The Krembil

March 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

New Krembil Podcast

Stay tuned for a new podcast from the Krembil Brain Institute all about Your Complex Brain.

On March 22, tune in to a new podcast from UHN's Krembil Brain Institute: Your Complex Brain.

Hosted by Krembil Research Institute Senior Public Affairs Advisor Heather Sherman, this educational podcast will be geared towards a general audience and will be freely available on all major podcast platforms, including Apple Podcasts, Spotify, and Google Podcasts. New episodes will air every other Tuesday, beginning on March 22, 2022.

The podcast will feature interviews with leading neuroscientists and clinicians from the Krembil Brain Institute and personal accounts of brain injury, disease and recovery from patients and health care professionals.

Season 1 will explore a wide range of brain-related topics, including:
- What it will take to cure Alzheimer disease;
- The long-term effects of concussion;

- Biomarkers for brain diseases; and
- Radical advancements in treating spinal cord injury

The Krembil Brain Institute is home to one of the world's largest and most comprehensive teams of scientists and clinicians dedicated to developing treatments for diseases of the brain and spine. This podcast will celebrate the work of this exceptional multidisciplinary team and break down barriers between scientists and the public.

Click here for a sneak peak of Your Complex Brain and stay tuned for the first episode on March 22.

For more information about the podcast, visit https://www.uhn.ca/Krembil/.

Join the World Community Grid

Donate your idle computer time to advance science projects, including those led by Krembil.

The Krembil Research Institute assumed management of the World Community Grid in September 2021 and is **asking members of the Krembil community to donate their idle computing power to this exciting research platform.**

The World Community Grid is a global computing initiative that connects thousands of devices and uses them to run complex calculations in parallel, forming a distributed supercomputer that scientists can use to advance their research projects.

To contribute to this initiative, simply download and install the BIONIC app on your desktop or mobile devices and choose the projects you want to support. Upon selecting projects, the app will run computations in the background on your device—without slowing down your device's performance or draining its battery.

The process is safe and secure, and you can choose what projects to run and when, and how much computing power to share. Contributing to the World Community Grid will not waste your mobile data, because the BIONIC app only downloads jobs and uploads results while your device is connected to Wi-Fi.

Many of the research projects conducted at Krembil require considerable computational power. "With support from our funding partners and volunteers around the world, people will be able to participate in Krembil-led research, in collaboration with Canada's New Digital Research Infrastructure Organization, Compute Ontario and SHARCNET, bringing the community together to raise awareness for the various diseases that we study," says Krembil Senior Scientist, Dr. Igor Jurisica, who oversaw the transfer of the World Community Grid from IBM to Krembil.

