitement for the opportunity to come together to discuss discoveries and foster collaborations.

“You are the lifeblood of this Institute. You bring the energy, the ideas and the talent. Thank you for everything you do,” said Dr. Bains.

Throughout the event, eight trainees gave short oral presentations that showcased the depth and breadth of the work being conducted across the Institute’s three research pillars: brain and spine, vision, and bone and joints.

The event also featured poster presentations led by over 70 trainee and staff researchers. These presentations enabled attendees to directly engage with presenters, fostering intellectual discussions and knowledge exchange.

The event concluded with a keynote address from Dr. Sheena Josselyn, a Senior Scientist at The Hospital for Sick Children and a distinguished researcher in the field of memory and cognition. Her talk, titled “Making Memories in Mice”, explored the intricacies of memory formation and the neural circuits involved in information storage in the brain.

Dr. Josselyn also spoke about her journey in science and the importance of mentorship and collaboration, encouraging trainees to leverage their unique perspectives to push the boundaries of knowledge in their fields.

Click here to watch a short video recapping the event.

*The Krembil community thanks the many individuals who made this year’s Research Day possible, including the Krembil Trainee Affairs Committee—chaired by Dr. Mary Pat McAndrews—and the Krembil Research Administration and Public Affairs teams, the oral presentation session Chairs—Drs. Joan Wither and Bill Hutchison—and everyone who served as judges for the poster presentations.*

*We also extend our sincere gratitude to the Nadler family for their generous donation in the memory of Murray G. Nadler, which contributed to the prizes that were awarded for top oral and poster presentations.*

**Presentation Awards**

The following trainees and postdoctoral researchers are recipients of awards for best oral and poster presentations:

Poster Presentations Graduate Student Category
1st place (tied): Anca Maglaviceanu
1st place (tied): Jacob Schulman
2nd place: Hayley Peters
3rd place: Syeda Hania Qamar

Poster Presentations Postdoctoral Researcher Category
1st place: Dr. Sonja Di Gregorio

2nd place: Dr. James Young
3rd place: Dr. Mohammed Alvi

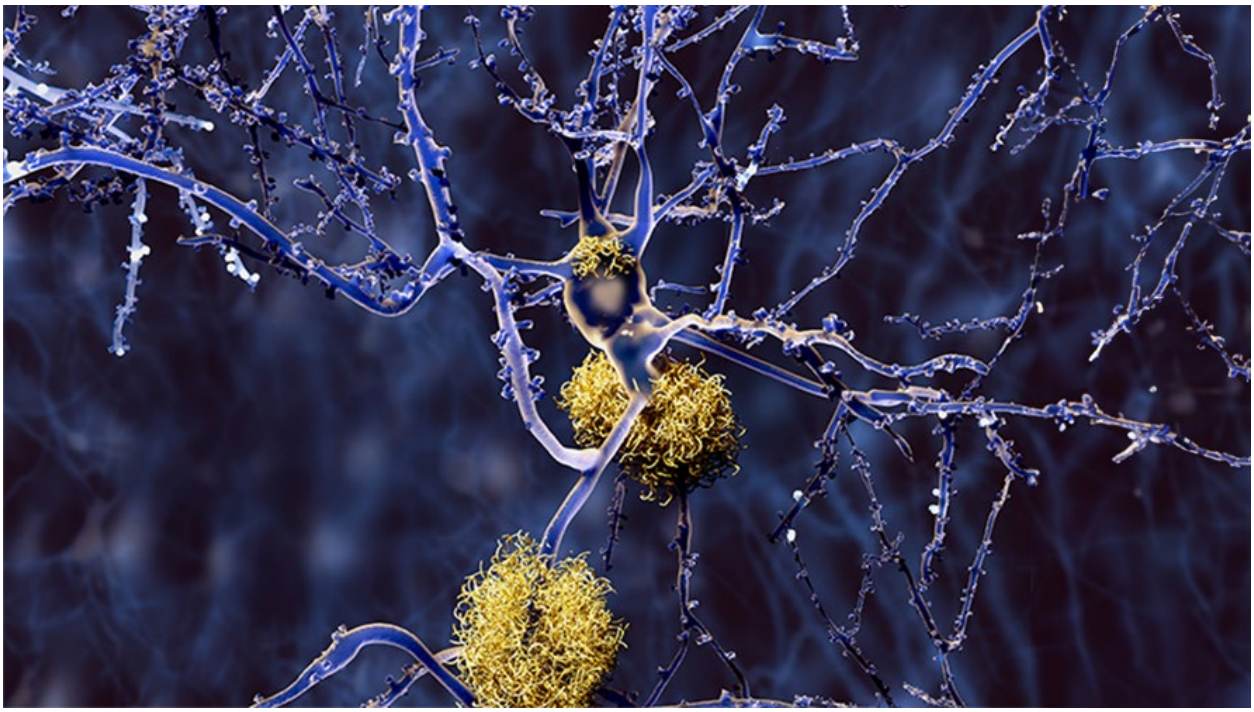
Oral Presentations Graduate Student Category
1st place: Navona Calarco
2nd place: Kristen Ashworth
3rd place: Yijinmide Buren

