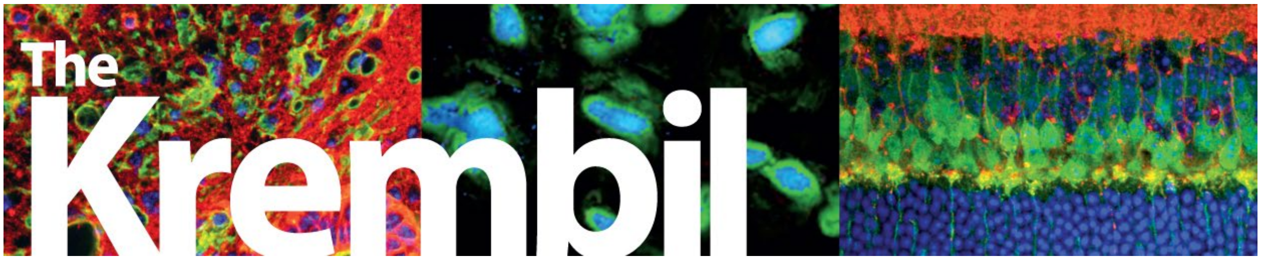
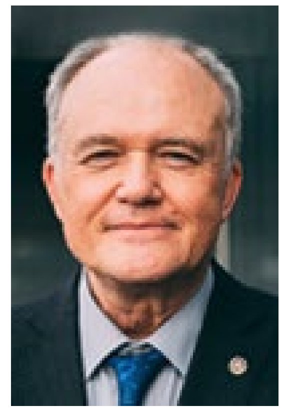


January 2022



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

Remembering Dr. Fred Gentili

The Krembil Research Institute remembers the life and legacy of neurosurgeon Dr. Fred Gentili.

Dr. Fred Gentili was a world-class neurosurgeon and a trailblazer in skull base surgery.

University Health Network (UHN) neurosurgeon, Dr. Fred Gentili, died on January 15, 2022, of glioblastoma—an aggressive brain cancer for which he treated many of his patients.

Dr. Gentili specialized in skull base surgery, pituitary surgery and radiosurgery. He completed neurosurgical training at the University of Toronto in 1980 and joined the neurosurgical staff at Toronto General Hospital in 1982.

At the time of his death, Dr. Gentili was a Professor in the Department of Surgery at the University of Toronto and a Clinician Investigator at the Princess Margaret Cancer Centre. He authored more than 100 publications and over 25 book chapters, and received numerous awards and honours, including the inaugural Gold Medal of Honour from the World Federation of Skull Base Societies.

Dr. Gentili touched the lives of innumerable colleagues and patients, and his legacy of surgical innovation, research excellence and patient care lives on through the generations of neurosurgeons and scientists whom he trained.

"Fred advanced traditional neurosurgery and he was able to skillfully adapt to changes in the field," says Dr. Alan Hudson, former President and CEO of UHN, and a long-time friend and colleague of Dr. Gentili. "He will always be remembered as the guy who never hesitated to take on the toughest clinical cases."

In a touching tribute video about his career and experience becoming a patient, Dr. Gentili and his colleagues discussed their deepened appreciation of the difficulties that their patients face and emphasized the importance of patient advocacy.

“Following through to true patient advocacy, I think it’s hard work, takes commitment—and everybody should be doing it,” explained Dr. Gentili.

“I think, ultimately, if we’re able to gather as many perspectives as possible, to be guided by those who live through the disease to improve the care that we deliver, then we have it right,” said Dr. Gelareh Zadeh, Co-Director of the Krembil Brain Institute, Head of the Division of Neurosurgery at the Sprott Department of Surgery, and friend and colleague of Dr. Gentili.

To honour Dr. Gentili's illustrious career and legacy, UHN is establishing the Dr. Fred Gentili Skull Base Clinic. Click here to donate to this fund in honour of Dr. Gentili.

Women in Science

Krembil to host livestream for the International Day of Women and Girls in Science.

Left to right: Drs. Tahani Baakdhah, Sindhu Johnson, Mary Pat McAndrews and Eugenia Addy.

The Krembil Research Institute is hosting a free, one-hour livestream in honour of the seventh annual International Day of Women and Girls in Science. This is a unique opportunity to hear from trailblazing women scientists and clinicians that are developing treatments and cures for diseases of the brain, eyes, and bones and joints.

