The Krembil

November 2021

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

A Historic Gift

UHN celebrates a transformative gift to the Donald K. Johnson Eye Institute.

In celebration of his belated 86th birthday, legendary Bay Street investment banker and philanthropist Donald K. Johnson announced an incredibly generous $50 million donation to support and expand his namesake, the Donald K. Johnson Eye Institute.

As the largest donation to a vision program in Canada, this investment will advance vision research and patient care for the more than five million Canadians living with eye disease. With this donation, Mr. Johnson will have committed over $65 million to support the exceptional vision scientists and clinicians at UHN.

"Don's support has totally changed the vision research landscape in Canada. With his significant gift six years ago, we built our discovery research capacity and enhanced clinical research," says Dr. Valerie Wallace, Research Director of the Donald K. Johnson Eye Institute and the Donald K. Johnson Chair in Vision Research. "Now, with his new, transformative gift, the impact will be global and the legacy long-lasting."

The Donald K. Johnson Eye Institute at the Toronto Western Hospital is home to Canada's largest concentration of vision researchers and the most comprehensive

clinical program dedicated to vision. Comprised of more than 54 clinicians, residents, researchers and fellows, the Institute completes more than 6,000 surgeries and 120,800 patient visits each year, spanning nine specialty clinics and services.

Through leading-edge research and clinical trials, the Institute's scientists and clinicians are developing real-world treatments to change the lives of individuals living with vision impairment and blindness.

Mr. Johnson's gift will provide long-term financial resources to expand clinical research, retain and recruit top talent in vision science and clinical care, and accelerate technological innovation. In addition, this gift will create three endowed clinical fellowships—in tribute to Drs. Robert Devenyi, Allan Slomovic and Graham Trope—clinicians who have helped restore Mr. Johnson's sight.

"We are humbled by and so grateful for Don's continued generosity and commitment to investing in the best talent, tools and training, to ensure that our hospital leads the world in vision care," comments Tennys Hanson, Chief Executive Officer of the UHN Foundation.

Congratulations and thank you to Drs. Valerie Wallace and Robert Devenyi (Clinical Director, Donald K. Johnson Eye Institute, and Ophthalmologist-in-Chief, UHN) and to the Institute's scientists, clinicians and staff for their work to change the way people see the world.

Donald K. Johnson and his late wife, Anna McCowan-Johnson, have been long-time supporters of vision research and patient care at UHN. Mr. Johnson has served on the UHN Foundation Board of Directors for 22 years.

Dementia Researcher Joins Krembil

Dr. Martin Ingelsson studies the mechanisms underlying Alzheimer disease and related dementias.

Dr. Martin Ingelsson is a new Senior Scientist at the Krembil Brain Institute.

The Krembil Research Institute is pleased to welcome Dr. Martin Ingelsson as its newest Senior Scientist. Dr. Ingelsson is a geriatrician and neuroscientist with expertise in neurodegenerative diseases.

Dr. Ingelsson's research is focused on characterizing the molecular mechanisms that underlie neurodegenerative diseases, such as Alzheimer disease, and developing strategies to diagnose and treat these conditions.

Prior to moving to Krembil, Dr. Ingelsson published a detailed characterization of the Uppsala mutation—a mutation in the amyloid precursor protein gene that leads to an early-onset form of Alzheimer disease. His study of this mutation has generated important insights into the formation of amyloid-beta, a peptide that accumulates in the brain of patients with Alzheimer disease.

"I am fascinated by the function of the brain and how dysregulation of molecular pathways can cause disease," explains Dr. Ingelsson. "There is currently no effective treatment for Alzheimer disease, likely because of our limited understanding of its underlying mechanisms. It is thrilling to characterize disease-causing processes and develop strategies to counteract them."

At Krembil, Dr. Ingelsson will continue to explore the causes of Alzheimer disease and other dementias. He will also explore biomarkers of neurodegeneration and work to develop treatments for dementia, with a focus on gene therapies.

