The Krembil

January 2023

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 exciting news and innovative research happening at the Krembil Research Institute.

Stories in this month's issue:

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

News

Let’s Talk About Stress

Krembil Director Dr. Jaideep Bains shares his insights about stress on Bell Let’s Talk Day.

In honour of Bell Let’s Talk Day, the Krembil Brain Institute welcomed members of UHN and the public to a free seminar about the science of stress.

January 25th was Bell Let’s Talk Day, a day to promote mental health awareness, acceptance and action. To commemorate the day, Krembil Research Institute Director and Senior Scientist Dr. Jaideep Bains gave a presentation about the latest science of stress for members of the Krembil community and the public.

Watch a recording of the seminar here.

“Bell Let's Talk day is a perfect opportunity to strengthen our commitment to mental health awareness and support, within the Krembil community and across UHN,” said Dr. Bains.

Dr. Bains is an internationally recognized expert in the neurobiology of stress. For the past two decades, his research team has made important discoveries into how stress changes brain circuitry and behaviour, and how stress can be transmitted to others.

In this seminar, with the goal of raising awareness about stress and mental health, Dr. Bains shared his insights into:

- the physiological effects of stress on the brain;
- how we can detect stress experienced by others and transmit our own stress; and
- the benefits of control or perceived control of a situation on stress.

“Stress leaves imprints on our brain—particular cellular, molecular and biochemical changes that vary depending on the type of stress,” explained Dr. Bains. “Over time, our brains start to interpret situations differently—something that was not stressful in the past might come to elicit a major stress response—and this can lead to long-term changes in our behaviour.”

Dr. Bains went on to explain that stress-related brain changes can sow the seeds of serious mental health conditions such as anxiety disorders and depression.

More than 700 people registered for the talk, which was offered in-person to UHN staff at the Krembil Discovery Tower BMO Conference Centre and virtually to our external community. Dr. Bains also appeared on CBC Metro Morning to discuss his research.

For more information about Bell Let’s Talk day and for resources available to improve mental health, click here.

New Faces at Krembil

Sara Yuan and Lynn Saber join the Krembil Research Institute communications team.

The newest members of the Krembil communications team are (left) Sara Yuan, Public Affairs Associate for the Donald K. Johnson Eye Institute; and (right) Lynn Saber, Communications Specialist for the Schroeder Arthritis Institute.

The Krembil Research Institute is pleased to welcome **Sara Yuan** and **Lynn Saber** to the Krembil communications team.

Meet Sara Yuan
Sara is a recent graduate of the Master of Media in Journalism and Communication program at Western University. In 2022, she completed a summer internship with UHN's Public Affairs and Communications team, during which she learned about and was inspired by the cutting-edge research conducted by Krembil investigators.

As a Public Affairs Associate for the Donald K. Johnson Eye Institute, Sara will work closely with the Institute's research and clinical teams to promote their work. She will also develop and manage the Institute's social media accounts.

Sara was drawn to the Krembil Research Institute for the opportunity to work with our world-leading scientists and clinicians, and to contribute to UHN's goal of improving the health and wellbeing of individuals around the world.

“I am looking forward to working with the team and using the skills that I gained in my internship to help build awareness and excitement around the incredible research taking place at the Donald K. Johnson Eye Institute.”

Meet Lynn Saber
Lynn holds a Bachelor of Science from the University of Ottawa and a Master’s in Professional Communication from Toronto Metropolitan University. She joined the Schroeder Arthritis Institute in 2021 as a Social and Visual Communications intern and transitioned to her current role in April 2022.

As a Digital Content and Communications Specialist for the Schroeder Arthritis Institute, Lynn's responsibilities include developing internal and external communications to highlight the Institute’s discoveries in the fields of arthritis and rheumatic diseases, including digital content, websites and the Institute's quarterly newsletter, and managing the Institute's social media channels. She also helps to coordinate large events such as the International Conference on Arthritis and to organize seminars such as the Arthritis Web Seminar Series.

Lynn is excited to engage the public and find the best ways to share the Institute’s research activities and successes with the world. “I am so grateful that I get to work with this inspiring team and contribute to work that makes a difference.”

Please join us in welcoming Sara and Lynn!

Research

Protein-Level Insights

Study digs deeper than genes by analyzing protein interactions associated with autism.