Oral Presentations Postdoctoral Researcher Category
1st place: Dr. Laura Whittall Garcia
2nd place: Dr. Amit Sandhu

Congratulations to the winners and to everyone who presented their work. We look forward to seeing you at next year's event!

# New Treatment Option

***FDA grants full approval to lecanemab, a disease-modifying drug for Alzheimer disease.***



*In Alzheimer disease, misfolded amyloid beta protein accumulates as plaques in the brain and interrupts neuron function. Lecanemab targets toxic forms of the protein and promotes its clearance by the immune system.*

In a landmark development in the fight against Alzheimer disease, the United States Food and Drug Administration (FDA) has granted full approval to the disease-modifying therapeutic lecanemab.

Alzheimer disease is a devastating neurodegenerative condition that affects millions worldwide. A key characteristic of the disorder is the presence in the brain of plaques that are made up of clumps of misfolded amyloid beta. Toxic species of this protein—called oligomers or protofibrils—are believed to disrupt brain cell function, eventually leading to memory loss and cognitive decline.

Most treatments for Alzheimer disease help to manage symptoms but do nothing to slow or halt disease progression. Lecanemab, on the other hand, is designed to target a fundamental disease process—the build-up of toxic amyloid beta species—to change the course of the disorder.

Lecanemab, marketed as Leqembi, is the second drug in a new class of anti-amyloid beta immunotherapies, which target toxic amyloid beta species, enabling their removal by the immune system.

Dr. Martin Ingelsson, a Senior Scientist and geriatrician at the Krembil Brain Institute, was an active member of the research team of Dr. Lars Lannfelt at Uppsala University in Sweden where the first steps in the development of lecanemab took place. He expressed his enthusiasm for the FDA announcement, saying the drug's full approval "marks a significant milestone for patients and their families."

"Alzheimer disease is relentless, and we have so far not had any good medications to offer. Lecanemab is a much-needed treatment option that we hope can make a difference to our patients."

Since the partial approval of lecanemab by the FDA (through the Accelerated Approval pathway), a multinational phase III clinical trial led by pharmaceutical company Eisai Inc.—involving nearly 1800 patients—showed that the drug can significantly slow cognitive decline.

As the drug becomes available to more people, researchers will continue to study its long-term effects, optimal dosing regimens and potential use in combination with other therapies.

"Lecanemab is not a cure, and it comes with potentially serious risks for some patients," cautions Dr. Ingelsson. But there is still a lot to be excited about. The relatively modest clinical effects seen in the clinical trial will hopefully be more pronounced when patients are treated for a longer period.

"We need to remember that Alzheimer disease occurs over decades. We hope that, over time, the drug could have a major impact on quality of life by preserving patients' cognitive function and prolonging their independence."

Beyond treating Alzheimer disease, lecanemab also represents a new strategy to manage other neurodegenerative conditions. In collaboration with Dr. Lannfelt and BioArctic AB—the Swedish biotech company behind the development of lecanemab—Dr. Ingelsson has been involved in the development of an antibody-based therapy for Parkinson disease, which was recently tested in a phase I clinical trial.

*Dr. Martin Ingelsson, a Senior Scientist and geriatrician at UHN's Krembil Brain Institute.*

Similar to lecanemab, this therapy targets toxic forms of a protein, called alpha-synuclein, which accumulates in the brains of those living with Parkinson disease.

"Alzheimer disease and Parkinson disease share several molecular features, so general disease-modifying approaches that work in one condition could also work in the other," explains Dr. Ingelsson.

