The Krembil

January 2018

The Krembil is the official newsletter of the Krembil Research Institute (formerly the Toronto Western 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.

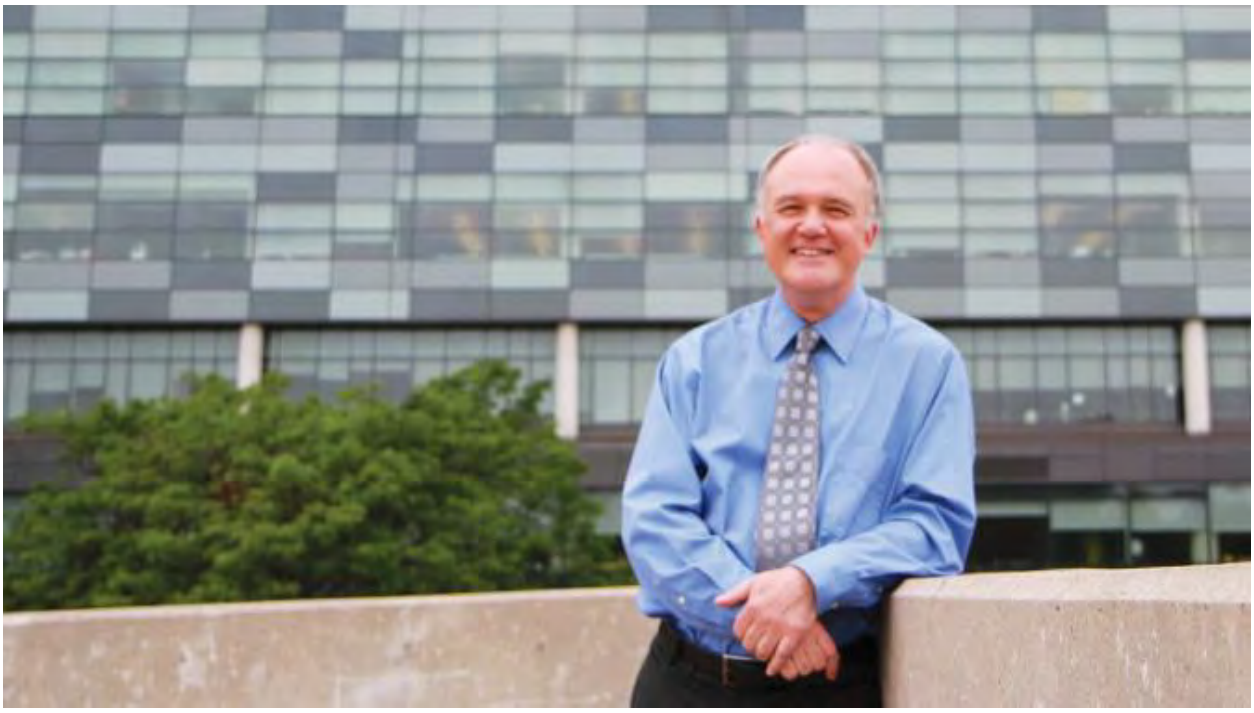
Stories in this month's issue:

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

News

Krembil in Focus

Letter from Krembil Director highlights key advancements made in 2017.



As we enter 2018, I wish to take this opportunity to express my gratitude to the staff, faculty and trainees here at the Krembil Research Institute. Last year we achieved many research successes, which have been showcased in our newsletter and through our three-part Krembil magazine series in partnership with *The Globe and Mail*.

First, I am pleased to share that we have expanded an important niche at the Krembil—computational science. On this front, our key progress includes: new space provided for the computational group at the Krembil Discovery Tower (KDT), the welcoming of computational expert Dr. Igor Jurisica as a Krembil Senior Scientist, and the establishment of a collaboration with the Centre for Addiction and Mental Health (CAMH) Neuroinformatics group. These changes will support and advance a wide range of research initiatives across the institution, and will be furthered by the planned hire of a new computational neuroscientist in the spring of 2018.

Another noteworthy boost includes upgrades to our Wright Cell Imaging Facility. Thanks to a generous donation, and funding from the Canadian Foundation for Innovation, the facility

acquired three new advanced microscopes and amalgamated with UHN's Advanced Optical Microscopy Facility (link is external).

