

The Krembil

January 2016

Introducing *The Krembil*: the official newsletter of Krembil Research Institute (formerly Toronto Western Research Institute). *The Krembil* informs the Toronto Western Hospital community, external stakeholders and interested community members about the exciting news and innovative research happening at Krembil Research Institute.

In this special "Year in Review" issue you can read about the top news stories of 2015:

- [The Krembil Research Institute renaming](#)
- [Krembil being a Canadian leader in brain, eye and bone research](#)



You can also catch up on some of Krembil Research Institute's highest impact discoveries from the last year:

- [The link between arthritis and vascular-related death](#)
- [The protein associated with memory loss in Parkinson disease](#)
- [What causes immune cells to malfunction in Lupus patients](#)
- [How visual nerves develop and connect within the brain](#)
- [How deep brain stimulation can help those with Parkinson disease](#)
- [A new mechanism responsible for osteoarthritis](#)

Donald Weaver, PhD, MD, FRCPC, FCAHS
Director, Krembil Research Institute
University Health Network

News

Krembil Research Institute Renaming a 2015 Highlight



The Toronto Western Hospital ended a successful 2015 by renaming its research arm the Krembil Research Institute (Krembil). The renaming, which took place on November 13, 2015, honours a family whose name now appropriately graces the face of the Institute after supporting research at Toronto Western Hospital for nearly two decades.

Krembil operates under the leadership of its Director, Dr. Donald Weaver. Its strategic research focus—finding cures for degenerative diseases of the brain, spine, bones, joints and eyes—will have an increasingly significant impact on

society as the global population ages.

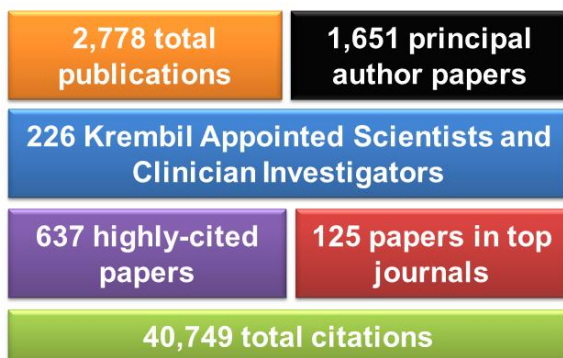
This important research is not possible without the continued support of philanthropists like the Krembil family, who has a deep appreciation for the research excellence at Krembil. Krembil Senior Scientists Drs. Mary Pat McAndrews, Nizar Mahomed and Antonio Strafella, who are working relentlessly to find cures for some of the more debilitating disorders of our day, know first-hand the significance of the Krembil's continued investment in research.

"Philanthropy is extremely important because it enables us to train the next generation of scientists, and they are the ones who are going to discover the cures we haven't yet dreamed about," says Dr. Mary Pat McAndrews.

"The Krembil family has really set an example for others to follow, working with us to lead the way in developing new health care solutions," says Dr. Nizar Mahomed.

"It is extremely important to have people like the Krembil family continue their personal commitment to helping researchers," says Dr. Antonio Strafella.

Krembil is a Canadian Leader in Brain, Eye and Bone Research



The publications of appointed Scientists, Senior Scientists, Affiliate Scientists and Clinical Investigators were compared to those of other research hospitals in Toronto and across Canada. The comparators were selected from ReSearch InfoSource's *Top 40 Research Hospitals* list, based on total research funding, and included SickKids, McGill University Health Centre, Centre for Addiction and Mental Health, and Mount Sinai Hospital.

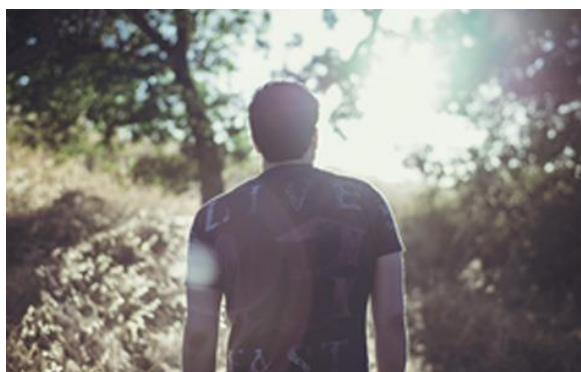
Krembil ranked first in the number of publications, citations and the number of highly cited papers (top 10% according to year) in the fields of brain, vision and arthritis research. These results truly demonstrate the wealth of research activity at the Institute and the impact it has in those fields.