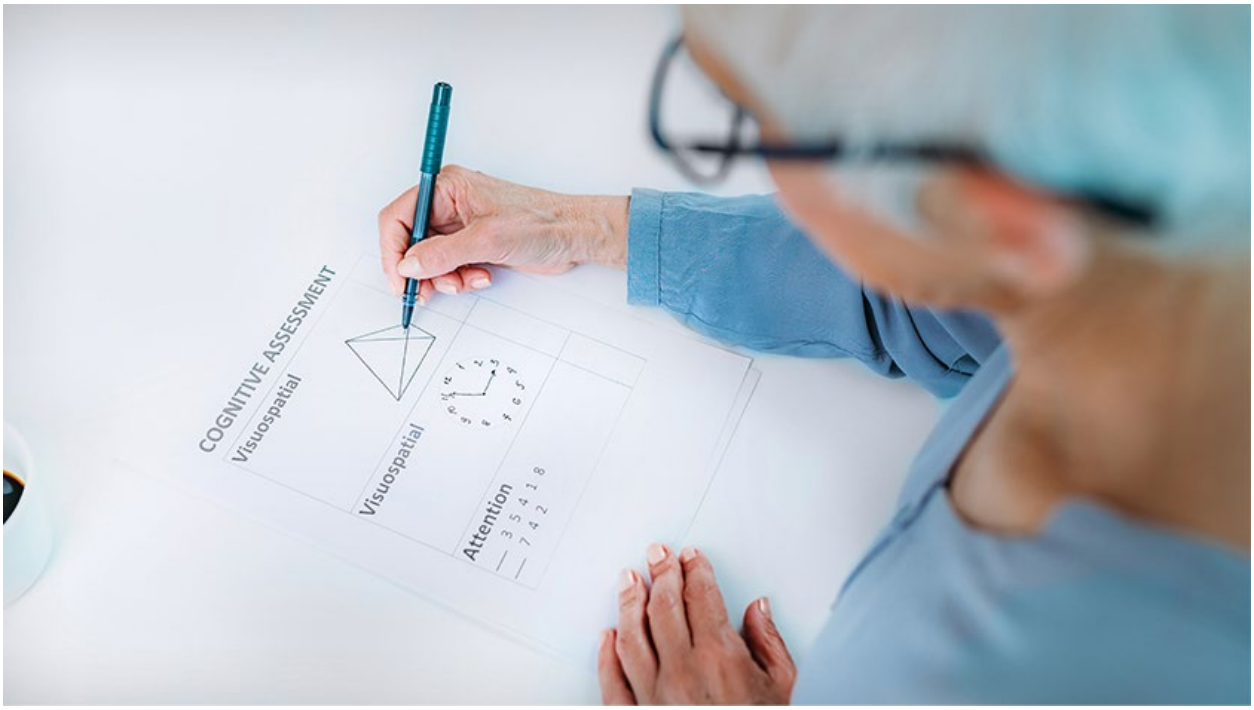
IBM launched the World Community Grid in 2004 to enable the public to support scientific research by donating their unused computing power to computationally intensive data processing. This initiative has enabled the public to participate in numerous health-related research projects. For example, the Scripps Institute recently used the World Community Grid to identify potential drugs to treat COVID-19. This project highlights the incredible power of distributed computing—a year's worth of calculations were completed in just 10 days.

To learn more about how you can contribute to the Word Community Grid, click here.

Research

Helping Clinicians

UHN researchers have developed a faster way to detect cognitive changes in patients with lupus.



People with lupus often experience cognitive changes, such as reductions in memory, attention and problem-solving ability. Clinicians typically assess cognitive impairment using lengthy standardized tests that examine a range of cognitive functions.

Researchers at the Schroeder Arthritis Institute have validated a screening tool that could streamline the diagnosis of cognitive impairment in individuals with lupus.

Individuals with lupus commonly experience cognitive impairment—often known as brain fog or lupus fog—but it is rarely diagnosed because screening for this symptom is time-consuming and costly.

The standard test for cognitive impairment in lupus is the American College of Rheumatology Neuropsychological Battery (ACR-NB). This one-hour test is costly because it requires trained personnel to administer and score.

“Screening for cognitive impairment in lupus is often delayed or entirely lacking,” explains Dr. Zahi Touma, a Scientist at the Schroeder Arthritis Institute and senior author of the study. “We need tests that can quickly and accurately assess cognitive function in the clinic, and tools to help clinicians interpret the results of these tests.”

Dr. Touma’s team examined the effectiveness of an alternative to the ACR-NB, called the Automated Neuropsychological Assessment Metrics (ANAM). ANAM is a collection of computer-based tests that assess a wide range of cognitive functions, including attention, reaction time, processing speed and decision making.

The research team administered the ANAM test to 300 adults with systemic lupus erythematosus (SLE), and compared the results with those obtained using the ACR-NB. The ANAM accurately identified cognitive impairment in over 90% of cases that were previously identified using the ACR-NB, suggesting that clinicians can use it as a screening tool for patients with SLE.

The researchers also identified the eight ANAM subtests that are most useful for identifying cognitive impairment, including tests for attention, language processing, and learning and memory. Focusing on only this subset of tests reduced the total test time from 40 minutes to as little as 15 minutes.

