The Krembil

May 2020

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

Staying Connected

A message from Dr. Donald Weaver, Director of the Krembil Research Institute.

As we navigate our temporary ‘new normal’, our goal is to ensure that the Krembil community remains strong, healthy and vibrant.

The importance of taking care of ourselves cannot be understated. To that end, the Krembil team is working hard to launch online sessions and share helpful resources with our members each week, to keep you informed and connected.

Ultimately, science will prevail. Research will help us to better understand the virus and reveal the path back to normality. So stay focused and motivated, and remain as relentless as ever in your pursuit of science to heal those who are suffering from chronic illnesses.

Thank you all for doing your part by going into the hospital or KDT only for essential work, continuing your research activities at home and supporting our clinical colleagues by volunteering or participating in the redeployment.

Below is a list of resources and good news that may be of use to you.

Relentlessly yours,

Don Weaver
Director, Krembil Research Institute

- *Nature* article on the impact of COVID-19 on research culture → https://go.nature.com/2XQLrVa

- *Harvard Business Review* article – Tips for running a great virtual meeting → https://bit.ly/2yxi8MP

- New UHN resource for COVID-19 information → www.UHNLibraries.ca/Covid19

- Krembil Callouts:
  - Dr. Sowmya Viswanathan was elected to the Board of Directors of the International Society for Cell & Gene Therapy
  - Through their new initiative Stitch4Corona, Krembil trainees Kramay Patel and Chaim Katz have made and donated approximately 2,500 masks to a variety of local organizations, including walk-in clinics, respite centres and food banks
  - Dr. David Tang-Wai received the Teacher of the Year Award from the Department of Medicine at the University of Toronto
  - Dr. Alfonso Fasano has been awarded the Krembil Brain Institute's first Movement Disorders Chair in Neuromodulation and Multidisciplinary Care.
  - Dr. Esther Bui received the William Goldie Prize and Travel Award for Education at the Department of Medicine at the University of Toronto

- UHN Wellness webinar about emotional well-being during pandemic → https://bit.ly/2XQbL1F

- UHN Research Wellness Hub with lots of different resources to maintain emotional and physical well-being, such as UHN Virtual Research Meetups and links to free exercise and yoga classes → https://bit.ly/2Vu92t0 (link only accessible internal to UHN)

- Toronto Journalist Naomi Parness puts out a weekly video featuring 'The Good Stuff' from around the world → https://bit.ly/3eIn7Lh

- UHN Research COVID-19 Preparedness Resource page with links to redeployment information, COVID-19 research at UHN, updates from granting agencies and links to the livestream of Research COVID-19 Town Halls held Wednesdays 11am-12pm → https://bit.ly/34UCGLg (link only accessible internal to UHN)

- Inspirational quote → "You have power over your mind—not outside events. Realize this, and you will find strength." - Marcus Aurelius

Research

Mapping Out Memory

Study combines experimental and computational research to link a type of brain cell to memory.

Spatial memory enables us to record information about our environment and our spatial orientation in it. Impaired spatial memory can be an early clinical sign of Alzheimer disease.

Imagine how difficult life would be if we had to use a map every time we went somewhere—even to places where we travel to every day, like to work or to the grocery store.

Luckily, an area of the brain known as the hippocampus stores and remembers this type of information. The hippocampus plays a key role in learning and spatial memory, and helps us to navigate through our surroundings.

During learning and memory formation, the hippocampus displays rhythmic patterns of electrical activity known as theta waves. Although theta waves were discovered in the 1950s, researchers still do not fully understand how different types of cells in the hippocampus contribute to and/or are controlled by theta waves.

Krembil Senior Scientist Dr. Frances Skinner and Laval University Professor Dr. Lisa Topolnik led a tour de force study leveraging experimental and computational methods to determine whether a particular type of cell in the hippocampus, known as an IS3 cell, is linked to theta waves.

“It is very challenging—and sometimes impossible—to establish what a specific type of brain cell is doing during a behaviour or mental task by using laboratory experiments alone,” says Dr. Skinner.

To overcome this, Dr. Alexandre Guet-McCreight, then a member of the Skinner lab, developed computational models informed by experimental data from the Topolnik lab, simulating the activity of cells in the hippocampus. The models predicted that IS3 cells are active during theta waves.

Using a powerful imaging technique known as two-photon microscopy, Dr. Topolnik’s team corroborated these predictions by probing the activity of IS3 cells in an experimental model of the hippocampus producing theta waves.

“Our findings indicate that IS3 cells are recruited by theta waves and may thus play a vital role in controlling the flow of information in the hippocampus during learning and spatial navigation,” comments Dr. Skinner. “Understanding how specific cell types contribute to these mental processes could provide new insight into conditions that compromise memory, such as Alzheimer disease and epilepsy.”

This work was supported by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, the Savoy Foundation and the Toronto General & Western Hospital Foundation.

Luo X, Guet-McCreight A, Villette V, Francavilla R, Marino B, Chamberland S, Skinner FK, Topolnik L. Synaptic mechanisms underlying the network state-dependent recruitment of VIP-expressing interneurons in the CA1 hippocampus. Cereb Cortex. 2020 Feb 20. doi: 10.1093/cercor/bhz334.

Dr. Frances Skinner, Senior Scientist, Krembil Research Institute.

Over the Long Haul

A drug for the long-term management of psoriatic arthritis.

Psoriatic arthritis typically occurs in individuals in their twenties to forties. Early diagnosis and treatment are key to preventing severe joint damage.

Dr. Vinod Chandran, an Affiliate Scientist at Krembil Research Institute, is the lead author of a study demonstrating the consistent efficacy of ixekizumab in treating psoriatic arthritis for up to three years.

Psoriatic arthritis is caused by abnormal activity in the immune system that causes joint damage. The disease can occur in up to 30% of people living with psoriasis. There is no cure for psoriatic arthritis. However, there are treatments available to delay the progression of the disease.

Ixekizumab is a biologically derived drug that interacts with the immune system to help fight inflammation. Developed by Eli Lilly and Company, the drug is approved by the US Food and Drug Administration and Health Canada for treating two types of arthritis, including psoriatic arthritis.

To determine whether ixekizumab is safe for long-term use, the research team followed 381 patients receiving the medication for up to three years.

“We found that the safety of the drug remained consistent with previous reports. We also observed improvements in the signs and symptoms of psoriatic arthritis in patients taking the drug,” describes Dr. Chandran. “Long-term studies like this one are important

for evaluating the enduring benefits and safety risks of therapies for chronic progressive diseases, such as psoriatic arthritis."

Within two years of disease onset, 47% of individuals with psoriatic arthritis experience structural joint damage, which is likely to result in irreversible joint deformity and disability. Treatments like ixekizumab can help slow disease progression and improve the quality of life for individuals living with psoriatic arthritis.

This work was supported by Eli Lilly and Company.

Chandran V, van der Heijde D, Fleischmann RM, Lespessailles RM, Helliwell PS, Kameda H, Burgos-Vargas R, Erickson JS, Rathmann SS, Sprabery AT, Birt JA, Shuler CL, Gallo G. Ixekizumab treatment of biologic-naïve patients with active psoriatic arthritis: 3-year results from a phase III clinical trial (SPIRIT-P1). Rheumatology (Oxford). 2020 Feb 7. doi: 10.1093/rheumatology/kez684.

Dr. Vinod Chandran, Affiliate Scientist, Krembil Research Institute.

Hitting a Bull's-Eye

Krembil researchers identify a therapeutic target to stop vision loss and prevent blindness.

Retinitis pigmentosa (RP) is the most common subtype of inherited retinal degeneration. Its symptoms, including impaired peripheral vision and difficulty seeing in the dark, typically appear during childhood.

A new study from the Krembil Research Institute reveals a new putative target for the treatment of a broad family of eye diseases, known as inherited retinal degenerations (IRDs).

IRDs, which affect up to 1 in 2,000 individuals, are characterized by progressive vision loss that can lead to blindness. Presently, there are neither cures for IRDs nor treatments that can slow or stop disease progression. Visual impairment in patients with IRDs is caused by the gradual loss of photoreceptors, which are the cells in the eye that initiate vision.