(L-R) Donald K. Johnson Eye Institute postdoctoral researcher Dr. Nadeem Murtaza and Senior Scientist Dr. Karun Singh.

Researchers at the Donald K. Johnson Eye Institute (DKJEI) have mapped protein networks in brain cells to clarify how genes associated with autism spectrum disorder interact with one another.

Autism affects one in 50 Canadian children and youth and there is no cure. Individuals with this neurodevelopmental disorder often experience difficulties with learning, communication and social interactions.

Researchers have identified hundreds of risk genes for autism, but it is still unclear how genetic changes affect downstream cellular processes to trigger the condition. Because genes code for proteins, exploring how genetic mutations translate into changes in protein activity could provide deep insights into the root causes of autism and how to treat it.

“A long-standing question in autism research is whether risk genes act alone or through shared signalling pathways to cause the disorder,” says Dr. Karun Singh, a Senior Scientist at DKJEI and the senior author of the study. “A unique element of this study is that we used proteomics—the large-scale study of the structure and function of proteins—to determine if and how risk genes converge onto shared molecular pathways in neurons.”

Dr. Singh’s team developed a protein-mapping technique to identify interaction networks for the proteins that are encoded by 41 known autism risk genes.

The team discovered that many of the proteins encoded by these genes play important roles in basic neuron functions, such as cell-to-cell communication and energy production. While these findings highlight the known role of abnormal neuron communication in autism, they also point to a less well-studied disease mechanism: changes in cellular metabolism.

Using gene-editing techniques, the team confirmed that several of the risk genes regulate the activity of mitochondria, the energy factories within cells. Because brain cells are metabolically very active, disruptions in their mitochondrial activity can dramatically disrupt brain function.

The link between risk genes and mitochondrial dysfunction sheds light on how these genes might change brain cell activity and ultimately cause autism symptoms.

The next step for this research is to apply the protein-mapping technique to patient-specific brain tissues that the team generates from stem cells created from patients’ blood. These tissues display the patients’ unique gene and protein profiles and can be used to identify molecular signatures of their disease.

“Protein screening has the potential to reveal disease mechanisms that we can use to classify patients based on underlying biological processes, rather than symptoms alone,” says Dr. Nadeem Murtaza, a postdoctoral researcher in Dr. Singh’s lab. “Because autism is a highly variable disorder, identifying objective ways to classify patients with the condition is an important next step towards unlocking more personalized treatments.”

This work was supported by the Canadian Institutes of Health Research, the Ontario Brain Institute, the National Science and Engineering Research Council of Canada, the Network for European Funding for Neuroscience Research, the Donald K. Johnson Eye Institute and the UHN Foundation. Dr. James Ellis is a Tier 1 Canada Research Chair in Stem Cell Models of Childhood Disease at the University of Toronto (UofT). Dr. Evdokia Anagnostou is a Tier 2 Canada Research Chair in Translational Therapeutics in Autism Spectrum Disorder at UofT. Dr. Karun Singh is an Associate Professor in the Department of Ophthalmology & Vision Sciences at UofT.

Murtaza N, Cheng AA, Brown CO, Meka DP, Hong S, Uy JA, El-Hajjar J, Pipko N, Unda BK, Schwanke B, Xing S, Thiruvahindrapuram B, Engchuan W, Trost B, Deneault E, Calderon de Anda F, Doble BW, Ellis J, Anagnostou E, Bader GD, Scherer SW, Lu Y, Singh KK. Neuron-specific protein network mapping of autism risk genes identifies shared biological mechanisms and disease-relevant pathologies. Cell Rep. 2022 Nov 22. doi: 10.1016/j.celrep.2022.111678.

Genetic factors account for an estimated 40–80% of the risk for developing autism spectrum disorder.

How to Make a Memory

Study shows that new long-term memories are integrated into frameworks of related knowledge.

(L-R) Dr. Sam Audrain is a postdoctoral researcher at the National Institute of Mental Health and a former graduate student in Dr. McAndrews' laboratory. Dr. Mary Pat McAndrews is a Senior Scientist at the Krembil Brain Institute and a Professor of Psychology at the University of Toronto.

Humans have an immense capacity to recall events and experiences. Despite this knack for mental time-travel, we remember only a small fraction of our experiences and our memories often fade over time.

Memory storage and retrieval are critical for our day-to-day function, but there is still much to learn about why certain memories stick with us and how they change over time. Researchers at the Krembil Brain Institute have shed light on these processes.