Regarding his move to Krembil, Dr. Ingelsson comments that he looks forward to "...collaborating with the exceptional researchers at the institute to advance our understanding of devastating brain diseases and how to diagnose and treat them."

Dr. Ingelsson earned his MD and PhD at the Karolinska Institute, where he was trained in the laboratory of Dr. Lars Lannfelt, and completed postdoctoral training with Dr. Bradley Hyman at Harvard Medical School. He has been a Professor at Uppsala University since 2016.

Welcome to Krembil, Dr. Ingelsson!

Dr. Ingelsson's recruitment was made possible by a generous donation from the Krembil Foundation as part of the Krembil Strategic Research Plan Fund.

2021 Krembil Annual Report is Here

Read the latest annual report to learn how science is powering discovery at Krembil.

The 2021 report features recent discoveries from Krembil's three research institutes: the Krembil Brain Institute, the Donald K. Johnson Eye Institute and the Schroeder Arthritis Institute. (Top left, clockwise) Drs. Karen Davis, Sindhu Johnson, Lakshmi Kotra and Michael Reber.

Science is more important than ever.

COVID-19 has thrust science into the spotlight and shown the world that research is critical for solving global challenges.

From the outset of the pandemic, the Krembil community has adapted to change and pushed forward—steadfast in its mission to develop cures for diseases of the brain and spine, bones and joints, and eyes.

This year's Krembil Annual Report highlights a selection of our greatest research achievements over the past year, including:

● advancing our understanding of why men and women experience chronic pain differently;
● validating new classification criteria for systemic lupus; and

● developing a molecular model of the brain connections that are involved in visual processing

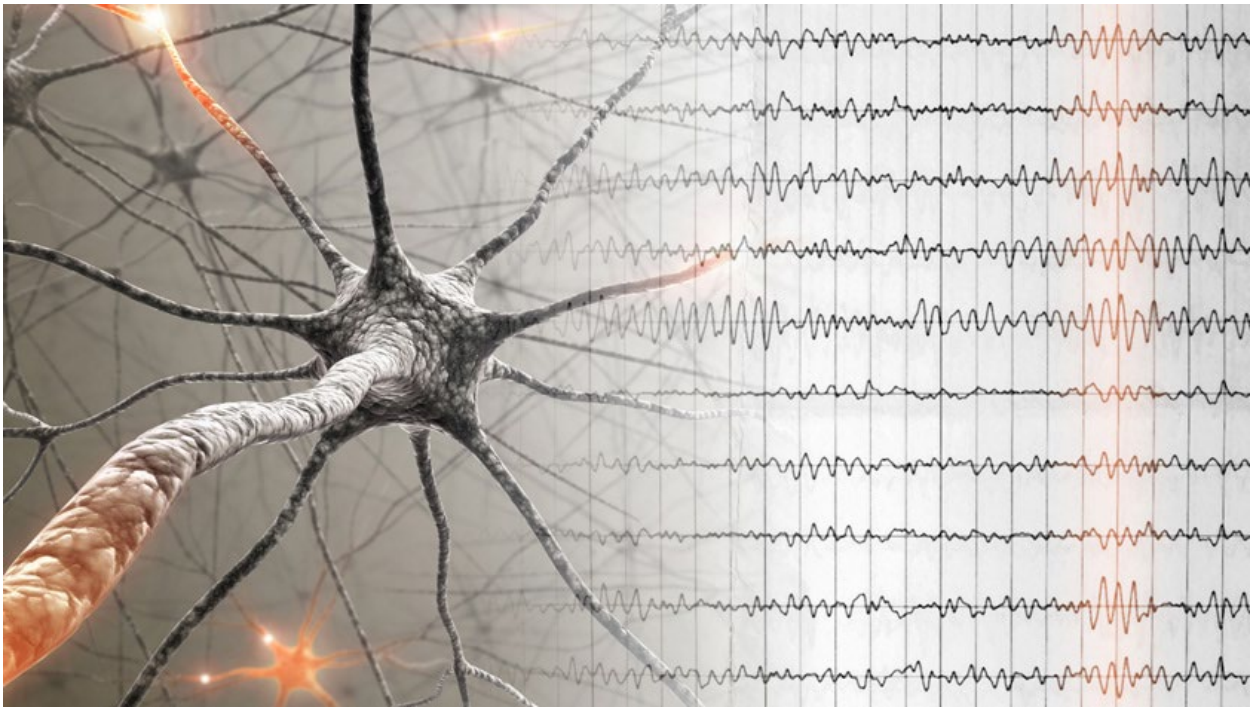
The report also highlights recent events at which Krembil scientists and trainees shared their expertise with the community to promote public engagement and ensure continued support for research.