In his lab at Krembil, Dr. Ingelsson has recently started a project focused on developing other therapeutic antibodies that could help address the diverse disease processes that are at play in individuals with Alzheimer disease and Parkinson disease.

"Different forms of amyloid-beta and alpha-synuclein are present in different patients, so personalized immunotherapies that selectively target specific protein variants could yield even greater benefits," speculates Dr. Ingelsson.

For more information, click here to read the FDA announcement.

Dr. Martin Ingelsson is a paid consultant for BioArctic AB, the Swedish biotech company behind the development of lecanemab.

Research

# Making a Mark on Depression

***Study identifies markers of treatment response in people with major depressive disorder.***

*(L-R) Dr. Daphne Voineskos, Clinician Investigator at the Krembil Brain Institute, and Rebecca Strafella, a former graduate student in Dr. Voineskos' lab.*

A recent study from the Krembil Brain Institute revealed specific changes to brain function that occur in individuals treated for major depressive disorder.

Approximately one-third of cases of major depressive disorder are untreatable—they do not respond to medications or other types of therapy, such as talk therapy. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive form of brain stimulation that helps some individuals who are treatment-resistant—with a response rate of 50%. Despite a growing understanding on how this therapy works, it is unclear why some individuals respond and others do not.

"Psychiatry is plagued with trial and error, and we do not have reliable tests to diagnose patients or let them know whether a particular treatment is right for them, like we do in other areas of medicine," says Dr. Daphne Voineskos, a Clinician Investigator at the

Krembil Brain Institute and lead author of the study. “By examining changes in brain activity during and following rTMS, we can gain deep insights into how the treatment works and pinpoint which individuals are most likely to benefit.”

To identify treatment-related changes in brain activity, the researchers analyzed data from 90 adults with treatment-resistant depression who received up to 30 rTMS sessions over a maximum period of 6 weeks.

Before and after the rTMS treatment program, participants underwent a brain stimulation and recording procedure called transcranial magnetic stimulation and electroencephalography (TMS-EEG). Using this method, the team studied changes in two markers of cortical inhibition, known as the N100 and N45 signals.

The team found that both markers changed following rTMS in individuals who responded to treatment. Specifically, these individuals showed a weaker N100 signal and a stronger N45 signal after treatment compared to non-responders.

“We also discovered that as individuals’ levels of depression decreased, their N100 and N45 signals began to resemble those of healthy individuals,” says Rebecca Strafella, a former graduate student in Dr. Voineskos’ lab and first author of the study.

Interestingly, the team also found that features of the N100 signal before treatment can help to predict whether an individual will benefit from rTMS. “With these findings, we are getting closer to developing a non-invasive test to guide treatments for our patients,” says Dr. Voineskos.

“Our findings reveal a robust way to identify individual patients that will benefit from rTMS. These insights could lead to improved clinical protocols that avoid the frustration that comes with current trial and error approaches for the treatment of depression.”

*This work was supported by the CAMH Foundation, the Krembil Foundation, the Labatt Family Network, the Government of Ontario, the Japan Society for the Promotion of Science, the Japan Agency for Medical Research and Development, the Japan Health Foundation, Takeda Science Foundation, SENSHIN Medical Research Foundation, Health Science Center Foundation, Mochida Memorial Foundation for Medical and Pharmaceutical Research, Taiju Life Social Welfare Foundation, the Daiichi Sankyo Scholarship Donation Program, Brain Canada, the Brain and Behaviour Research Foundation, the Bright Focus Foundation, the Canada Foundation for Innovation, the Canadian Institutes of Health Research, the Centre of Aging and Brain Health Innovation, the National Institutes of Health, the Weston Brain Institute, the Vancouver Coastal Research Health Institute, the Seedlings Foundation, the National Institutes of Mental Health, the Canadian Biomarker Integration Network in Depression, the Ontario Brain Institute, the Klarman Family Foundation, the Arrell Family Foundation, the Edgestone Foundation, the Temerty Family, Grant and Kreutzcamp Family Foundations, the University of Toronto and the UHN Foundation. Dr. Tarek Rajji holds a*

*Tier 2 Canada Research Chair in Neurostimulation in Cognitive Disorders. Please see the research article for statements of competing interests.*