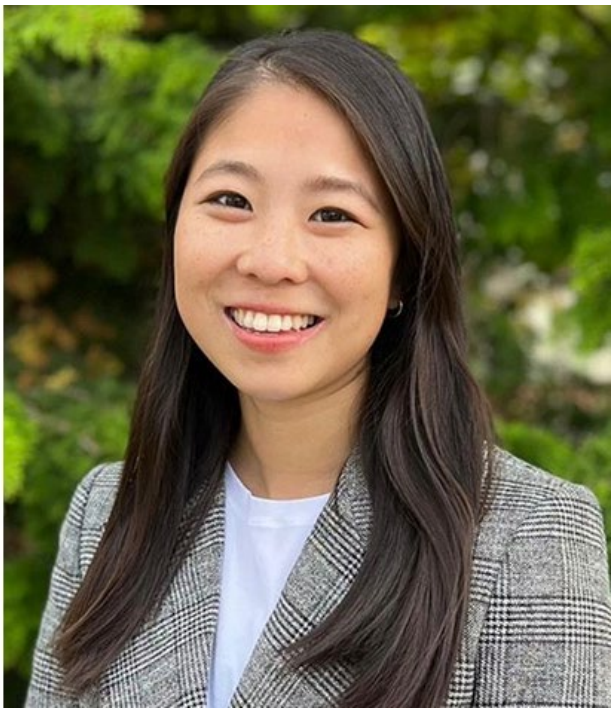
To complement the shortened ANAM, the team developed a decision tree—a tool that clinicians can use to easily interpret test results. Using this tool, a clinician can answer a series of simple yes or no questions related to a patient’s ANAM scores and age to determine whether this patient has cognitive impairment.

“Our decision tree makes it easy for clinicians to interpret test results, which enables faster screening,” says Kimberley Yuen, a summer student in Dr. Touma’s lab and the first author of the study. “The faster clinicians can detect cognitive impairment, the faster they can intervene to help their patients.”

An important next step for the researchers is to determine the effectiveness of the ANAM and decision tree in patients who have arthritis, joint stiffness or reduced sensation in their hands—common symptoms of lupus. For these patients, scores on ANAM tests that involve hand movements, such as finger tapping, may be influenced by motor impairments and would be less useful for detecting cognitive changes.

This work was supported by the Arthritis Society, the Canadian Rheumatology Association, the Canadian Institutes of Health Research, Physician’s Services Incorporated, the Province of Ontario Early Research Award, the Lupus Research Alliance and the UHN Foundation. Dr. Touma’s laboratory is supported by donations from the Kathi and Peter Kaiser family, the Lou and Marissa Rocca family, and the Bozzo family.

Yuen K, Beaton D, Bingham K, Katz P, Su J, Diaz Martinez JP, Tartaglia MC, Ruttan L, Wither JE, Kakvan M, Anderson N, Bonilla D, Choi MY, Fritzler MJ, Green R, Touma Z. Validation of the automated neuropsychological assessment metrics for assessing cognitive impairment in systemic lupus erythematosus. Lupus. 2022 Jan. doi: 10.1177/09612033211062530.



Dr. Zahi Touma (L) is a Scientist at the Schroeder Arthritis Institute, an Associate Professor in the Department of Medicine at the University of Toronto, and a Staff Rheumatologist at the Toronto Western Hospital and Mount Sinai Hospital. Kimberley Yuen (R) is a medical student at Queen's University and has been a summer research student in Dr. Touma's lab for the past two years.

After a Concussion

Classifying subtypes of post-concussion syndrome brings us closer to precision medicine.

After a concussion, some people develop what is known as post-concussion syndrome. These individuals experience symptoms such as headaches, anxiety and depression, which can persist for weeks or months.

Researchers at the Krembil Brain Institute have identified distinct subtypes of post-concussion syndrome. The research team was able to define these subtypes by analyzing brain structure and function.

“The changes that occur in the brain following a concussion are poorly understood and the severity of symptoms can vary considerably between patients,” explains Dr. Carmela Tartaglia, a Clinician Investigator at the Krembil Brain Institute and the senior author of the study. “If we can identify the biological signatures of post-concussion syndrome, we can more effectively diagnose and treat the condition”.

The researchers set out to understand how brain changes experienced after a concussion lead to symptoms. To do this, they examined brain scans from 96 patients who were treated for a concussion at University Health Network’s Canadian Concussion Centre. Patients who experienced post-concussion symptoms such as headache, dizziness, anxiety or memory problems for at least three months were included in the study.