The event is geared towards middle school, high school and early university-age students of all genders and is open to anyone interested in a career in the fields of science, technology, engineering and math (STEM).

Event details

- **Date:** Friday, February 11, 2022
- **Time**: 10:00 AM EST
- **Contact**: krembil@uhnresearch.ca
- **Registration link:** https://www.eventbrite.ca/e/international-day-of-women-and-girls-in-science-tickets-216970964997

The virtual event will be moderated by Dr. Eugenia Addy, founder & CEO of the Toronto not-for-profit Visions of Science Network for Learning, which promotes

STEM engagement among youth from low-income and marginalized communities. The event will also include a panel discussion, in which the speakers will answer questions submitted by participating students.

Krembil researchers Drs. Tahani Baakdhah, Sindhu Johnson and Mary Pat McAndrews will give short TED talk-style presentations about their lives and careers, as well as what inspired them to enter the fields of brain, arthritis and vision research. Their talks will focus on the following research topics:

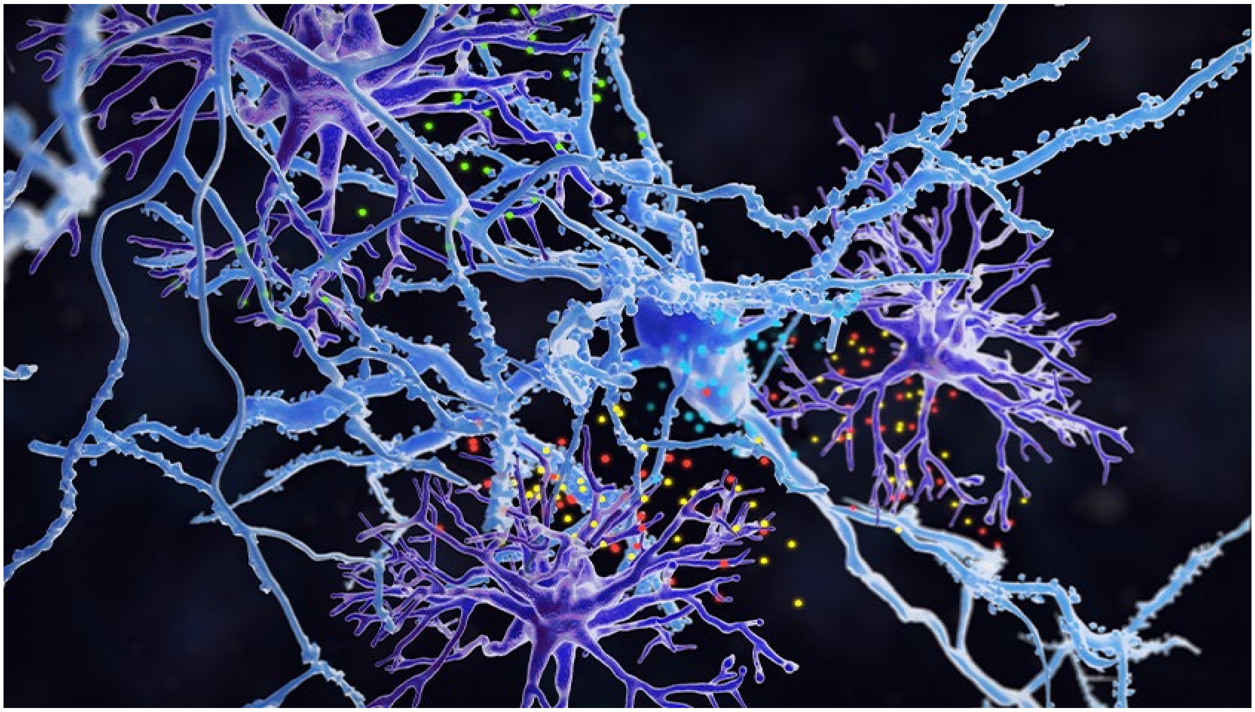
- glaucoma and retinal diseases;
- rheumatic diseases; and
- memory and brain diseases.

According to the United Nations Educational, Scientific and Cultural Organization (UNESCO), women account for less than 30% of researchers globally. To address gender inequities in STEM fields, the United Nations declared February 11 as the *International Day of Women and Girls in Science*.

Join us in learning about the inspiring stories and important contributions being made by women at Krembil towards improving the lives of patients and expanding our fundamental understanding of health and disease.