*Strafella R, Momi D, Zomorrodi R, Lissemore J, Noda Y, Chen R, Rajji TK, Griffiths JD, Vila-Rodriguez F, Downar J, Daskalakis ZJ, Blumberger DM, Voineskos D. Identifying Neurophysiological Markers of Intermittent Theta-Burst Stimulation in Treatment-Resistant Depression using Transcranial Magnetic Stimulation-Electroencephalography. Biol Psychiatry. 2023 Apr 19:S0006-3223(23)01207-6. doi: 10.1016/j.biopsych.2023.04.011.*

*Major depressive disorder—also called depression—is the most commonly diagnosed mood disorder. It affects 1 in 10 Canadians and is most prevalent among working adults between the ages of 15 and 64 years old.*

# Building Brain Blood Vessels

***Study reveals that nucleolin, a brain development protein, becomes reactivated in tumours.***

*Dr. Marc Schwab (left) is a researcher in Dr. Thomas Wälchli's group and first author of the article; Dr. Thomas Wälchli (right) is a neurosurgeon-neuroscientist and senior author of the article.*

A collaborative study conducted by researchers at the Krembil Brain Institute and Neuroscience Center Zurich has revealed that the protein nucleolin acts through similar pathways to promote the growth of blood vessels in brain tumours and in the healthy brain during fetal development.

"Our findings suggest that nucleolin and related proteins could be therapeutic targets to slow or stop the growth of brain tumour vasculature and, in turn, brain tumours such as glioblastomas," says Dr. Thomas Wälchli, a neurosurgeon-neuroscientist who led the international team of scientists. Dr. Wälchli is currently a neuroscientist at the Krembil Brain Institute and at Neuroscience Center Zurich.

Glioblastoma is an aggressive form of brain cancer. Few treatments are available, and most patients survive less than 15 months after their diagnosis. One of the key features of glioblastomas is their ability to stimulate the formation of blood vessels to supply nutrients.

"Blood vessel formation—a process called angiogenesis—is crucial for fetal brain development. The process becomes largely dormant in the healthy adult brain but can

be activated in conditions such as stroke, neurodegenerative diseases, brain vascular abnormalities and brain cancer," says Dr. Wälchli.

"Understanding how blood vessels grow during fetal brain development can help us understand how they grow in brain tumours. Accordingly, identifying proteins like nucleolin that regulate blood vessel formation in the developing brain can provide valuable insights into these conditions and reveal potential targets for new treatments."

Using experimental models and samples of developing brain and brain tumour tissue, the research team discovered that nucleolin promotes blood vessel growth in the developing brain by stimulating the sprouting of new vessel branches and the production of endothelial cells—the cells that line the vessels. Nucleolin accomplishes this by regulating the activity of enzymes that are involved in energy consumption in endothelial cells.

The team also found that nucleolin is reactivated in blood vessels that form within brain tumours; higher levels of the protein are associated with increased energy consumption and vessel formation, and more aggressive tumours.

"Our results suggest that nucleolin contributes to tumour growth by facilitating angiogenesis through molecular pathways similar to those that are active in the healthy developing brain," says Dr. Marc Schwab, a researcher in Dr. Wälchli's lab.

"Inhibiting nucleolin reduced the production of blood vessel cells in the laboratory," adds Dr. Schwab. "This finding holds promise for guiding the development of novel treatments."

With a better understanding of the complex processes that are involved in angiogenesis, researchers could develop novel therapies for glioblastoma and other disorders that affect the brain's blood vessels.

Previous treatments that have been developed to slow or halt glioblastoma growth by inhibiting pro-angiogenic proteins have not improved survival rates. This is in part due to our limited understanding of how blood vessels develop in brain tumours.