Click here to read the report.

Research

A Wave of Discovery

Study reveals key determinants of a pattern of brain activity that is important for memory.



Neurons are brain cells that communicate through electrical and chemical signals. When large groups of neurons are activated simultaneously, they generate patterns—or rhythms—of brain activity, which can be distinguished based on their frequencies.

Researchers from the Krembil Brain Institute have uncovered how distinct cell populations contribute to a pattern of brain activity known as the hippocampal theta rhythm.

The hippocampal theta rhythm is produced when concerted groups of neurons in the hippocampus—a brain region involved in information processing and memory formation—cycle between periods of activity and inactivity.

Together, Krembil Brain Institute Senior Scientist Dr. Frances Skinner and her former PhD student, Dr. Alexandra Chatzikalymniou, used mathematical models to simulate the activity of neurons in a specific region of the hippocampus that is known to produce theta activity.

“There is still a lot to be learned about hippocampal theta activity, such as which cell populations are involved and how,” explains Dr. Skinner. “By combining aspects of two existing models of the hippocampus—one general and one more detailed—we developed a strategy to explore the complex interactions that occur between neurons in a specific brain region. Using this strategy, we were able to reveal how different neurons interact to produce theta rhythms.”

Notably, the team used Canada’s most powerful supercomputer, known as Niagara, to complete their experiments, which required 200 years of computer time. The supercomputer was made available through the University of Toronto’s SciNet service, which was funded by the provincial and federal governments.

The researchers found that hippocampal theta rhythm is initiated by the activity of excitatory neurons—cells that release chemicals that increase the activity of nearby cells. The activity of these neurons is regulated by other neuron populations—inhibitory neurons—that release chemicals that suppress the activity of nearby cells.

“Our study shows that hippocampal theta activity is initiated by excitatory neurons, which take in information from nearby inhibitory neurons to set the clock, or frequency, of the rhythm,” comments Dr. Chatzikalymniou. “When excitatory cells receive increased or decreased current inputs, the frequency changes proportionally.”

Going a step further, the team showed that the way that excitatory neurons respond to a given level of inhibitory input depends on their electrical and structural properties, such as the number of interconnections between excitatory cells. These properties can influence how neurons transmit electrical signals and relay information.

These findings bring us one step closer to unraveling how neurons interact to control hippocampal theta rhythm and related cognitive functions, such as learning and memory.

“By combining the advantages of existing models of neuron activity, we have developed a new approach to study the biology of brain rhythms,” explains Dr. Skinner. “We tested this approach on a model of the hippocampus, so the next step is to confirm our findings experimentally. Eventually, we can apply our knowledge of how hippocampal theta activity is controlled to improve our understanding of conditions in which it is disrupted, such as Alzheimer disease and epilepsy.”

This work was supported by the Natural Sciences and Engineering Research Council of Canada and the UHN Foundation. Computations were performed on the Niagara supercomputer at the SciNet HPC Consortium, funded by the Canada Foundation for Innovation, the Ontario Research Fund and the University of Toronto.

Chatzikalymniou AP, Gumus M, Skinner FK. Linking minimal and detailed models of CA1 microcircuits reveals how theta rhythms emerge and their frequencies controlled. Hippocampus. 2021 Sep. doi: 10.1002/hipo.23364.