Research Day 2017 was a huge success. The event was well attended and provided an important opportunity for trainees to hone their communication skills through either 10-minute presentations or three-minute 'elevator' pitches.

Our funding opportunities have also boosted the resources available to our researchers and trainees. These include our Small Equipment Competition, Post-doctoral Fellowship Award, and a Collaborative Seed Program, which was launched in 2017. All have been well received by our membership.

In the fall we welcomed the new Program Medical Director for Krembil Neuroscience Centre, Dr. Gelareh Zadeh with whom we look forward to working, enabling us to bridge patient care, education and research. I would also like to acknowledge the following leadership changes that took place in 2017:

- Dr. Mary Pat McAndrews, new Chair of the Trainee Affairs Committee
- Dr. Mohit Kapoor, named Research Director of the Arthritis Research Group
- Dr. Jeremy Sivak, promoted to Senior Scientist
- Addition of 33 newly appointed Clinician Investigators
- Creation of the KDT Joint Health and Safety Committee

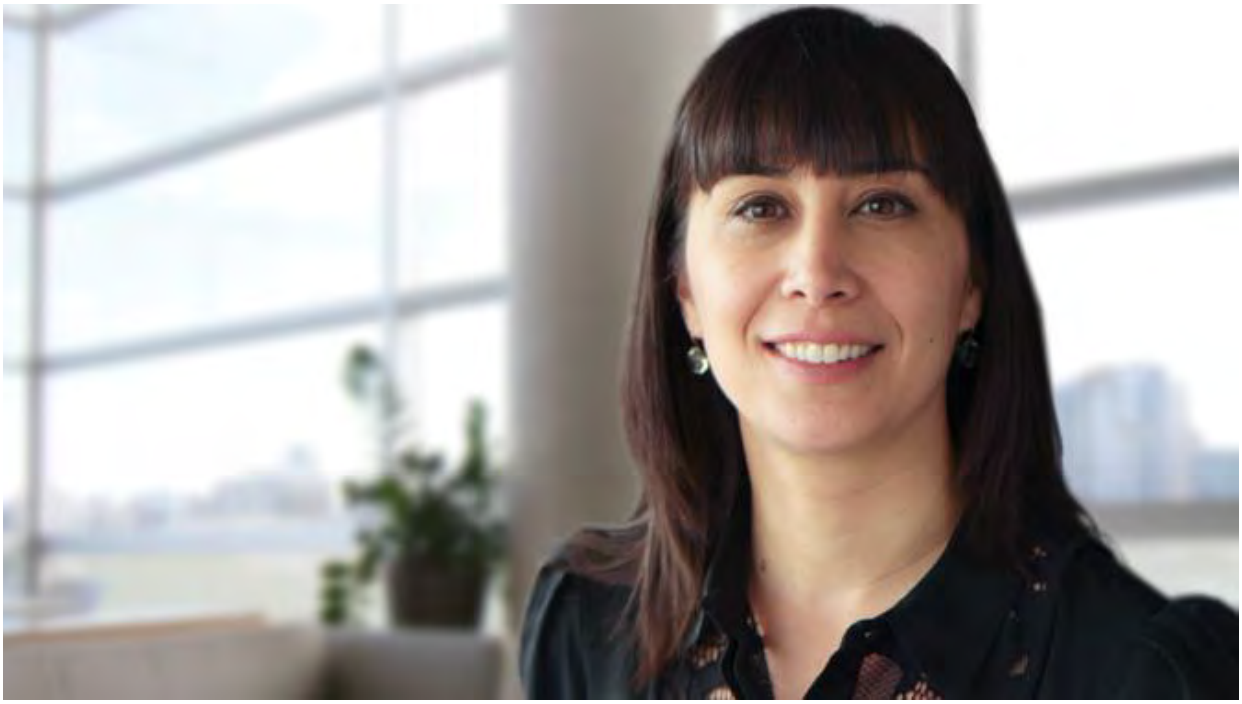
Moving into the new year, I want to thank everyone for their dedication to the relentless pursuit of new diagnostics, treatment and management strategies for chronic debilitating disorders in the areas of brain, arthritis and vision. We hope to continue new and exciting initiatives, recruitments and investment in core resources as we propel the Krembil into the position of an internationally recognized biomedical institute.