"Photoreceptors contain a protein known as neogenin. We knew that neogenin acts as a major trigger of cell death in several other eye pathologies, so we decided to investigate whether the protein influences photoreceptor survival in IRDs," says Krembil Senior Scientist Dr. Philippe Monnier, who led the study.

The researchers found that neogenin levels are higher in eye tissues from experimental models of IRDs. Neogenin levels were also shown to be higher in the eyes of people

living with an IRD. Next, the researchers showed that inhibiting the activity of neogenin in the IRD models prevented the loss of photoreceptors and preserved visual function.

“Our findings suggest that neogenin could be a novel target for protecting the eyesight of people diagnosed with an IRD by promoting the survival of photoreceptors,” comments Dr. Monnier.

“This work would not have been possible without the generosity of our philanthropic supporters, namely Don and Nita Reed and the Krembil Family. We are very grateful for their continuous support over the years and enthusiasm for vision research.”

This work was supported by the Krembil Foundation, Fighting Blindness Canada, Brain Canada, the National Institutes of Health, the National Eye Institute, the Cleveland Clinic Foundation, the University of Toronto and the Toronto General & Western Hospital Foundation.

Charish J, Shabanzadeh AP, Chen D, Mehlen P, Sethuramanujam S, Harada H, Bonilha VL, Awatramani G, Bremner R, Monnier PP. Neogenin neutralization prevents photoreceptor loss in inherited retinal degeneration. J Clin Invest. 2020 Mar 16. doi: 10.1172/JCI125898.

Dr. Philippe Monnier, Senior Scientist, Krembil Research Institute.

Helping Hand

A strategy to restore movement after spinal cord injury shows promise in experimental model.

Neurons transmit information throughout the brain, spinal cord and nerves. Recent findings have revealed that neurons can repair damage to the spinal cord.

Dr. Michael Fehlings and his research team at UHN's Krembil Research Institute have identified a way to improve a cell therapy that might be able to restore function after spinal cord injury.

Paralysis can happen in individuals when certain cells die as the result of the spinal cord injury. Cell therapy works by replacing these lost cells.

Currently, a number of preliminary cell therapy clinical trials have shown promising results using a type of cell known as a neural progenitor cell (NPC). These cells have the potential to become different cells in the brain and spinal cord—including neurons—which are key to recovery.

"Current strategies involve injecting NPCs into the injured spinal cord. A major hurdle is that, rather than becoming neurons, most NPCs injected into the spinal cord become other cell types, such as astrocytes, which are involved in the scarring process," says Dr. Fehlings, Krembil Senior Scientist and senior author of a recent study in Science Translational Medicine.

The researchers, including lead author Dr. M. Khazaei, a scientific associate in the Fehlings lab, conducted a screen for factors capable of improving functional recovery after spinal cord injury. This screen identified a protein known as glial cell–derived neurotrophic factor (GDNF). Using experimental models, the research team discovered that when levels of GDNF were increased in NPCs the cells were more likely to produce neurons. The neurons that resulted from these cells also survived better than those from NPCs with lower levels of GDNF.

“While preliminary, these findings provide a promising strategy for optimizing NPCs before they are injected into the damaged spinal cord. By enhancing the ability of NPCs to become neurons, our approach could serve to promote repair and restore function after spinal cord injury.

This work was supported by the Ontario Institute of Regenerative Medicine, Wings for Life, the Krembil Foundation, the Canadian Institutes of Health Research and the Dezwirek Foundation

Khazaei M, Ahuja CS, Nakashima H, Nagoshi N, Li L, Wang J, Chio J, Badner A, Seligman D, Ichise A, Shibata S, Fehlings MG. GDNF rescues the fate of neural progenitor grafts by attenuating Notch signals in the injured spinal cord in rodents. Sci Transl Med. 2020 Jan 8;12(525). pii: eaau3538. doi: 10.1126/scitranslmed.aau3538.

Dr. Michael Fehlings, Scientist, Krembil Research Institute.