Dr. Frances Skinner (L) is a Senior Scientist at the Krembil Brain Institute. Dr. Alexandra Chatzikalymniou (R) is a Postdoctoral Scholar in the Department of Neurosurgery at Stanford University.

Homing in on a Target

Researchers clarify disease mechanisms and therapeutic targets in axial spondyloarthritis.

Axial spondyloarthritis is a debilitating form of arthritis, for which there is no cure. Researchers are investigating the underlying disease mechanisms with the aim of developing molecularly targeted treatments.

UHN researchers have shed light on a potential therapeutic target for axial spondyloarthritis, a chronic inflammatory disease that affects the joints and other tissues.

In a new study published in *Science Translational Medicine*, an international research team led by Schroeder Arthritis Institute Scientist Dr. Nigil Haroon examined how a particular protein contributes to the disease.

Patients with axial spondyloarthritis have elevated levels of a protein called macrophage migration inhibitory factor (MIF) in their blood and tissues. MIF regulates inflammatory immune responses and the levels of this protein in a patient's blood are associated with disease severity.

"Axial spondyloarthritis is a devastating disease with very few therapeutic options for most patients," explains Dr. Haroon. "Because MIF activates inflammatory pathways, we examined whether it contributes to the clinical features of the disease and whether we can target it for treatment."

Using experimental models of the disease, the researchers observed that MIF is produced in large quantities by a type of white blood cell. They also found that increasing the levels of MIF or these specialized cells was sufficient to induce disease symptoms, such as inflammation of the skin and joints. In contrast, inhibiting the production or activity of MIF reduced disease severity.

The researchers also determined how MIF triggers inflammation. “We found that MIF increases the production of a subtype of T cells—immune cells that cause inflammation,” explains Dr. Akihiro Nakamura, a rheumatologist and first author of the study. “This is in line with what we see in the clinic, where blood and joint fluids from patients with the disease contain high levels of these T cells.”

This study indicates that MIF plays an important role in axial spondyloarthritis and is a potential therapeutic target for this disease and other inflammatory conditions. If a drug can reduce levels of MIF in patients, it may slow or stop the progression of the disease.

“Moving forward, we need to further characterize how MIF causes T cells to change and induce inflammation,” says Dr. Haroon. “Although more research is needed, our study lays a strong foundation for clinical trials to test the safety and efficacy of new therapies that target this protein.”

This work was supported by the Canadian Institutes of Health Research, the Arthritis Society, the American College of Rheumatology Research Fund, the National Institutes of Health, the Natural Sciences Research Council, the Canada Foundation for Innovation, the Ontario Research Fund, IBM, the Ian Lawson van Toch Fund, the Krembil Foundation and the UHN Foundation. M Kapoor holds a Tier 1 Canada Research Chair in Synthetic Neuro-Immunology and Stem Cell Bioengineering.

Nakamura A, Zeng F, Nakamura S, Reid KT, Gracey E, Lim M, Leng L, Jo S, Park YS, Kusuda M, Machhar R, Boroojeni SF, Wu B, Rossomacha E, Kim TH, Ciccia F, Rockel JS, Kapoor M, Inman RD, Jurisica I, Crome SQ, Bucala R, Haroon N. Macrophage migration inhibitory factor drives pathology in a mouse model of spondyloarthritis and is associated with human disease. Sci Transl Med. 2021 Oct 20. doi: 10.1126/scitranslmed.abg1210.


Dr. Nigil Haroon (L) is a rheumatologist, Scientist at the Schroeder Arthritis Institute and Co-Director of UHN's spondylitis program. Dr. Akihiro Nakamura (R) is a rheumatologist, a spondylitis program fellow and a PhD candidate in Dr. Haroon's laboratory.

Light at the End of the Tunnel

Cells transplanted into the retina transfer materials to recipient cells through nanotubes.