Cleaning up After Neurons

Stimulating support cells may help treat brain disorders by correcting chemical imbalances.



Astrocytes (purple) are a type of brain cell that support neurons (light blue). One of their many functions is to help regulate signal transmission.

Researchers at the Krembil Brain Institute have shown that stimulating a specialized type of brain cell—known as astrocytes—can correct chemical imbalances associated with disorders such as migraine and epilepsy.

When the brain is active, concentrations of charged molecules called ions change, allowing for messages to be transmitted. A particular ion—potassium—accumulates outside neurons in high concentrations after brain activity. Astrocytes, a type of support cell that helps to regulate signal transmission, normally help to take up excess potassium.

This cleanup process is important to maintain the delicate equilibrium of chemicals in the brain and maintain normal brain activity. However, when astrocytes malfunction, potassium builds up in the extracellular space.

“Abnormally high potassium levels are associated with several conditions, such as migraine, epilepsy and stroke,” explains Dr. Peter Carlen, a Senior Scientist at the Krembil Brain Institute and senior author of the study. “We explored whether we could stimulate these cells to increase the absorption of potassium and prevent the adverse effects of abnormal brain activity.”

In an experimental model, the researchers used genetic approaches to introduce a light-sensitive protein into astrocytes. This protein enabled the team to selectively stimulate astrocytes by applying light. When stimulated, the cells became hyperpolarized—meaning that the charge cell became even more negative than normal (i.e., they exhibited a more negative resting potential). “A negative resting potential is key to astrocyte function. The negative charge enables the cell to attract potassium ions, which are positively charged,” says Dr. Carlen.

The researchers then looked at how stimulating astrocytes—while either activating or not activating neurons—affected potassium concentrations. They found that, regardless of whether neurons were active or resting, stimulating astrocytes increased their ability to take up potassium from the extracellular space.

“We found that there was a limit to how much we could drive astrocytes to take up potassium—stronger stimulation did not necessarily translate into greater absorption,” explains Azin Ebrahim Amini, first author of this study. “This finding suggests that other regulatory mechanisms might be involved in normalizing ion concentrations following brain activity.”

These findings provide an important insight: stimulating astrocytes can help regulate ion concentrations and promote healthy brain activity. The results also point to astrocytes as a potential therapeutic target for patients suffering from debilitating conditions associated with abnormally high potassium levels—including neurotrauma, migraine, strokes and seizures.

This work was supported by the Canadian Institutes of Health Research and the UHN Foundation. B Stefanovic holds a Tier 1 Canada Research Chair in Neuroimaging and is a professor at the department of Medical Biophysics at the University of Toronto.

EbrahimAmini A, Mylvaganam S, Bazzigaluppi P, Khazaei M, Velumian A, Stefanovic B, Carlen PL. In Vivo Neocortical [K]o Modulation by Targeted Stimulation of Astrocytes. Int J Mol Sci. 2021 Aug 12. doi: 10.3390/ijms22168658.


Dr. Peter Carlen (left), Senior Scientist at the Krembil Brain Institute, and Azin Ebrahim Amini (right), PhD student at the department of Biomedical Engineering at the University of Toronto.

Protecting the Brain

UHN researchers verify how neck compression collars prevent mild traumatic brain injury.

Concussions are common among athletes, with up to 10% of contact sport players sustaining a concussion in any given year. The Q-Collar is an FDA-approved neck compression collar that protects against concussion.

Researchers at University Health Network and the University of Toronto have verified the mechanism by which neck compression collars protect against concussions.

To prevent concussions in athletes, a team of doctors, including Dr. Joseph Fisher from the Toronto General Hospital Research Institute and Dr. David Smith, an internist in Richmond Indiana, developed a unique piece of protective equipment called the Q-Collar. This small neck collar gently compresses the muscles that surround the veins that drain blood from the head. Researchers have shown that the Q-Collar reduces the cumulative impact of head injuries over time, but the mechanism underlying this protective effect remained uncertain.

When the head is jolted or hit, the brain, which is suspended in protective fluid, can bounce or 'slosh' around. This sloshing can damage the brain and lead to concussions. Neuroscientists believe that the Q-Collar works by increasing the brain's blood volume, causing it to fit more snugly within the skull and reducing the amount of brain slosh after impact.