All publication data and metrics were derived from Thomson Reuters data sources, including Web of Science, Journal Citation Reports and Essential Science Indicators, and are current as of November 2015. Publication metrics reflect primary research, review and proceedings papers published in a Thomson Reuters indexed journal in the five-year period from the start of 2010 to the end of 2014. Only journals in the subject area of the Krembil's main research themes (brain, vision and arthritis) were included in the analysis. There were a total of 26 journal categories used in the search, including pharmacology, neuroimaging, immunology, ophthalmology and rheumatology.

Note: Remember to list your Krembil affiliation on all of your publications so that they will be included in future publication analyses.

Research

Arthritis Linked to Vascular Disease



Ankylosing spondylitis (AS) is a form of chronic inflammatory arthritis that predominantly affects the spine. In addition to suffering from chronic lower back pain, patients with AS are at increased risk for heart disease and stroke. Coronary artery disease and heart attacks occur at a much higher rate in these patients, and AS has been shown to be an independent risk factor for coronary artery bypass graft surgery. Whether this translates to an increased risk of cardiovascular-related death is not known.

A recent study, led by Krembil Scientist Dr. [Nigil Haroon](#) and his team, assessed whether patients with AS are at increased risk for mortality due to cardiovascular and cerebrovascular disease (vascular death). By analyzing the administrative health data of over 21,000 patients, they found that patients with AS were at significantly higher risk for vascular death than those without the disease. Major risk factors for death included age, chronic kidney disease and lack of exposure to nonsteroidal anti-inflammatory drugs. Moreover, male patients with AS had significantly higher mortality—whether this indicates that inflammation is less severe or that the disease is milder in women is not known.

"These findings indicate that a comprehensive strategy to screen and treat modifiable risk factors for vascular disease in patients with AS is needed," says Dr. Haroon. "Further investigation is required to study the effect of therapeutic interventions in preventing the elevated vascular mortality in these patients."

This work was supported by The Arthritis Society, the UHN Arthritis Program, the Ministry of Health and Long-term Care, and the Toronto General & Western Hospital Foundation.

Patients with ankylosing spondylitis have increased cardiovascular and cerebrovascular mortality: a population-based study. Haroon NN, Paterson JM, Inman RD and Haroon N. Annals of Internal Medicine. 2015 Aug. [\[Pubmed Abstract\]](#)

Parkinson Disease: Networks that Control Memory Decline



Patients with Parkinson disease (PD) often suffer from a slight decline in their ability to think and learn (also known as mild cognitive impairment). This symptom is sometimes accompanied by difficulty remembering previous experiences or events. New research from Krembil Senior Scientist Dr. [Antonio Strafella](#) has identified that in patients with PD, certain brain regions have impaired dopamine signalling and that this may contribute to the development of memory loss.

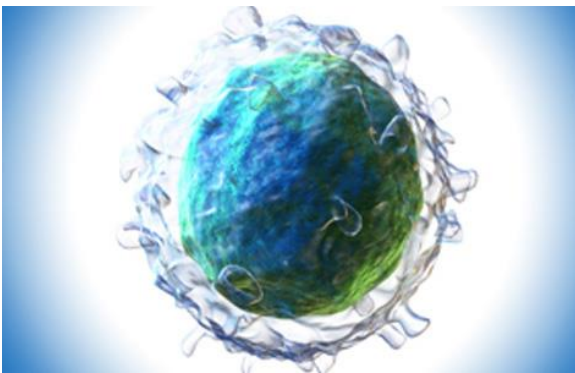
Dr. Strafella and his team made the discovery by analyzing brain imaging scans from healthy individuals and by comparing them to three different groups of PD patients: those with mild cognitive impairment and memory loss; those with mild cognitive impairment alone; and those without any impairment. The team found that patients with memory loss had a significant decrease in the proteins that allow dopamine to transmit signals in the brain. Importantly the imaging scans identified two different regions of the brain with decreased dopamine signalling, both of which are normally involved in memory retrieval.

“Our study demonstrates that in PD patients with memory loss, specific brain regions are more vulnerable to neuron dysfunction. Future studies should focus on determining the roles of these regions in memory decline.”

This work was supported by the Canadian Institutes of Health Research, the National Parkinson Foundation and the Toronto General & Western Hospital Foundation. A Strafella is a Tier 2 Canada Research Chair in Movement Disorders and Neuroimaging.

Saliency network and parahippocampal dopamine dysfunction in memory impaired PD. Christopher L, Duff-Canning S, Koshimori Y, Segura B, Boileau I, Chen R, Lang AE, Houle S, Rusjan P, Strafella AP. Annals of Neurology. 2014 December 2. [[Pubmed Abstract](#)]

Blood Molecule a Bad Influence



In the immune system, B cells are responsible for identifying invading viruses and bacteria and releasing antibodies that target these threats. In the autoimmune disease systemic lupus erythematosus, commonly known as lupus, B cells behave differently—they mis-identify healthy tissues and signal the immune system to attack. Why these cells target healthy tissue in lupus is still a mystery.