Relentlessly yours,

Don Weaver
Director, Krembil Research Institute, UHN

Powering Research Forward

Krembil researchers working with IBM Watson to accelerate drug discovery for Parkinson disease.



Krembil Scientist Dr. Lorraine Kalia is one of a group of researchers using IBM Watson to find off-label drugs to treat Parkinson disease.

When IBM business development executive Jonathan Rezek was diagnosed with Parkinson disease, he was faced with the uncomfortable reality that there is currently no cure for the disease. As an executive at IBM, he knew he might be able to help change that.

While he was being treated at Toronto Western Hospital, he proposed something that had not been tried before: could IBM Watson—a computer system that can read and understand natural language—be used to help find new therapies?

While many people remember the Watson computer system from 2011 when it made history by winning the quiz show *Jeopardy!*, its first commercial application was in health care. In 2013 it was customized for use at Memorial Sloan Kettering Cancer Center in New York City to manage health care decisions for lung cancer treatment.

The question asked by Jonathan Rezak at Toronto Western Hospital has now flourished into a collaboration between IBM Watson Health, the Ontario Brain Institute and UHN's Movement Disorders Clinic (MDC). This has led to Canada's first ever search for Parkinson disease therapeutics using a version of Watson known as *IBM Watson for Drug Discovery*. This

computing system is cloud-based, can draw from nearly 31 million sources of relevant literature, and has the ability to analyze high volumes of medical literature and data.

Such computing power can be transformative to researchers. The project team in Toronto has set out to use this computing power to screen a vast number of pharmaceuticals already on the market to see if an existing drug can be effective in the fight against Parkinson disease.

"The platform gives us the ability to look at connections that researchers might not have found without dedicating weeks or months of time," said Dr. Lorraine Kalia, a movement disorders neurologist and Scientist at the Krembil Research Institute. "This includes identifying compounds that we have not previously considered investigating for the treatment of Parkinson disease."

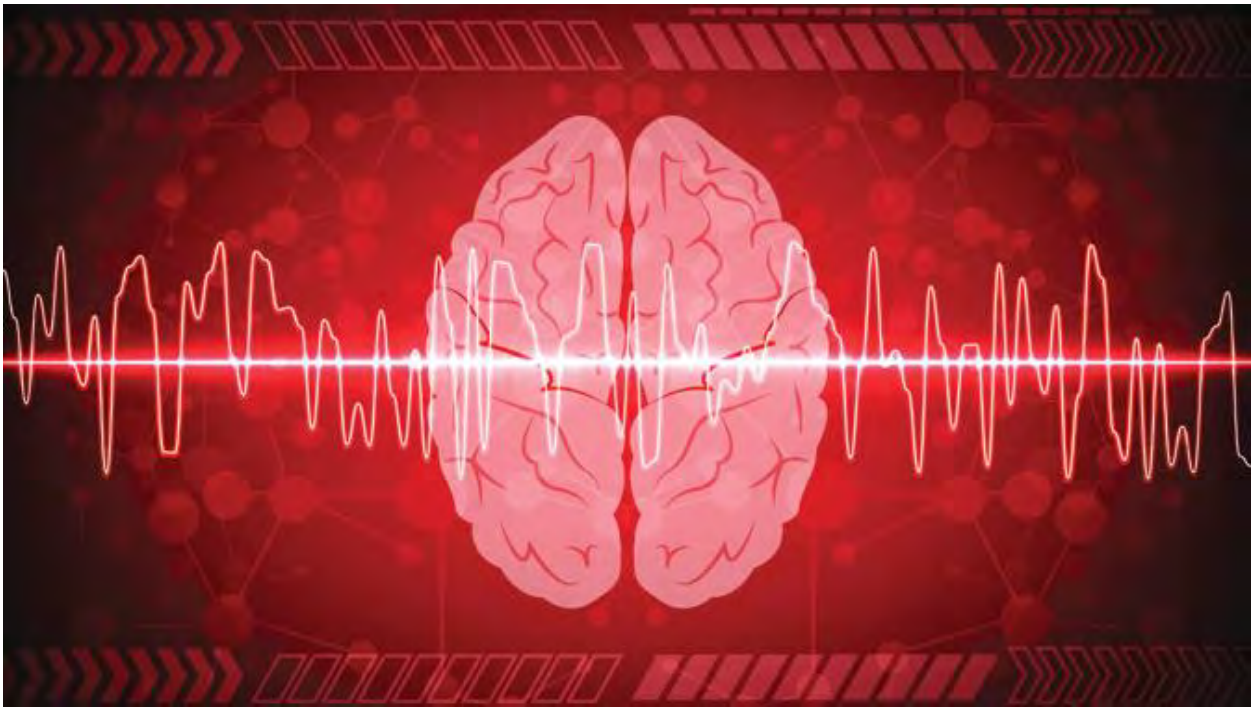
In the fall, the TED Institute caught up with Jonathan Rezak and members of the project to showcase this novel approach. Dr. Naomi Visanji, who is part of the research team at MDC, shared her enthusiasm, "The results we've been finding so far have us quite intrigued. We hope to be able to one day see these drugs tested in our patients."