“Demonstrating the filling of the empty space within the skull was the missing link in understanding how neck compression collars protect the brain,” explains Dr. Lashmi Venkat Raghavan, senior author of the study and Clinician Investigator at the Krembil Research Institute. “This mechanism has been challenging to confirm experimentally, because brain volume naturally increases when an individual lays down, as they do during traditional brain imaging procedures.”

To overcome the difficulties associated with measuring brain volume, the team instead measured pressure inside the skull, which is closely linked to brain volume. They also ensured that all participants were seated during the tests to avoid volume changes caused by laying down.

To measure pressure, the team took advantage of the fact that when pressure increases, the membranes around the optic nerves balloon out a bit—an effect that can be observed noninvasively using ultrasound.

The researchers carried out ultrasound measurements in 19 adults before and after compressing the internal jugular veins low in the neck for three to four minutes. This compression would be expected to mimic the effects of wearing a Q-Collar. The team found that the optic nerve sheath increased in size from 4.6 mm to 4.9 mm, signalling increased pressure within the skull.

"We have provided clear evidence that neck compression leads to filling of the space inside the skull, which would reduce brain slosh and the potential for injury,” says Dr. Michael Dinsmore, lead author of the study and an Assistant Professor in the Department of Anesthesiology and Pain Medicine at the University of Toronto. “Important next steps are to determine the magnitude and duration of the protective effect of neck compression, and the influence of individual characteristics such as age, sex and body mass.”

This work was supported by the UHN Foundation.

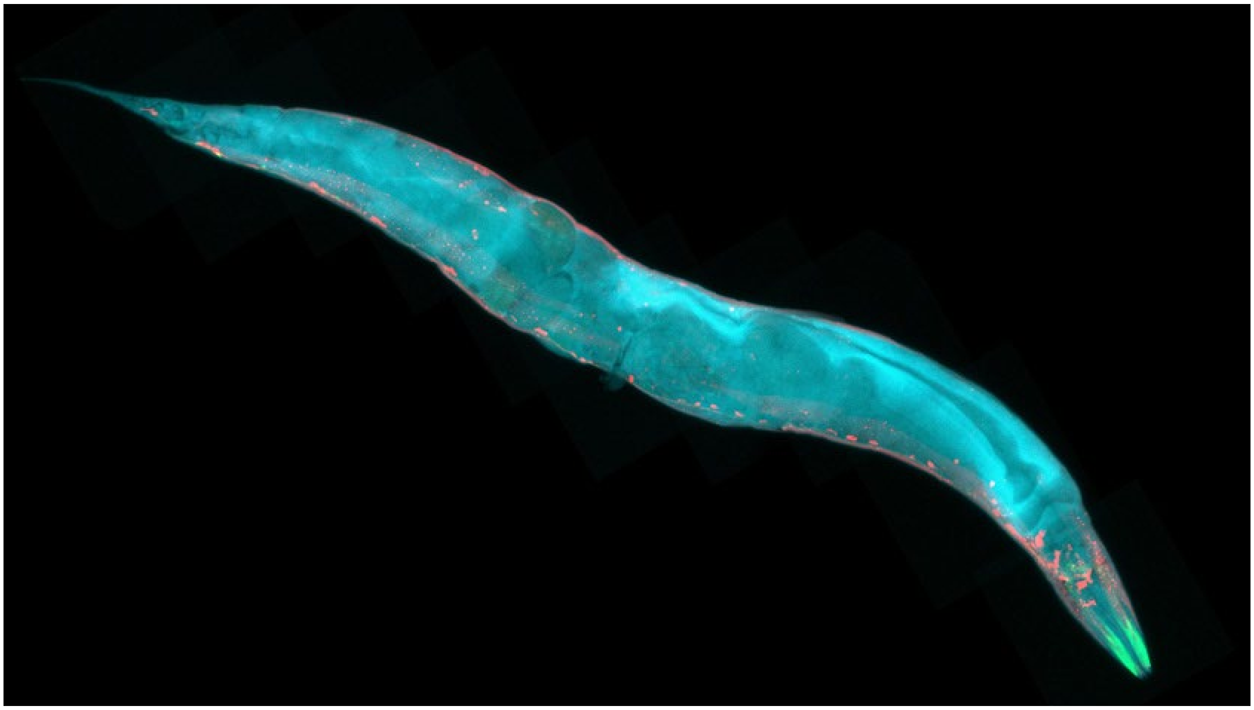
Dinsmore M, Hajat Z, Brenna CT, Fisher J, Venkatraghavan L. Effect of a neck collar on brain turgor: a potential role in preventing concussions? Br J Sports Med. 2021 Nov 25. doi: 10.1136/bjsports-2021-103961.