The nanotubes observed by Dr. Wallace are analogous to human-made tunnels. Instead of connecting cities separated by mountains, the nanotubes serve as a conduit between photoreceptor cells that are transplanted into the retina at the back of the eye and existing photoreceptor cells.

Millions of photoreceptor cells in the eye are responsible for converting light into signals that can be transmitted to the brain and processed. When these cells malfunction or are damaged, vision loss often results.

Laboratory tests over the past two decades have shown that when photoreceptors are transplanted into the retina (i.e., the light-sensitive layer of tissue at the back of the eye) vision loss can be reversed. Dr. Valerie Wallace, Co-Director and Senior Scientist at the Donald K. Johnson Eye Institute, and her research team have observed a phenomenon that helps explain how these cells restore vision.

“Transplanted cells rarely integrate into the retina, yet they are somehow still able to rescue vision,” says Dr. Arturo Ortin-Martinez, a Scientific Associate in Dr. Wallace’s lab and the lead author of the study. “Understanding this process will enable us to improve the success of transplants.”

The researchers found that donor cells form microscopic, tunnel-like bridges—called nanotubes—with the host photoreceptors. Materials that are essential to photoreceptor function can move between the cells via these nanotubes.

Using microscopy techniques that can track proteins and other components of cells, the team observed the nanotubes forming and extending as protrusions from the donor cells towards the recipient cells. They then saw materials moving between the cells.

Among the techniques used to gain this insight was an exciting method developed by Dr. Wallace's group called InVision. This method makes eye tissue transparent, enabling researchers to image whole eyes, rather than thin sections of tissue. After examining the eye at this scale, the team concluded that around 80% of the donated photoreceptors formed nanotubes with host photoreceptors.

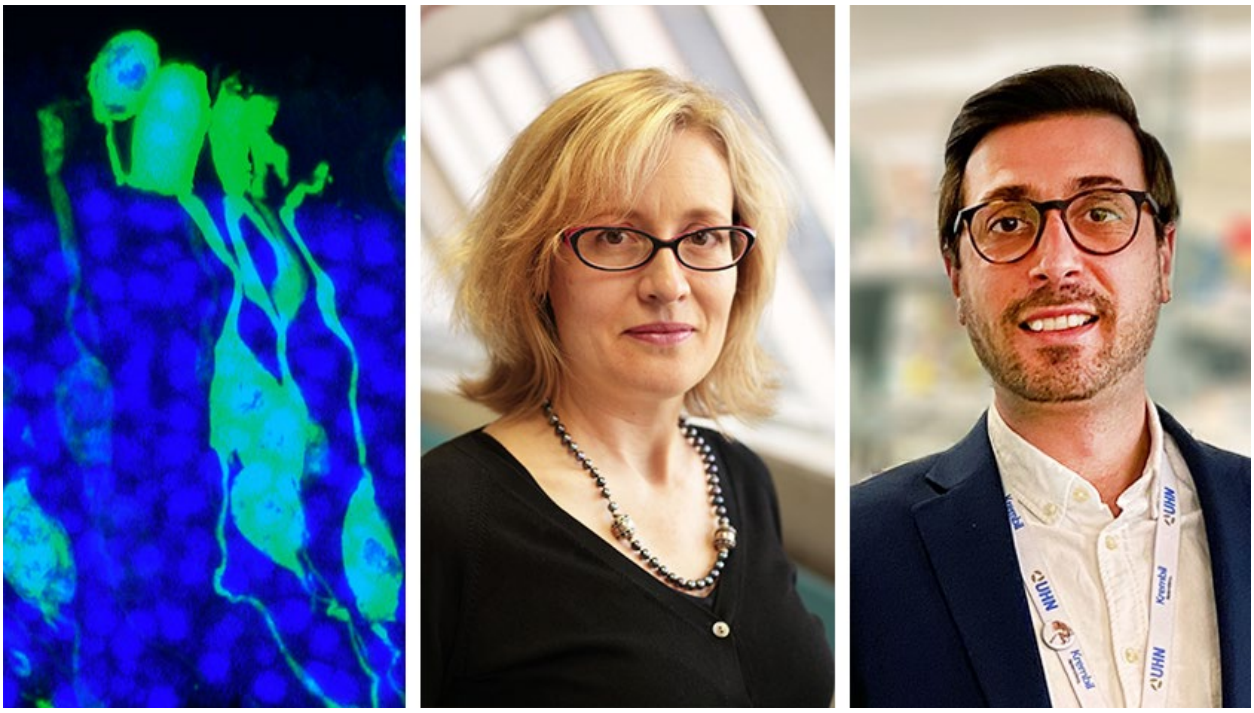
When tracking the movement of cellular materials, the researchers found that the amount of material transferred to the host cells depended on the persistence of the donor cells—more material was transferred when the cells survived longer. The research team also discovered that materials were only transferred when the donor cells were photoreceptors; materials were rarely transferred from other types of cells, such as brain neurons.