A team led by Krembil Senior Scientist Dr. Mary Pat McAndrews showed that new memories are integrated into frameworks of existing and related knowledge—and it identified the brain regions involved in this process.

Long-term memory involves two interconnected brain regions: the hippocampus and neocortex. Memories form in the hippocampus and gradually integrate into the neocortex for long-term storage. As memories are stored in the neocortex, they lose contextual details such as place and time, becoming more 'fact-based' or 'gist-based'.

These coarse memories can then be retrieved without the help of the hippocampus, which continues to be important for recalling more detailed, contextual memories.

Researchers do not know how memories are transformed and stored in the neocortex, but they believe the answer lies in schemas—mental frameworks that organize information around core concepts.

Dr. McAndrews explains that memories are not integrated into blank neocortical slates. “Numerous experiences are represented in the brain as schematic knowledge, and we know that prior knowledge supports memory for related information. However, no studies have shown if or how schemas support memory integration into the human neocortex.”

To explore this, the researchers showed participants a series of object-scene pairs. Some of the pairs made sense—they were congruent with existing schemas—while others did not (e.g., a starfish on a beach versus an elephant in a kitchen). After delays of 10 minutes and three days, participants were shown the objects again and asked to recall information about the corresponding scenes—the general context (e.g., a beach versus a kitchen) and specific details (e.g., one beach versus another).

After three days, participants had stronger memories for congruent object-scene pairs that aligned with existing schemas. Memories for these pairs became less detailed over time compared to memories for incongruent pairs, suggesting a loss of contextual information.

Using functional magnetic resonance imaging, the researchers discovered that long-term memory for congruent information involved communication between the front portion of the hippocampus—the region responsible for ‘gist-based’ memory—and a specific area of the neocortex called the medial prefrontal cortex. They also found that these memories were gradually integrated into existing schemas in the neocortex.

“Our findings suggest that schemas act as scaffolds to integrate the core elements of memories into the neocortex for long-term storage,” says Dr. Sam Audrain and former graduate student in Dr. McAndrews’ laboratory and first author of the study. “As one might expect, prior knowledge serves as a base for building new and related knowledge. The caveat is that when this knowledge is integrated for long-term storage, we can lose details and contextual information.”

This study expands our understanding of the brain networks that support memory storage and helps to explain how related experiences become difficult to disentangle when we try to remember them.

This work was supported by the Natural Sciences and Engineering Research Council of Canada, the Toronto Neuroimaging Facility at the University of Toronto and the UHN Foundation. Dr. McAndrews is a Professor in the Department of Psychology at the University of Toronto.

Audrain S, McAndrews MP. Schemas provide a scaffold for neocortical integration of new memories over time. Nat Commun. 2022 Oct 2. doi: 10.1038/s41467-022-33517-0.

Anyone who has studied for an exam can attest that remembering new information is easier when we already know something about the subject. Our brains use schemas to organize new information and facilitate memory retrieval.

Reading the Genome

Study investigates the genetic basis of reading disability by focusing on key gene variants.

(L-R) Dr. Kaitlyn Price, a former PhD student in Dr. Barr's lab, and Dr. Cathy Barr, a Senior Scientist at the Krembil Brain Institute.

A recent study from the Krembil Brain Institute has identified genetic variants that are linked to reading disability.

Reading disability, also known as developmental dyslexia, is a complex neurodevelopmental disorder that affects 5–7% of individuals in North America.

Individuals with the disorder have difficulty with word reading and spelling, despite typical overall intelligence. Children with reading disability often have co-existing conditions, such as attention-deficit/hyperactivity disorder (ADHD) and other language-based disorders.

"Although the molecular mechanisms that underlie reading disability are not fully understood, studies have identified genes associated with the condition," says Krembil Senior Scientist Dr. Cathy Barr. "Several of these genes play important roles in different aspects brain development, such as neuronal migration and axon guidance, and have been associated with autism."

Recent studies have analyzed millions of common genetic variants to uncover those associated with reading disability. However, the numbers of individuals included in these studies have often been too small for the findings to be conclusive.

To address this limitation, Dr. Barr's team used a more powerful approach. They conducted a genome-wide association study that focused on DNA sequences that have been previously linked to brain development or autism susceptibility.