Dr. Lashmi Venkat Raghavan (left) is a Clinician Investigator at the Krembil Research Institute. He is also the Director of the Neuroanesthesia Program at Toronto Western Hospital. Dr. Michael Dinsmore (right) is an Assistant Professor in the Department of Anesthesiology and Pain Medicine at the University of Toronto and a Staff Anesthetist at Toronto Western Hospital.

Worms and Drug Discovery

Researchers develop a C. elegans model to screen potential drugs for Parkinson disease.



The adult C. elegans nematode, or roundworm, has 302 neurons—one third of all the cells in its body.

Krembil Brain Institute researchers have developed an experimental model for early-stage Parkinson disease using *Caenorhabditis elegans*, a small transparent worm. They also incorporated the model into a drug-screening pipeline to rapidly identify potential therapies for Parkinson disease.

Currently, experimental models of early-stage Parkinson disease are limited. Such models are needed for the discovery of new therapies. A research team led by Drs. Lorraine Kalia and Suneil Kalia explored whether the roundworm *C. elegans* could be used to address this issue. *C. elegans* is particularly well-suited for studying neurons because scientists have mapped this animal's nervous system in exquisite detail.

Parkinson disease is associated with the accumulation of the protein alpha-synuclein in neurons. The protein can kill the neurons that control movement. Because these cells do not regenerate, researchers are looking for ways to detect and treat the disease in its early stages.

"Our *C. elegans* model has an alpha-synuclein defect that causes motor dysfunction—worms with this defect coil up much more frequently than worms without it. At the molecular level, the neuronal processes that occur in these worms are similar to those that occur in humans with early-stage Parkinson disease," says Dr. Lorraine Kalia, Senior Scientist at the Krembil Brain Institute.

The team used artificial intelligence to rank a library of drugs approved for human use based on their potential to reduce alpha-synuclein accumulation. They next tested the six most promising drugs using the *C. elegans* model. The team found that five of the drugs reduced the frequency of the worms' coiling behaviour. The team then tested these drugs in mammalian models in the lab to determine which could prevent alpha-synuclein from killing brain cells. Using this approach, the researchers identified the antibiotic rifabutin as a potential treatment option.

"Most experimental models of Parkinson disease that are used for drug discovery do not have measurable markers of neuron degeneration caused by alpha-synuclein in the early stages of the disease, before the neurons are lost," says Dr. Suneil Kalia, Senior Scientist at the Krembil Brain Institute. "Coupled with artificial intelligence technologies, our *C. elegans* model has the potential to be scaled up to help identify drugs that might treat the disease in humans."

"It is important to note that Parkinson disease is very complex, and a single experimental model cannot capture all of its features," adds Dr. Lorraine Kalia. "Our multi-step drug screening strategy combines complementary experimental models so that we can rapidly translate potential drugs to human clinical trials."

This work was supported by the Natural Sciences and Engineering Research Council of Canada, Ontario Brain Institute, Parkinson's UK and UHN Foundation. Dr. Lorraine Kalia is an Associate Professor of Medicine at the University of Toronto. Dr. Suneil Kalia is an Associate Professor of Surgery at the University of Toronto.

Chen KS, Menezes K, Rodgers JB, O'Hara DM, Tran N, Fujisawa K, Ishikura S, Khodaei S, Chau H, Cranston A, Kapadia M, Pawar G, Ping S, Krizus A, Lacoste A, Spangler S, Visanji NP, Marras C, Majbour NK, El-Agnaf OMA, Lozano AM, Culotti J, Suo S, Ryu WS, Kalia SK, Kalia LV. Small molecule inhibitors of α-synuclein oligomers identified by targeting early dopamine-mediated motor impairment in C. elegans. Mol Neurodegener. 2021 Nov 12. doi: 10.1186/s13024-021-00497-6.

(Left to Right) Dr. Suneil Kalia, Senior Scientist, Krembil Brain Institute; and Dr. Lorraine Kalia, Senior Scientist, Krembil Brain Institute. Photography by Brian Simon.

Coiling behaviour of a C. elegans roundworm with the alpha-synuclein defect. Video taken by Kevin Chen, the lead author of the study.