"We think that this exchange helps restore vision in transplant recipients by supplying materials that are missing in the damaged retina," says Dr. Wallace. "Next we need to explore what cargo is moving between cells and how we can optimize the transfer process."

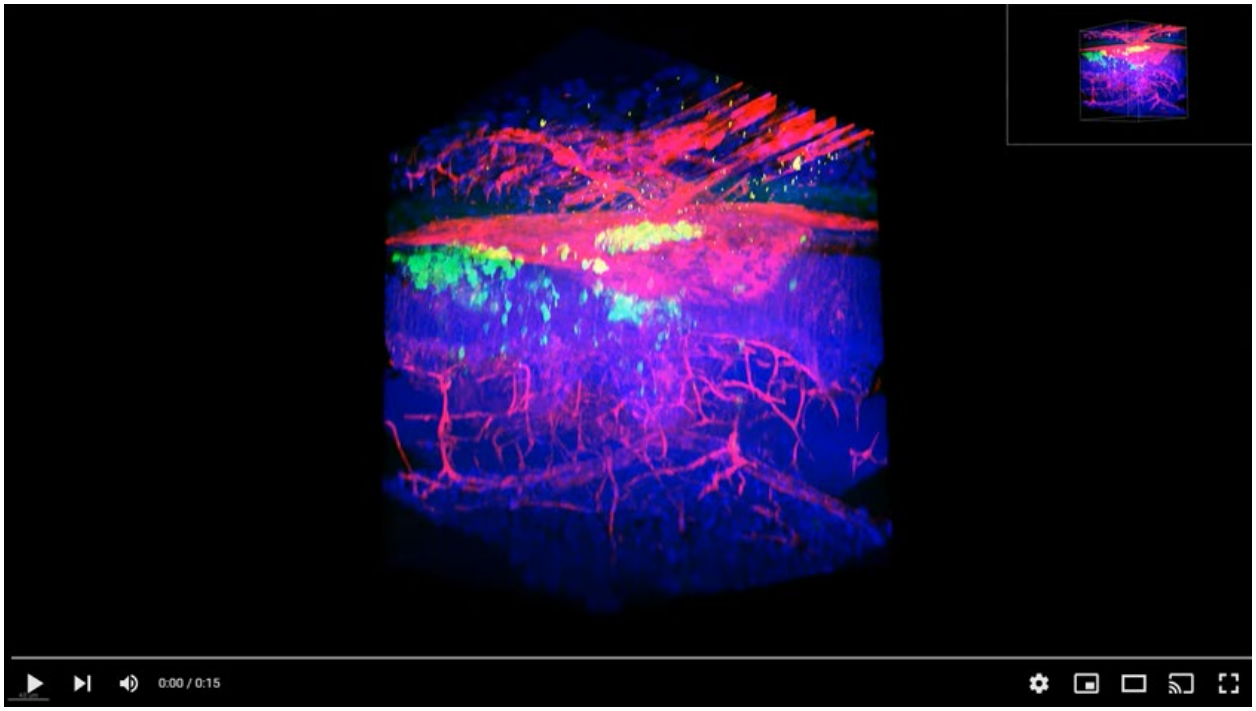
Because photoreceptors are a type of nerve cell, these new observations may impact the design of cell-based strategies for treating degeneration in other parts of the nervous system.

This work was supported by the Ontario Institute of Regenerative Medicine, Medicine by Design at the University of Toronto, the Krembil Foundation and the UHN Foundation. V Wallace holds a Tier 1 Canada Research Chair in Retina Regeneration.

Ortin-Martinez A, Yan NE, Tsai ELS, Comanita L, Gurdita A, Tachibana N, Liu ZC, Lu S, Dolati P, Pokrajac NT, El-Sehemy A, Nickerson PEB, Schuurmans C, Bremner R, Wallace VA. Photoreceptor nanotubes mediate the in vivo exchange of intracellular material. EMBO J. 2021 Sep 8. doi: 10.15252/embj.2020107264.



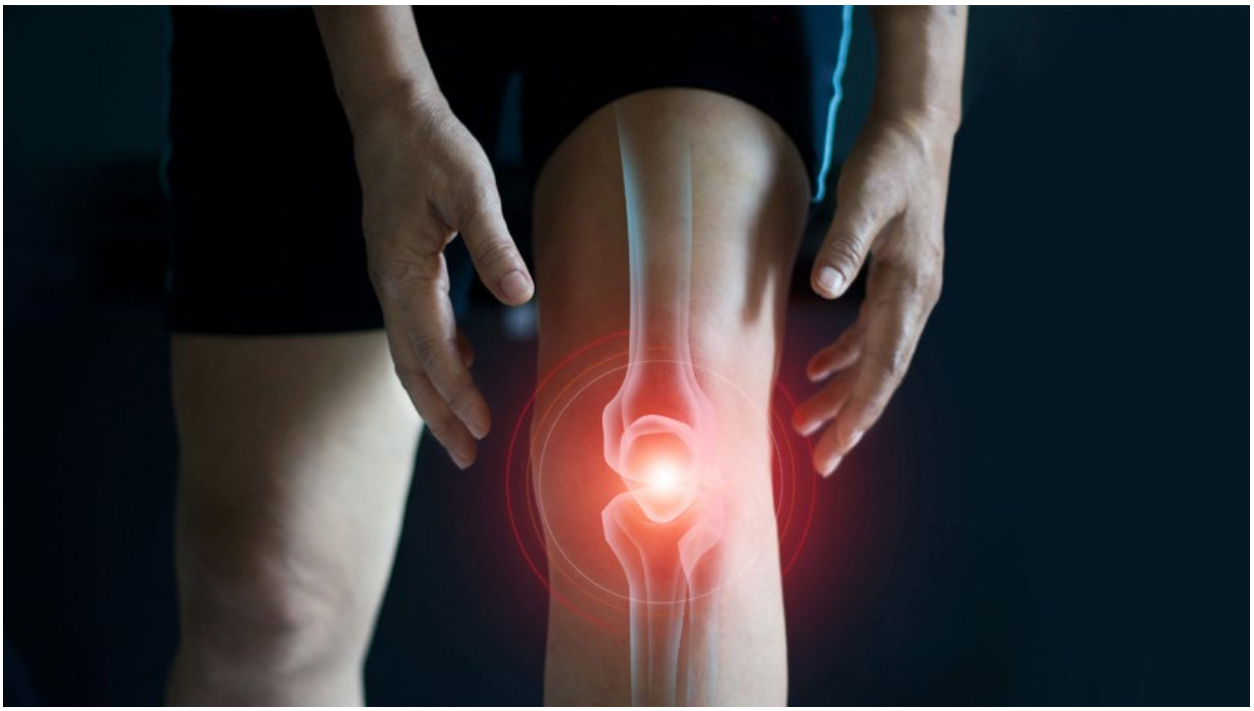
Left: Immunofluorescence image showing protein (green) being transferred between donor (top) and recipient (bottom) photoreceptor cells. Centre: Dr. Valerie Wallace is the Donald K. Johnson Chair in Vision Research at UHN. Right: Dr. Arturo Ortin-Martinez is the first author of the study and a Scientific Associate in Dr. Wallace's lab.