“We grouped patients based on their patterns of brain connectivity and examined whether the groups differed in terms of cognitive, neuropsychiatric and behavioural symptoms,” says Melisa Gumus, a PhD student and first author of the study, who completed this research while a master’s student in Dr. Tartaglia’s lab.

The research team looked at the structural and functional brain connectivity in those with post-concussion syndrome and compared what they saw to healthy individuals. By doing this, they were able to split the individuals with post-concussion syndrome into two groups: one with brain connectivity similar to healthy individuals; and another with distinct brain changes.

The team then looked at these two groups to see what symptoms were experienced by each. Only mild symptoms were experienced by those who had brain connectivity similar to healthy individuals. The second group, which had distinct brain changes, experienced more severe symptoms and higher levels of depression, anxiety and aggression.

These results suggest that there is variability in the brain changes that follow a concussion, and that examining changes in brain connectivity may help clinicians predict symptom severity.

“More research is needed to determine whether changes in brain connectivity can serve as biomarkers to distinguish between mild and severe post-concussion syndrome. When it comes to recovering from a concussion, one size does not fit all. Being able to identify subtypes of the syndrome could enable us to provide patients with personalized therapies,” concludes Dr. Tartaglia.

This work was supported by the Government of Ontario, the Canadian Traumatic Brain Injury Research Consortium and the UHN Foundation.

Gumus M, Mack ML, Green R, Khodadadi M, Wennberg RA, Crawley A, Colella B, Tarazi A, Mikulis D, Tator CH, Tartaglia MC. Brain Connectivity Changes in Postconcussion Syndrome as the Neural Substrate of a Heterogeneous Syndrome. Brain Connect. 2022 Feb 14. doi: 10.1089/brain.2021.0127.

Dr. Carmela Tartaglia (L) is a Clinician Investigator at the Krembil Brain Institute and an Associate Professor at the Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto. Melisa Gumus (R) is a PhD Student in Dr. Tartaglia's lab.

Game Changing

Study reveals new blood biomarkers that could help identify acute brain injury in soccer.

While soccer requires skilled footwork, it also requires players to use their head. Known as 'heading', players intentionally hit the ball with their head to pass the ball to teammates or to score.

A team of researchers has identified sets of blood-based markers for brain injury that athletes experience while playing soccer.

"Because millions of individuals play soccer, developing tools to study repetitive head impacts in this context could have major implications on public health and, ultimately, how the game is played," says Dr. Igor Jurisica, a Senior Scientist at UHN's Schroeder Arthritis Institute who co-led the study with Dr. Stian Bahr Sandmo, a Researcher at the Oslo Sports Trauma Research Center at the Norwegian School of Sport Sciences.

Soccer is the most popular sport in the world. It is also a potential source of brain injury. Over a fifth of all soccer injuries are concussions and professional soccer players are susceptible to chronic brain damage. Despite these risks, the effects of playing soccer on brain health are not well understood.

To identify biomarkers of brain injury, the research team examined the levels of a relatively stable molecule in the blood known as microRNA (miRNA). These molecules are produced throughout the body (including in the brain) and are known to affect the

activity of genes. “Because miRNA molecules can affect gene expression, in addition to serving as reliable markers of injury, they could provide deeper insights into underlying disease processes,” says Dr. Jurisica.

For their analyses, the team examined 274 blood samples from males aged 18 to 35 who played in the Norwegian premier league during the 2004 and 2005 seasons. The team analyzed samples from players at one and 12 hours after one of three conditions: 1) high-intensity exercise alone, 2) soccer training that involved repetitive headers or 3) accidental head impacts, with or without concussion, during a match.

The research team used samples from players that experienced high intensity exercise alone as a baseline and compared these samples with those from players that repeatedly headed the ball or experienced head impacts. This enabled the researchers to refine their findings and narrow down their search for blood markers for the potentially more damaging activities.

The team found that rigorous exercise led to changes in the levels of seven miRNAs associated with 31 different signalling pathways. In addition to these changes, accidental head impacts led to changes in eight other miRNAs that are linked to 12 signalling pathways. Repetitive headers led to changes in six miRNAs—all of which were linked to the transforming growth factor-beta (TGFB) signalling pathway, which is known to be involved in the inflammatory process.