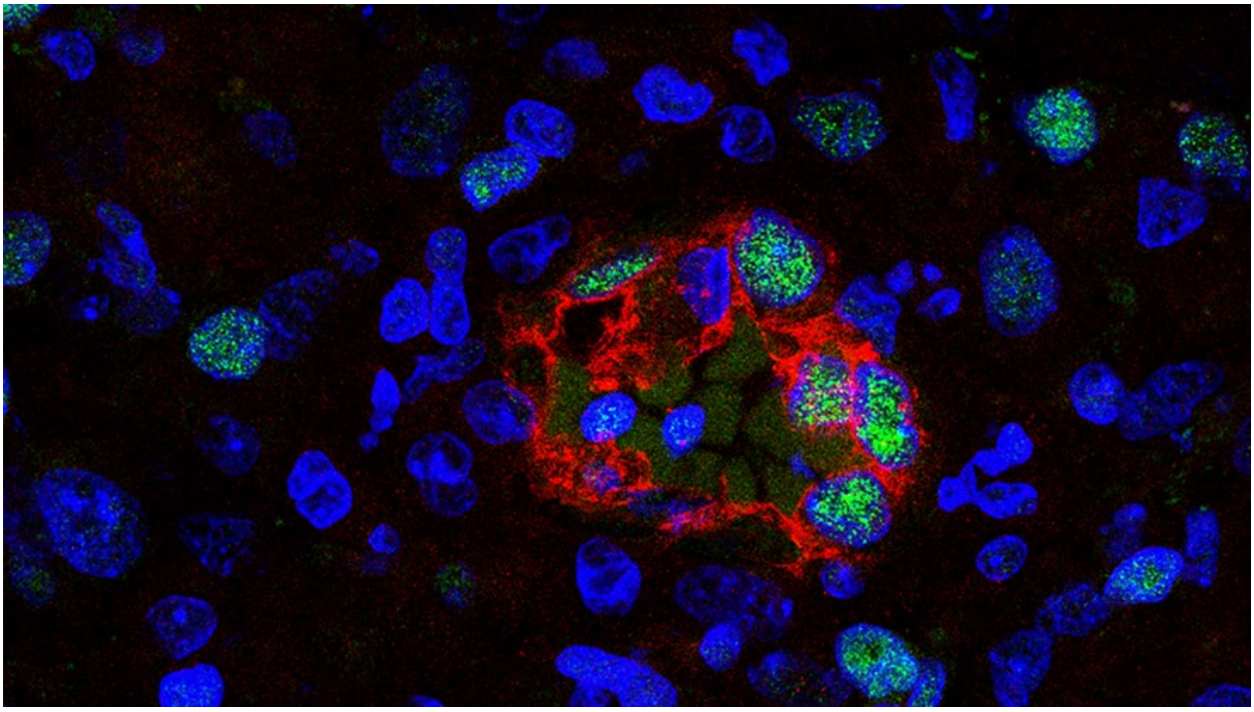
"Nucleolin is one of a large number of proteins that contribute to blood vessel formation in the developing and diseased brain, and more research is needed to fully understand the role of each in tumour growth," cautions Dr. Wälchli. "Nonetheless, this study sheds light on a fundamental process involved in blood vessel development and lays a solid foundation for future studies and drug development."

*This work was supported by the OPO Foundation, the Swiss Cancer Research foundation, Stiftung zur Krebsbekämpfung, the Kurt und Senta Herrmann Foundation, Forschungskredit of the University of Zurich, the Zurich Cancer League, the Theodor und Ida Herzog-Egli Foundation, the Novartis Foundation for Medical-Biological Research, the HOPE Foundation, the Swiss National Science Foundation, the*

*European Research Council, the Commission of the European Communities, ETH Zurich and the UHN Foundation. Dr. Thomas Wälchli is a neurosurgeon-neuroscientist and currently a neuroscientist at the Krembil Brain Institute; he is also a Research Group Leader at Neuroscience Center Zurich, University Hospital Zurich and the University of Zurich. Neuroscience Center Zurich is a joint center of the University of Zurich, ETH Zurich and the University Hospitals and Clinics in Zurich.*

*Schwab M, de Trizio I, Ghobrial M, Shiu JY, Sürücü O, Girolamo F, Errede M, Yilmaz M, Haybaeck J, Moiraghi A, Monnier PP, Lawler SE, Greenfield JP, Radovanovic I, Frei K, Schlapbach R, Vogel V, Virgintino D, De Bock K, Wälchli T. Nucleolin promotes angiogenesis and endothelial metabolism along the oncofetal axis in the human brain vasculature. JCI Insight. 2023 Apr 24. doi: 10.1172/jci.insight.143071.*

*To learn more, click here for a review of brain vasculature in development and disease at single-cell resolution published in Nature Reviews Neuroscience (as featured on the journal cover), and click here for a preprint article describing the molecular atlas of the human brain vasculature across development, adulthood and disease at the single-cell level (under third revision at Nature).*



*Immunofluorescence image of glioblastoma cells where blood vessel endothelial cells are stained red, nucleolin is stained green and the cell nucleus is stained blue.*

# Decoding Roifman Syndrome

***Study provides deep insights into why vision impairments occur in Roifman syndrome.***

*(L-R) Dr. Brian Ballios at the Donald K. Johnson Eye Institute, and Dr. Ajoy Vincent at The Hospital for Sick Children.*

A recent study conducted at UHN's Donald K. Johnson Eye Institute (DKJEI), in collaboration with The Hospital for Sick Children (SickKids), has provided valuable insights into why individuals with Roifman syndrome experience vision-related symptoms.