A 3D reconstruction of immunofluorescence images captured from a whole, intact eye that was prepared using the InVision method. Donor and host photoreceptors (green) are localized in the same region and are connected by nanotubes.

A New Model for Osteoarthritis

Researchers devise a fast and robust method to test potential therapies for osteoarthritis.



Osteoarthritis is a degenerative joint disease that commonly affects the hands, neck, back, hips and knees. Treatments include medications for pain relief, physical therapy and surgery.

Dr. Sowmya Viswanathan, a Scientist at the Schroeder Arthritis Institute, recently led the development of an experimental model of late-stage osteoarthritis that enables scientists to rapidly test potential therapies in the lab.

Osteoarthritis occurs when the cartilage in joints wears away, causing pain and reduced flexibility. Its progression is caused by many factors, including inflammation in the synovium, a tissue that lubricates and protects the joint.

“Existing models fail to capture key features of this disease because it is difficult to replicate the conditions of the tissue outside the body,” says Mable Chan, a PhD candidate in Dr. Viswanathan’s group who co-led the study. “We need to devise better tools to test potential therapies: experimental models that replicate how the disease affects the cartilage and synovial tissues at the molecular level.”

The research team developed a strategy to preserve cartilage and synovial tissues that were donated by patients who underwent knee-replacement surgery for late-stage

osteoarthritis. They kept the tissues alive for up to a week and conducted sensitive chemical analyses to regularly monitor how the tissues changed over time.

By examining changes in immune cells, genes, proteins and chemicals in the tissues, the team created a more detailed picture of how joints are affected by osteoarthritis. Using this approach, the researchers were also able to monitor the differences in how the disease progressed between patients.

“This analysis enabled us to monitor changes in tissue degradation and inflammation,” explained Dr. Viswanathan. “Within two days, we were able to characterize the changes that continue to occur in cartilage and synovium that are undergoing late-stage osteoarthritis.”

The team also tested how the tissues are affected by dexamethasone—a steroid that is commonly used to reduce pain in osteoarthritis. They found that the drug reduced the expression of genes associated with inflammation, which is consistent with how dexamethasone provides relief to damaged joints.

“One limitation of our experimental model is that it does not yet support the testing of therapies over long periods of time, due to challenges associated with keeping donated tissues alive,” cautions Dr. Viswanathan. “Even so, it is an effective tool for screening new drugs, with the potential to accelerate the development of effective therapies.”

There is currently no cure for osteoarthritis and existing joint damage cannot be reversed. The best way to prevent the disease is to stay active and maintain a healthy weight to avoid placing excess stress on joints.

This work was supported by the Arthritis Society, the Schroeder Arthritis Institute and the UHN Foundation. Mable Chan is funded by the Barbara and Frank Milligan Graduate Fellowship from the University of Toronto, Mount Sinai Hospital Graduate Scholarship in Science and Technology and an Ontario Graduate Scholarship from the Government of Ontario.

Chan MWY, Gomez-Aristizábal A, Mahomed N, Gandhi R, Viswanathan S. A tool for evaluating novel osteoarthritis therapies using multivariate analyses of human cartilage-synovium explant co-culture. Osteoarthritis Cartilage. 2021 Sep 20. doi: 10.1016/j.joca.2021.09.007.

Dr. Sowmya Viswanathan (L) is a Scientist at the Schroeder Arthritis Institute and the senior author of the study; Mable Chan (R) is a PhD candidate in Dr. Viswanathan's lab and the first author of the study.