While potential drugs have already been identified, rigorous preclinical testing in the lab is required before clinical trials can begin. In Dr. Visanji's words, "We're at this very exciting point with the potential for huge reward but we've got a lot of work to do in the lab before we get there."

To watch a short video about this project, visit https://youtu.be/l-1AC6CHSJM.

Pinpointing the Cause of Stroke

Mutation of KRAS gene, best known for its role in cancer, increases risk of hemorrhagic stroke.



Abnormal blood vessels in the brain known as brain arteriovenous malformations (BAVMs) have a 25% chance of bleeding and causing a hemorrhagic stroke.

An international team of researchers have shown—for the first time—that mutation of the KRAS gene can promote the development of abnormal blood vessels in the brain, increasing a person's risk of hemorrhagic stroke.

During a hemorrhagic stroke, a blood vessel in the brain leaks or ruptures, spilling blood into the brain and damaging surrounding tissues. This damage can lead to a variety of complications including difficulty speaking, paralysis and even death. Approximately 40% of all stroke-related deaths are attributed to hemorrhagic stroke.

Particular regions of the brain's vasculature can be more susceptible to ruptures or leaks. For example, up to 20% of hemorrhagic strokes in children are located in brain arteriovenous malformations (BAVMs), consisting of tangles of abnormal blood vessels. BAVMs are present in 15 out of every 100,000 people and are most often found in patients with no family history

of them. Beyond this, very little is known about BAVMs, including how they develop or why they are prone to rupture or leak during a hemorrhagic stroke.

"Even if they don't bleed, BAVMs can cause seizures or other stroke-like symptoms," says Krembil Scientist Dr. Ivan Radovanovic. "Patients aren't always good candidates for the few treatments that are available for BAVMs such as surgery or radiation. So it's really a condition that requires new therapeutic options, and understanding its cause will open the door to other possibilities."

Dr. Radovanovic and TGHRI Senior Scientist Dr. Jason Fish, along with researchers in Finland and Switzerland, co-led a study that provides new insight into the biology of BAVMs. Their findings were recently published in the prestigious *New England Journal of Medicine*.

As part of the study, the research team examined the genetic content of BAVM tissue that was surgically excised from patients. They found that BAVMs from 45 of 72 patients (~60%) contained a mutated version of the KRAS gene, best known for its role in promoting the growth and survival of cancer cells. The altered gene was specifically located in the cells lining the inner surface of the BAVMs' blood vessels, where it dysregulated the cell's behaviour and structure. Importantly, it weakened the 'glue' that holds the cells together to form blood vessels, potentially making the vessels more likely to leak or rupture.

The findings of the study not only reveal that KRAS plays an instrumental role in the development of BAVMs, but also identify new therapeutic targets to treat them. "Fortuitously, there are already cancer drugs used in clinical practice that dampen KRAS's effects on cells. The next step will be to test whether these drugs can reverse the effects of mutated KRAS in experimental models of BAVMs," says Dr. Radovanovic.