Krembil Senior Scientist Dr. [Joan Wither](#) and colleagues have helped shed light on this. The team showed that B cell behaviour changed over time and did not match up with the genetic risk factors of the patients, suggesting that another influence was at play.

In a key experiment, the research team placed B cells from healthy donors into blood plasma from someone with lupus, which caused the formerly healthy cells to behave just like those in lupus. These

results indicated that something in the blood causes the change in B cell behaviour. Further tests demonstrated that this abnormal B cell behaviour was being influenced by a molecule known as interferon-alpha (IFN- α) that is normally increased in the body during an infection.

The identification of IFN- α as a key player in the disturbance of B cell behaviour in lupus represents an important first step towards the development of new therapies to restore normal B cell function.

IMAGE CAPTION: *The B cell (illustrated above) is an important part of the immune system, but can target the body's own tissues in diseases like lupus.*

This work was supported by the Canadian Institutes of Health Research, the Arthritis Society, the Arthritis Centre of Excellence, the Arthritis Research Foundation and the Toronto General & Western Hospital Foundation. PR Fortin is a Tier 1 Canada Research Chair in Systemic Autoimmune Rheumatic Diseases. Image courtesy of Blausen gallery 2014. Wikiversity Journal of Medicine. DOI:10.15347/wjm/2014.010

Interferon- α induces altered transitional B cell signaling and function in Systemic Lupus Erythematosus. Chang NH, Li TT, Kim JJ, Landolt-Marticorena C, Fortin PR, Gladman DD, Urowitz MB, Wither JE. Journal of Autoimmunity. 2015 Feb 9. [[Pubmed Abstract](#)]

Vision Disorders: Connecting the Dots



When human eyes look at their environment they collect pictures that are sent to the brain. Together these pictures form a visual representation of our world. The eyes transmit visual images to the brain through a cable that is composed of nerve fibres called retinal axons. The retinal axons connect the eye to visual areas of the brain, including the optic tectum (OT).

Unfortunately, retinal axons can degenerate in conditions like glaucoma, eventually leading to irreversible blindness. Currently, it is unknown how developing retinal axons

connect with the brain, which has limited the creation of new therapies.

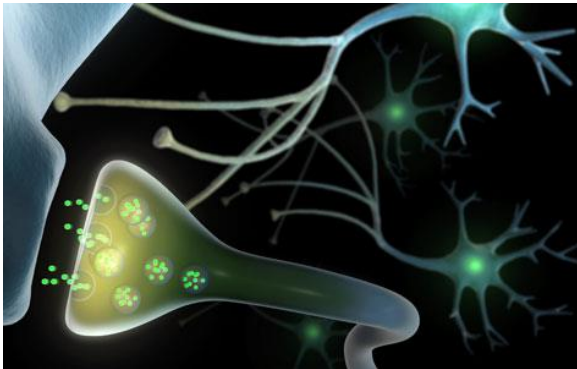
Recent findings from Krembil Senior Scientist Dr. [Philippe Monnier](#) have addressed this problem by shedding light on how retinal axons are guided during development. The researchers found that a group of peptides, known as Repulsive Guidance Molecule a (RGMa) subtypes, work in combination to help retinal axons target the OT. One of the subtypes, C-RGMa, inhibits deep projections in the optic tectum, while the other, N-RGMa, promotes deeper projections in the OT. A balance of both peptides ensures that retinal axons connect with the appropriate area of the OT.

Remarks Dr. Monnier, "Our work has uncovered the peptides responsible for ensuring that retinal axons integrate into the correct layer of the OT. These insights may help developing therapies aimed at restoring vision in patients with retinal axon damage."

This work was supported by the Canadian Institutes of Health Research, the Vision Science Research Program of the University of Toronto and the Toronto General & Western Hospital Foundation.

Y-secretase and LARG mediate distinct RGMa activities to control appropriate layer targeting within the optic tectum. Banerjee P, Harada H, Tassew NG, Charish J, Goldschneider D, Wallace VA, Sugita S, Mehlen P, Monnier PP . Cell Death and Differentiation. 2015 Aug 21. [[Pubmed Abstract](#)]

Parkinson Disease: How Deep Brain Stimulation Works



Parkinson disease is a movement disorder that causes rigidity, slowness of movement and uncontrollable shaking. Those with advanced stages of the disease experience debilitating symptoms that can lead to difficulty walking and, in some cases, dementia.