“The inflammation and other brain changes that athletes experience due to repeated head impacts can eventually lead to neurodegenerative conditions, such as Alzheimer disease and Chronic Traumatic Encephalopathy,” says Dr. Peter Filipčík, a Research Scientist at the Slovak Academy of Science. “Identifying the molecular links between brain injury and these diseases is necessary to better understand disease mechanisms in this population and can lead to improved diagnostic tools and therapies.”

“This is the first study to explore whether blood-based markers exist for the types of brain injuries that are commonly associated with playing soccer. Because we found distinct molecular signatures associated with heading the ball alone and with more serious, accidental head impacts, our approach may have the potential to discriminate between different degrees of brain injury,” concludes Dr. Sandmo.

Although these findings are preliminary, they lay the foundation for future studies aimed at developing a sensitive test for soccer-related brain injury. The blood markers that the team identified also represent a set of valuable tools to explore the mechanisms underlying soccer-related brain injury, as well as ways to prevent it.

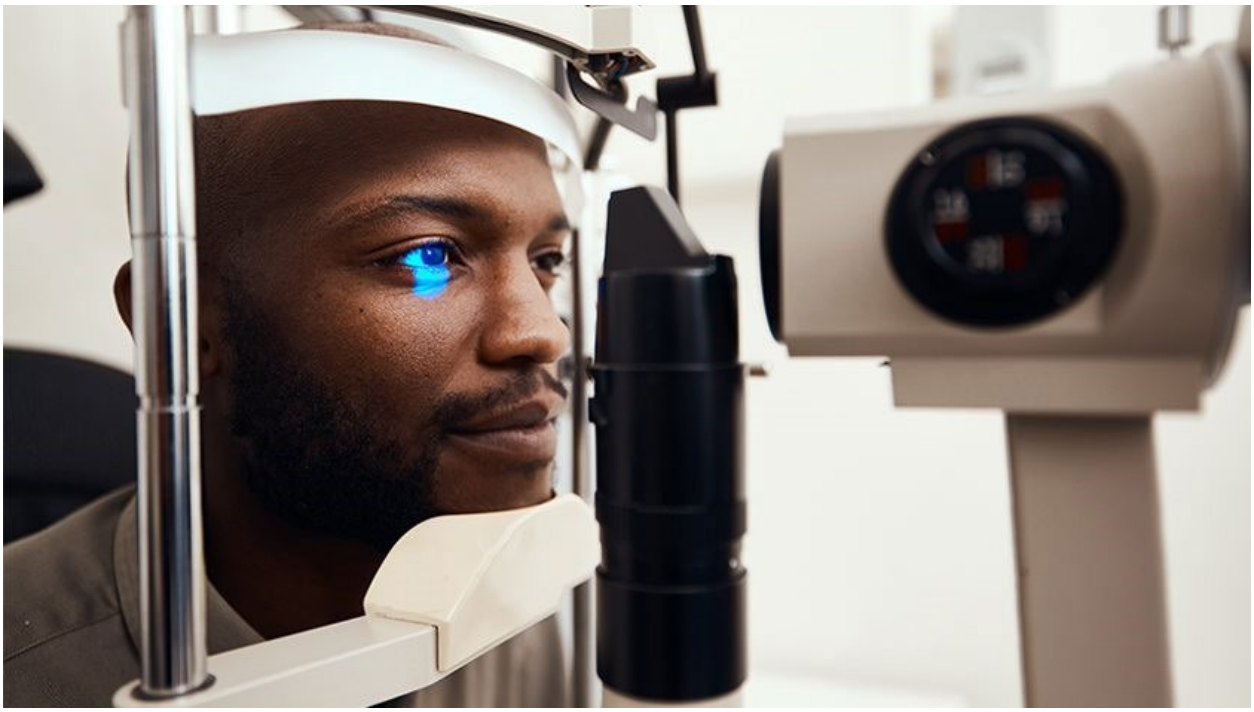
This work was supported by BrainTest, s.r.o. (Slovakia), The Ministry of Education, Science, Research and Sport of the Slovak Republic, ERA-NET Neuron, The Research Council of Norway, the International Federation of Association Football Medical Assessment and Research Center, and the UHN Foundation. Dr. Igor Jurisica is a Professor in Medical Biophysics and Computer Science at the University of Toronto.