Roifman syndrome is a rare genetic disorder characterized by abnormal growth of the bones and joints, disrupted immune function and cognitive delay. Individuals with the condition also have vision problems caused by degeneration of the retina—the thin layer of light-sensing tissue that lines the back of the eye.

Due to the rarity of this condition, very little is known about the features of associated eye disease.

"Our limited understanding of retinal degeneration in this condition hinders our ability to diagnose patients and manage their symptoms," explains Dr. Brian Ballios, a DKJEI Scientist and the lead author of the study. "We need a deeper understanding of underlying eye disease processes to better help our patients."

To address this knowledge gap, the team conducted a detailed structural and functional evaluation of the retina in ten people with Roifman syndrome. The team used multiple research techniques, including electroretinography to measure the electrical activity of retinal cells, and fundus autofluorescence imaging to visualize the structure and health of retinal cells.

“We discovered that the most common structural abnormality was a ring of heightened autofluorescence surrounding the central part of the retina,” says Dr. Ajoy Vincent, a Staff Ophthalmologist at SickKids and the senior author of the study. “This ring indicates abnormalities in the retinal pigment epithelium—a layer of cells that support the function and health of specialized neurons called photoreceptors. These photoreceptors are essential for vision and convert light into electrical signals.”

In line with these findings, many individuals with Roifman syndrome have photoreceptor dysfunction and corresponding visual impairments such as night blindness.

Follow-up studies conducted over several years revealed that some patients experience progressive retinal atrophy and decreased visual acuity, suggesting that the retinal degeneration associated with Roifman syndrome worsens slowly over time.

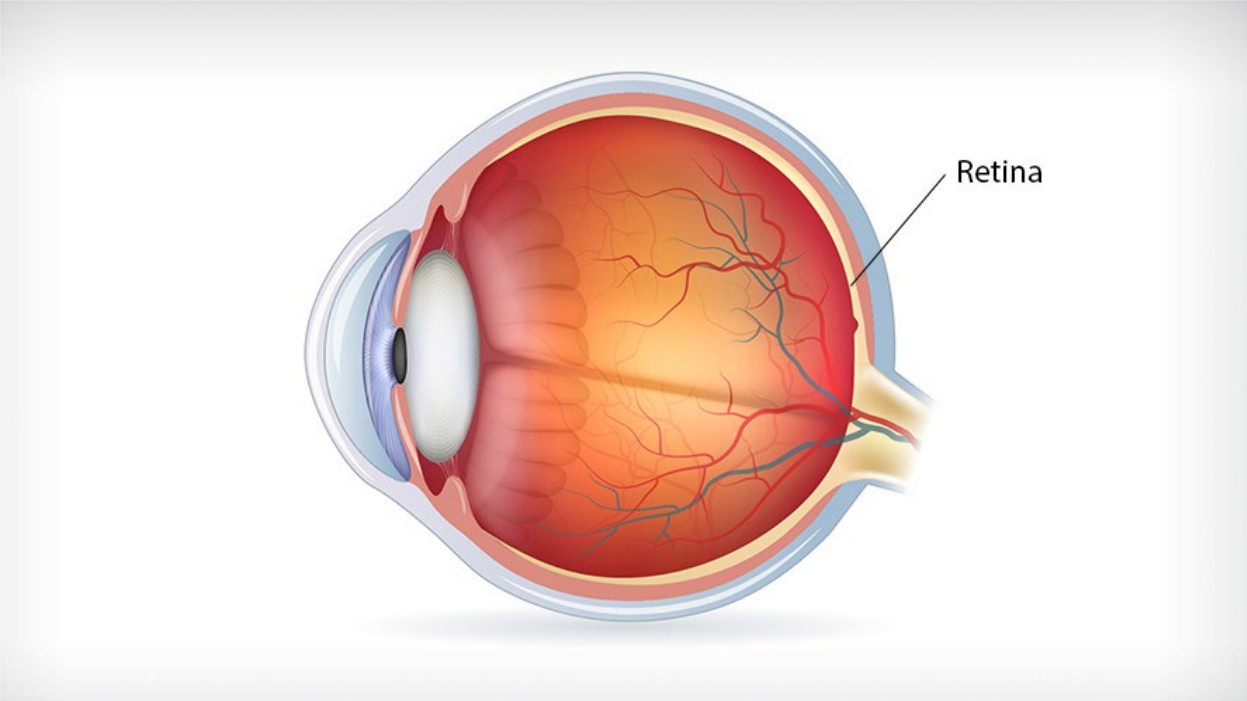
The team also found that age alone is not a key determinant of disease severity, highlighting the need to study other factors that might contribute to symptoms, such as sex and specific mutations in the Roifman gene.

This study lays a strong foundation for future research into the underlying mechanisms of Roifman syndrome and for the development of targeted treatments.

“It was immensely gratifying to conduct this research in collaboration with Dr. Chaim Roifman.  Dr. Roifman is a world-leading paediatric immunologist, and he was the first to describe the clinical features of the disorder in 1999,” says Dr. Ballios. “His expertise helped us understand how the specific features of eye disease fit into the bigger clinical picture of this disorder by considering patients’ overall health concerns.”

*This work was supported by the Foundation Fighting Blindness U.S. and the UHN Foundation. Drs. Ballios and Vincent are Assistant Professors in the Department of Ophthalmology and Vision Sciences at the University of Toronto.*

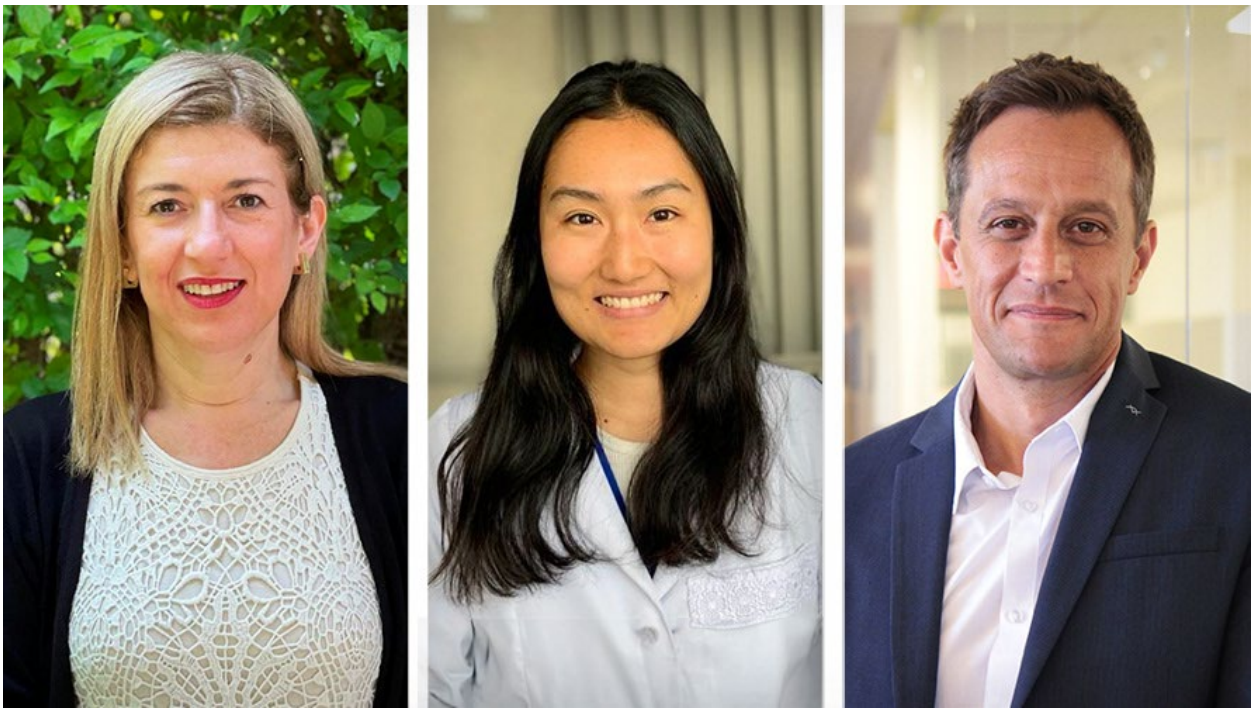
*Ballios, B. G., Mandola, A., Tayyib, A., Tumber, A., Garkaby, J., Vong, L., Heon, E., Roifman, C. M., & Vincent, A. (2023). Deep phenotypic characterization of the retinal dystrophy in patients with RNU4ATAC-associated Roifman syndrome. Eye (London, England), 2023 May 24. doi: 10.1038/s41433-023-02581-1.*




*Photoreceptors are specialized neurons that detect light and convert it into electrical signals that are transmitted to the brain. These cells are found in the retina, the thin layer of tissue that lines the back of the eye.*

# Rehabilitation for Vision Loss

***Therapy involving visual tasks with auditory feedback effectively treats form of vision loss.***



*(L-R) Dr. Monica Daibert-Nido, co-senior author; Dr. Mariana Misawa, first author and clinical fellow under the supervision of Dr. Daibert-Nido; and Dr. Michael Reber, co-senior author.*

New research from UHN's Donald K. Johnson Eye Institute (DKJEI) has shown for the first time that biofeedback therapy can improve vision in people with homonymous hemianopsia.

Homonymous hemianopsia (or hemianopsia) is a form of vision loss in which a person sees only one side of the visual field from each eye. The condition typically results from a brain injury or tumour that affects the nerves that connect the eyes to the brain's visual processing centres.

"People with hemianopsia often struggle with daily activities. Their balance, mobility and ability to read are all affected, which significantly impacts their quality of life," explains Dr. Michael Reber, Senior Scientist at the DKJEI. "Unfortunately, there are no standardized vision rehabilitation protocols to help these people."

Biofeedback training is a rehabilitation technique that improves vision by enhancing eye control and shifting the focus of the visual field. This approach has shown promise for treating various forms of visual impairment.

“Biofeedback therapy is gaining popularity for vision rehabilitation but it has never been used to treat people with hemianopsia. We see an exciting opportunity to use biofeedback in a novel way to address treatment gaps,” says Dr. Monica Daibert-Nido, a DKJEI Clinician Investigator.

The study engaged 12 participants that had hemianopsia due to a previous brain injury. For five weeks, these individuals completed biofeedback training that involved completing computer-assisted tasks. As participants completed the tasks, feedback was provided in the form of visual and auditory queues.

“Over the study period, participants completed 20-minute training sessions in which they focused on a small red circle on a screen while listening to an intermittent beep,” says Dr. Mariana Misawa, a clinical fellow at UHN. “Participants had to move their eyes towards a target, guided by changes in the frequency of the beeps.”

After biofeedback training was complete, the team measured participants’ visual function. “We observed significant improvements, including increased ability to detect contrast and focus on targets—including close objects—and increased reading speed. Participants also felt positive about their progress and improvements in visual performance,” says Dr. Misawa.

These findings suggest that biofeedback training can improve vision in individuals with hemianopsia. Next steps for this research include validating the results in larger studies with more participants. Future studies are also needed to determine whether the benefits of this rehabilitation program are long-lasting.

“Our findings suggest that biofeedback training is a low-cost, effective treatment for people with hemianopsia, with the potential to significantly improve independence and quality of life,” concludes Dr. Daibert-Nido.

*This work was supported by the UHN Foundation. Dr. Michael Reber is an Associate Professor in the Department of Ophthalmology & Vision Sciences at the University of Toronto (UofT). Dr. Monica Daibert-Nido is an Assistant Professor in the Department of Ophthalmology & Vision Sciences at UofT. Dr. Mariana Misawa is a clinical fellow in Ophthalmology & Vision Sciences at UofT.*

*Misawa M, Pyatova Y, Sen A, Markowitz M, Markowitz SN, Reber M, Daibert-Nido M. Innovative vision rehabilitation method for hemianopsia: Comparing pre- and post audio-luminous biofeedback training for ocular motility improving visual functions and quality of life. Front Neurol. 2023 Apr 11;14. doi: 10.3389/fneur.2023.1151736. eCollection 2023.*

*A person with homonymous hemianopsia cannot see things on one side (e.g., the right side) of their visual field in each eye.*