This work was supported by the Swiss Cancer League; Novartis; the European Research Council; the American Heart Association; the Canadian Institutes of Health Research; the Canada First Research Excellence Fund; the Canada Foundation for Innovation; the Ontario Ministry of Research, Innovation and Science; the Natural Sciences and Research Council of Canada; the Brain Aneurysm Foundation; the Department of Surgery and Division of Neurosurgery at the University Health Network; and the Toronto General & Western Hospital Foundation. JE Fish holds a Tier 2 Canada Research Chair in Vascular Cell and Molecular Biology. M Tymianski holds a Tier 1 Canada Research Chair in Translational Stroke Research.

Nikolaev SI, Vetiska S, Bonilla X, Boudreau E, Jauhiainen S, Rezai Jahromi B, Khyzha N, DiStefano PV, Suutarinen S, Kiehl TR, Mendes Pereira V, Herman AM, Krings T, Andrade-Barazarte H, Tung T, Valiante T, Zadeh G, Tymianski M, Rauramaa T, Ylä-Herttuala S, Wythe JD, Antonarakis SE, Frösen J, Fish JE, Radovanovic I. Somatic Activating KRAS Mutations in Arteriovenous Malformations of the Brain (link is external). N Engl J Med. 2018 Jan 3.

Cures from the Past

Learn how a serendipitous discovery made during World War II is impacting lupus patients today.

Antimalarials, such as hydroxychloroquine and chloroquine, are often prescribed to patients with lupus because of their efficacy and low toxicity.

It's impossible to predict how the present will affect the future. Case in point: when World War II soldiers were given a drug to prevent malaria, a deadly tropical disease that was causing more deaths than the enemy, no one could have predicted that the drug would also be a safe and effective treatment for a lesser known autoimmune disease known as systemic lupus erythematosus (lupus).

Lupus is a disease in which the immune system attacks a number of organs including the skin, joints, lungs and kidneys. About 80% of those afflicted with the disease develop skin rashes on sun-exposed areas of their body.

It was during the war that doctors noted that rashes associated with lupus cleared up when soldiers were treated with an antimalarial drug. Since the discovery, several studies have gone on to show that antimalarial agents also prevent organ damage and improve survival in patients with lupus.

Krembil Emeritus Scientist Dr. Murray Urowitz's latest study provides further evidence of the safety and efficacy of antimalarial agents in treating lupus.

The five-year study investigated some of the long-term effects of antimalarial agents on lupus outcomes in three patient groups: those who took antimalarial drugs more than 60% of the time; those who took antimalarial drugs less than 60% of the time; and those who did not receive antimalarial drugs. The three groups were regularly assessed for lupus symptoms, rates of disease flare ups, antimalarial drug related toxicity and the use of steroids to manage their symptoms.

The study results revealed that patients who consistently took antimalarial drugs had fewer lupus symptoms compared to those who did not. These patients also had noticeably fewer flare ups and needed lower cumulative doses of steroids. Importantly, only two study participants experienced adverse effects as a direct result of the antimalarial treatment.

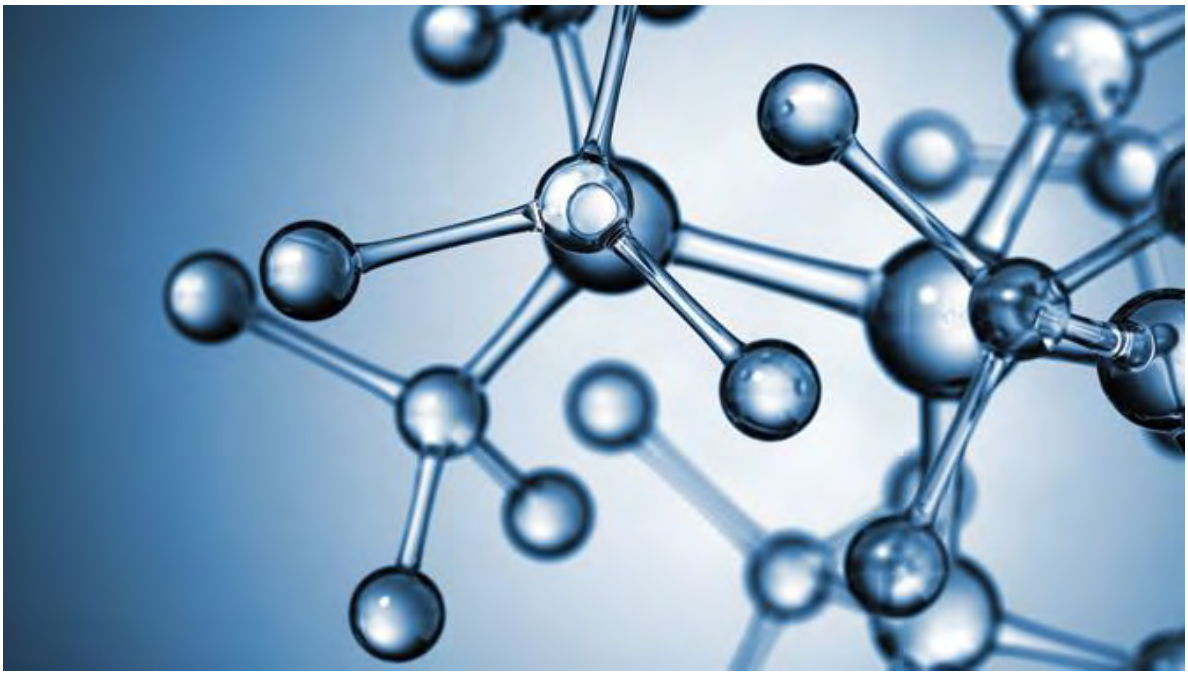
Explains Dr. Urowitz, "Our study highlights the importance of consistent intake of antimalarial agents early in the course of lupus. It builds upon the discovery that was made decades ago, which first identified the benefits of antimalarial therapy in treating lupus."

This work was supported by the Lou and Marissa Rocca, the Lupus Foundation of Ontario and the Toronto General & Western Hospital Foundation.

Pakchotanon R, Gladman DD, Su J, Urowitz MB. More Consistent Antimalarial Intake in First 5 Years of Disease Is Associated with Better Prognosis in Patients with Systemic Lupus Erythematosus). J Rheumatol. 2017 Nov 15. pii:jrheum.170645. doi: 10.3899/jrheum.170645.

A Big Deal for Alzheimer's

New therapy one step closer to reality as Krembil team partners with French company Servier.



A research team at the Krembil Research Institute has inked a deal with a multinational pharmaceutical company that could accelerate the development of a potential disease-modifying drug for Alzheimer's disease.

French drug company Servier has announced a new strategic research partnership agreement with Toronto-based Treventis Corp.—a biotech company founded by Krembil Director Dr. Donald Weaver—to co-develop a promising new therapeutic treatment already underway at UHN.

"This is a very big deal," said Dr. Weaver, a medicinal chemist, University of Toronto Professor, Canada Research Chair and neurologist who treats dementia patients at Toronto Western Hospital. "Drug discovery is a tremendously competitive field and this partnership demonstrates the ability of Krembil and UHN to achieve a level of excellence on the world stage. It also helps cement our place as one of the leading neuroscience research facilities in Canada."

As part of the collaborative agreement, researchers in Paris and Toronto will jointly develop compounds that target two key proteins known to play a role in Alzheimer's disease. Those proteins, called tau and beta-amyloid, are believed to have a deleterious effect on brain function when they misfold.

"We all have these proteins in our brains. When they misfold they become toxic to brain cells. They kill brains cells," said Dr. Weaver. "We have identified a class of compounds that we believe prevent beta-amyloid and tau from doing this."

Dr. Weaver's team has spent nearly two decades searching for a therapeutic strategy to slow or stop the neurodegenerative disease that affects more than 500,000 Canadians. There are currently no disease-modifying drugs for Alzheimer's on the market.

In 2013, Treventis was awarded $4.7-million in funding from the prestigious Wellcome Trust to investigate compounds, with the goal of designing a drug that can safely and effectively treat people with chronic neurological dementias, such as Alzheimer's. Funding from the Wellcome Trust, a British-based independent charity, is extremely competitive, difficult to obtain and is traditionally awarded to researchers in the U.K. "The Wellcome Trust funding allowed us to get to the point where we have a molecule that works, but needs some fine-tuning," said Dr. Weaver. "Partnering with a major pharmaceutical company like Servier is the next logical step."

Dr. Weaver is quick to also credit other funding agencies that have played a significant role in advancing the fundamental research to its current stage of applied drug discovery. Among the most generous contributors, he said, are the Alzheimer's Society of Canada, Canadian Institutes of Health Research, Toronto General & Western Hospital Foundation, The W. Garfield Weston Foundation, BrightFocus® Foundation and Krembil Foundation.

For its part, Servier has indicated that it is excited to partner with Treventis in taking this research to the next level. "We very much hope that this new collaboration will allow us to answer the huge unmet patient need for disease-modifying treatment of Alzheimer's disease, thanks to Treventis' unique and innovative technology," Christian de Bodinat, the Director of Servier's Center of Therapeutic Innovation in Neuropsychiatry, said in a statement. "We are very excited to be part of one of the first programs employing a dual approach in this field."

As part of the agreement, Servier will fund all research costs and maintain worldwide rights to develop and commercialize drugs advanced during the partnership. Dr. Weaver and his team are thrilled to partner with one of the most innovative pharmaceutical companies in the world. "I think it says that Servier has faith that we have a sound approach, excellent molecules and that there is a good foundation already in place," said Dr. Weaver. "This allows us to optimize and fine-tune the molecule and perform more elaborate biological evaluations."

Next steps for the research team include ramping up work in the laboratories at the Krembil Discovery Tower and JLabs, and attempting to identify a candidate for a Phase 1 clinical trial.

Dr. Weaver will discuss his research and this latest development on the January 23, 2018 edition of CBC's Ontario Today.

Dr. Donald Weaver, Director of the Krembil Research Institute and Senior Scientist at UHN, says major deal to develop Alzheimer's drug shows that UHN is a world leader in neuroscience research.

Wisdom of the Crowd

Pooling data from 30 resources enables large-scale research on how genes are regulated.

Since its release in 2011, Dr. Jurisica's mirDIP tool has been accessed by more than 13,500 unique users from 86 countries.

Crowdsourcing is a concept in which large groups of people work together to fulfill a common goal. The idea is that there is strength in numbers: as more people make individual contributions, the work that needs to be done is finished quicker.

In his own way, Krembil Senior Scientist Dr. Igor Jurisica has been applying a similar concept—called integrative computational biology—throughout his career. He is a pioneer in using this technique to create large-scale tools for the research community that integrate data from his own research and those of his peers. These tools offer pooled data to an unprecedented breadth and diversity that could not be created by one team alone.

Dr. Jurisica's latest release is an updated version of *mirDIP*, the microRNA Data Integration Portal that his group introduced in 2011. It uses sophisticated computational approaches to predict which genes are controlled by microRNAs, short RNA molecules that regulate the activity of specific target genes. Given this important function, the role of microRNAs in gene-related diseases such as cancer and arthritis are of great interest to the research community. Identifying which microRNAs modify which target genes would inform the development of new therapies to enhance—or block—these interactions.

To develop the mirDIP update, Dr. Jurisica and his research team summarized the data from 30 different microRNA prediction algorithms and databases. After applying complex

mathematical approaches to account for the different methodologies used by each of the databases, the team finalized a set of more than 151 million predictions—approximately 75% more predictions than the next largest microRNA prediction database—in this release focusing on human systems.

The team also developed an algorithm that assigns a score to each prediction. "This score provides users with a measure of the confidence of each prediction," explains Dr. Jurisica. "Researchers can now access these predictions in one place—accelerating the research pipeline towards creating new therapies for diseases."

The latest version of mirDIP is publicly available at http://ophid.utoronto.ca/mirDIP/.

This work was supported by the Krembil Foundation; the Ministry of Research, Innovation and Science; the Canadian Cancer Society Research Institute; the Natural Sciences and Engineering Research Council of Canada; the Canada Foundation for Innovation; the Canada Research Chairs Program; and IBM.

Tokar T, Pastrello C, Rossos AEM, Abovsky M, Hauschild AC, Tsay M, Lu R, Jurisica I. mirDIP 4.1-integrative database of human microRNA target predictions. Nucleic Acids Res. 2017 Nov 29. doi: 10.1093/nar/gkx1144.