Sandmo SB, Matyasova K, Filipcik P, Cente M, Koerte IK, Pasternak O, Andersen TE, Straume-Næsheim TM, Bahr R, Jurisica I. Changes in circulating microRNAs following head impacts in soccer. Brain Inj. 2022 Feb 16. doi: 10.1080/02699052.2022.2034042.

(L-R) Senior authors of the study, Dr. Igor Jurisica, a Senior Scientist at the Schroeder Arthritis Institute, and Dr. Stian Bahr Sandmo, a Researcher at the Oslo Sports Trauma Research Center at the Norwegian School of Sport Sciences.

Eyeing New Therapies

Researchers optimize and validate a new method to study drug distribution in the eye.



Intravitreal injection is a technique used clinically to deliver medication to an area at the back of the eye that is filled with a jelly-like fluid called vitreous humour.

Researchers co-led by Dr. Jeremy Sivak, a Senior Scientist at the Donald K. Johnson Eye Institute, have recently developed an experimental model to study the behaviour of drugs that are administered to the eye through intravitreal (ITV) injection.

ITV injection enables therapeutics to be delivered to an area at the back of the eye called the posterior chamber to target the retina; the sensitive nerve tissue that senses light and sends visual signals to the brain. The approach is widely used for treatment of eye diseases that lead to vision loss, such as macular degeneration.

Although ITV drug delivery is a promising approach for treating eye diseases, there have been reports that drug particles can move from the posterior chamber to the anterior chamber, the front portion of the eye. This forward drug movement can increase pressure inside the eye and increase one's risk of developing other conditions, such as glaucoma.

"It is challenging to predict how drugs will behave in the human eye, because what we observe in experimental models does not always match what happens in humans," says Darren Chan, a research technician in Dr. Sivak's lab. "The lack of suitable models to

study the behaviours of new drugs creates a major bottleneck to bringing new therapies to the clinic."

To address this issue, the research team adapted a previously developed model that mimics how fluid flows between different compartments within the eye. In the current study, the team optimized features of the model, such as temperature, pH and fluid flow, to more closely mimic the conditions within the eye. To mimic injected drugs, the team first used tiny synthetic beads, which enabled the researchers to see how particles move in the eye following ITV injection.

"To test how well the model can replicate a real clinical scenario, we then validated the optimized model using the drug GNE-947—a potential treatment for macular degeneration," says Dr. Sivak. The study was performed in collaboration with Dr. Vladimir Bantseev, a Senior Scientist and the Ophthalmology Therapeutic Area Lead at Genentech, an industry leader in the field that has been developing the drug. GNE-947 had been observed to migrate to the anterior chamber in pre-clinical studies, increasing risk of potential serious side effects. This issue would have been very challenging to study using current approaches. However, the team found that the drug behaved within the model the same way it did in the pre-clinical studies, suggesting that the model accurately predicts drug behaviour in the human eye.

"Here, we showed that a simple experimental model of the eye can replicate the complex movement of drug particles following ITV injection," continues Dr. Sivak. "This model can now serve as a platform for researchers to explore how new drugs will behave in the human eye, and could ultimately help to expedite the pre-clinical development of new therapeutics."

This work was supported by the Canadian Institutes of Health Research, Genentech Inc. and the UHN Foundation.

Chan D, Won GJ, Read AT, Ethier CR, Thackaberry E, Crowell SR, Booler H, Bantseev V, Sivak JM. Application of an organotypic ocular perfusion model to assess intravitreal drug distribution in human and animal eyes. J R Soc Interface. 2022 Jan. doi: 10.1098/rsif.2021.0734.

Dr. Jeremy Sivak is a Senior Scientist at the Donald K. Johnson Eye Institute, and an Associate Professor in the Departments of Ophthalmology and Vision Sciences, and Laboratory Medicine and Pathobiology at the University of Toronto.