"Identifying genetic variants can be difficult because the human genome contains over three billion nucleotides that code for over 20,000 genes," explains Dr. Barr. "By zeroing in on key locations within the genome that were identified in previous studies, we were able to focus our efforts."

The team analyzed a sample of 624 individuals from Toronto as well as a large genomic dataset that included over 27 thousand individuals from around the world (GenLang Consortium). Using their Toronto sample, the team found that certain genes associated with autism were also linked to reading disability. In the larger sample, the team uncovered disease-relevant variants in genes that had not been implicated in reading disability in previous studies, as well as genes that had.

"Our findings in the Toronto sample suggest that genes that contribute to autism and brain development may play a role in the genetic basis of reading disability, which makes sense as there is often overlap between neurodevelopmental disorders," says Dr. Kaitlyn Price, a former PhD student in Dr. Barr's lab and the first author of the study. "The next challenge is to define the molecular mechanisms that underlie how these DNA variations may alter the function of brain cells and cause reading disability."

This work was supported by the Canadian Institutes of Health Research, The Hospital for Sick Children, the Max Planck Society and the UHN Foundation. Dr. Barr is a Professor in the Departments of Psychiatry and Physiology at the University of Toronto and a Senior Scientist at The Hospital for Sick Children.

Price KM, Wigg KG, Eising E, Feng Y, Blokland K, Wilkinson M, Kerr EN, Guger SL; Quantitative Trait Working Group of the GenLang Consortium, Fisher SE, Lovett MW, Strug LJ, Barr CL. Hypothesis-driven genome-wide association studies provide novel insights into genetics of reading disabilities. Transl Psychiatry. 2022 Nov 29. doi: 10.1038/s41398-022-02250-z.

Reading disability can be a major obstacle to academic and occupational success. A clear picture of the genetic landscape of the condition can help us to identify children who are at risk and implement early interventions to help them succeed.

Job Matching for Cells

Researchers match traits of mesenchymal stromal cells to their suitability for therapeutic use.

(L-R) Kevin Robb, a doctoral student in Dr. Sowmya Viswanathan's laboratory and the lead author of the study, and Dr. Sowmya Viswanathan, a Scientist at the Schroeder Arthritis Institute and the senior author of the study.

New research led by Dr. Sowmya Viswanathan, a Scientist at the Schroeder Arthritis Institute, has identified key traits of mesenchymal stromal cells (MSCs) that will help to guide their use in cell therapies for osteoarthritis and other diseases.

When delivered to the body, MSCs help suppress inflammation, promote tissue regeneration and aid in the formation of new blood vessels. These properties make MSCs highly attractive for use in the clinic—especially as part of experimental cell therapies that aim to reduce inflammation in osteoarthritis.

Despite their broad potential, MSCs have not been consistently effective when injected into patients. Their variable success is largely due to variations among the cells and their therapeutic properties, which have not been thoroughly characterized.

"Scientists need a way to screen MSCs for desirable properties so they can identify the most promising candidate cells for treating a particular disease and more quickly advance them to the clinic," says Kevin Robb, a doctoral student in Dr. Viswanathan's

lab and lead author of the study. “To address this need, we created a tool that defines key attributes of MSCs and can be used to assess their therapeutic potential.”

Using MSCs isolated from samples of human fat tissue, obtained by Dr. Rajiv Gandhi, a Clinician Scientist at the Schroeder Arthritis Institute and study co-author, the research team explored which cell attributes vary across donor sources, growth conditions and treatments used to mature the cells. This process included examining features such as cell size and shape, as well as which genes are turned on in the cells and which proteins they produce.

For example, by studying how growth conditions affect cell size and shape, the researchers determined that MSCs grown on flat, two-dimensional surfaces become elongated and tapered, whereas those that are encouraged to cluster and grow in three dimensions become more round.

Next, the team investigated how these attributes affect desired therapeutic properties. They identified twenty attributes related to the ability of MSCs to regulate immune responses and ten more related to their ability to stimulate formation of new blood vessels.

The team discovered that the conditions used to grow and process MSCs have the greatest influence on their eventual immune functions. In particular, cells that are grown in three dimensions generate greater responses from white blood cells and are more effective at resolving inflammation than those grown in two dimensions.

In contrast, differences among cell donors have the greatest influence on the suitability of MSCs for helping to form blood vessels.

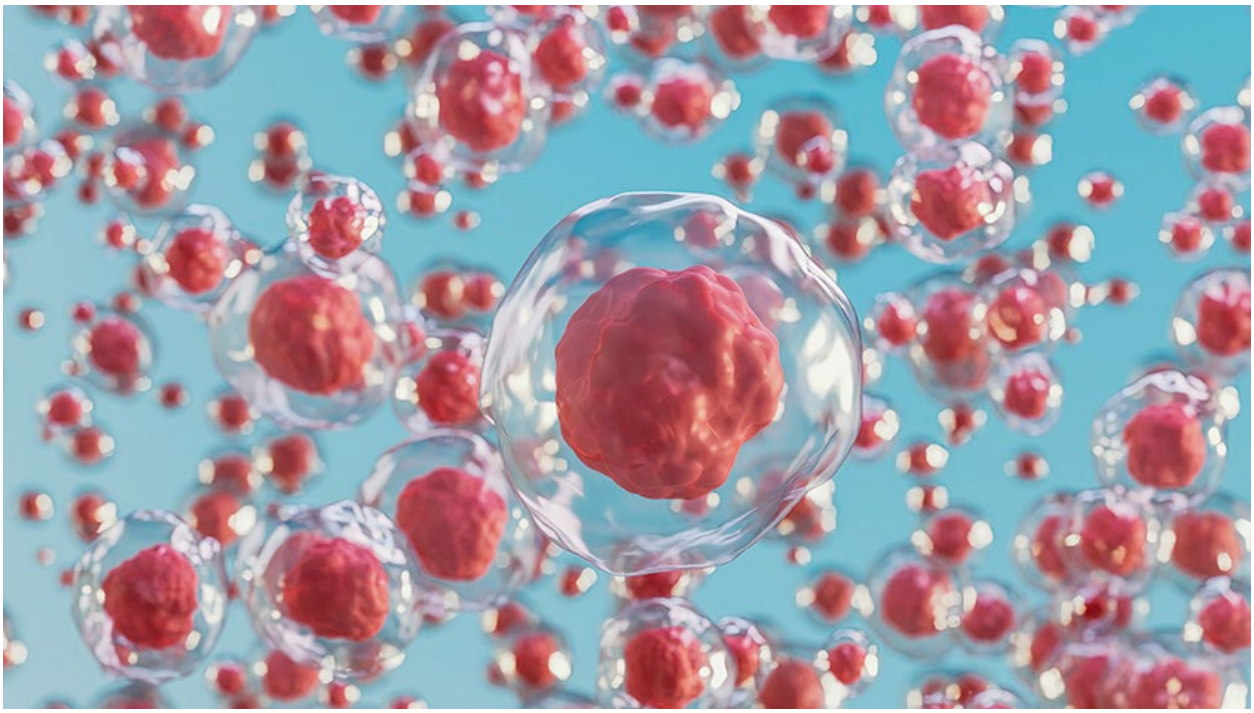
Interestingly, many of the traits that give MSCs better immune functions make them worse in helping to form blood vessels, and vice versa. According to Dr. Viswanathan, “this suggests that a one-size-fits-all approach is not suitable for applying MSCs in therapy. The cells need to be manufactured and selected according to their desired functions.”

By identifying the most relevant attributes of MSCs and how they relate to therapeutic functions, Dr. Viswanathan’s team has moved us closer to new therapies.

This work was supported by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, the Ontario Institute for Regenerative Medicine, the Arthritis Society Canada, the Ontario Ministry of Colleges and Universities, the Schroeder Arthritis Institute and the UHN Foundation. Dr. Sowmya Viswanathan is an Associate Professor of Haematology in the Division of Medicine at the University of Toronto and is cross-appointed to the University’s Institute of Biomedical Engineering.

Dr. Viswanathan has majority ownership of Regulatory Cell Therapy Consultants Inc., a private regulatory consulting company.

Robb KP, Audet J, Gandhi R, Viswanathan S. Putative critical quality attribute matrix identifies mesenchymal stromal cells with potent immunomodulatory and angiogenic "fitness" ranges in response to culture process parameters. Front Immunol. 2022 Nov 30. doi: 10.3389/fimmu.2022.972095.



With their ability to regulate immune responses and promote tissue repair, MSCs are being studied for their potential to treat a wide range of diseases, from osteoarthritis to COVID-19.