The disease is primarily caused by a drop in the amount of dopamine produced by certain cells (neurons) in the brain. The most common therapy, a drug known as levodopa, helps to reduce symptoms by restoring levels of dopamine. Unfortunately, after prolonged use, levodopa can cause rapid fluctuations in responses and complications such as excessive, uncontrolled movements.

For those that have developed levodopa-related side effects, an emerging therapy known as deep brain stimulation (DBS) has been shown to offer relief. While the therapy involves stimulating certain regions of the brain with implanted electrodes, researchers have not yet determined how it works.

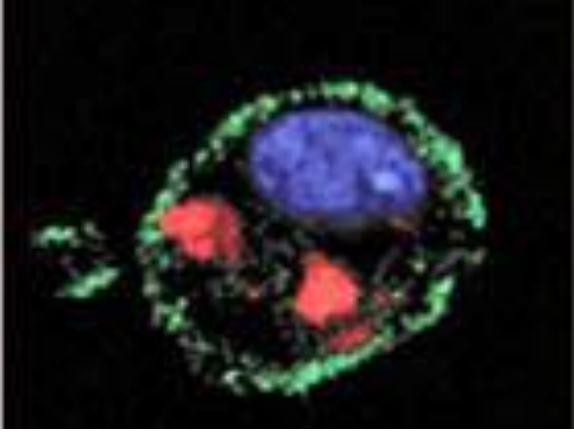
Krembil Senior Scientist Dr. [Robert Chen](#) has now provided new insight into DBS. His team found that a certain type of brain plasticity, which is compromised in those who suffer from Parkinson disease and advanced levodopa-related side effects, is restored in those that respond to DBS.

The finding suggests that restoration of brain plasticity (ie, the ability of the brain to reshape neural connections), which is required for learning and memory, may be how deep brain stimulation provides beneficial effects to Parkinson patients. Comments Dr. Chen, "This new understanding of the mechanism by which deep brain stimulation works may pave the way for more specific and targeted therapies."

This work was supported by the Canadian Institutes of Health Research and the Toronto General & Western Hospital Foundation. R Chen holds the Catherine Manson Chair in Movement Disorders. AM Lozano holds a Tier 1 Canada Research Chair in Neuroscience.

Effects of subthalamic nucleus stimulation on motor cortex plasticity in Parkinson disease. Kim SJ, Udupa K, Ni Z, Moro E, Gunraj C, Mazzella F, Lozano AM, Hodaie M, Lang AE, Chen R. Neurology. 2015 Jul 8. [[Pubmed Abstract](#)]

Osteoarthritis: Eating Away at the Joint



Osteoarthritis (OA) is characterized by the erosion of joint cartilage (the tough elastic material that protects the ends of bones). This damage is caused by inflammation, which can lead to joint stiffness and swelling that can be debilitating. The mechanisms responsible for joint inflammation and cartilage destruction in OA are not fully known; however, a recent study led by Krembil Senior Scientist, Dr. [Mohit Kapoor](#), has revealed one of the processes responsible.

Using an experimental model of OA, Dr. Kapoor and his team discovered that PPAR γ —a factor that governs genes that respond to inflammation and joint destruction—is critical to keep the disease under control. PPAR γ promoted autophagy, a self-protective process in which debris are recycled within cells. When PPAR γ function was lost, joint inflammation and cartilage destruction increased—two effects that when combined accelerated the progression and severity of OA.

This study suggests that therapeutics capable of promoting PPAR γ function may be effective for OA. These anti-inflammatory drugs, known as PPAR γ agonists, are already approved for treating diseases like diabetes. As such, they represent an accessible option for improving the quality of life of people with OA.

This work was supported by the Canadian Institutes of Health Research, the Canadian Arthritis Network/The Arthritis Society and the Toronto General & Western Hospital Foundation. Image modified from "Pan et al. Cathepsin S deficiency results in abnormal accumulation of autophagosomes in macrophages and enhances Ang II-induced cardiac inflammation. PLoS One. 2012. 7(4):e35315".

PPAR γ deficiency results in severe, accelerated osteoarthritis associated with aberrant mTOR signalling in the articular cartilage. Vasheghani F, Zhang Y, Li YH, Blati M, Fahmi H, Lussier B, Roughley P, Lagares D, Endisha H, Saffar B, Lajeunesse D, Marshall WK, Rampersaud YR, Mahomed NN, Gandhi R, Pelletier JP, Martel-Pelletier J, Kapoor M. Annals of Rheumatic Disease. 2015 January 8. [\[Pubmed Abstract\]](#)

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For inquiries related to The Krembil newsletter, please contact Nick Dery:

