THE QUEST FOR A CURE FOR RETT SYNDROME | GOING BACK TO THE FUTURE WITH ULTRASOUND | THE INNOVATIVE SPIRIT BEHIND STROKE DRUG BREAKTHROUGHS | HOW ONE FAMILY INVESTS IN OUR FUTURE

# KREMBIL

Krembil Research Institute | Neuro

## Alzheimer's drug could be on the horizon

Researcher Dr. Donald Weaver's pioneering work offers hope to worried Canadians

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# Brain research is a central mission at Krembil

Your brain is what makes you… you! It defines you as a unique, complex human being with fears, dreams, goals and aspirations. Comprising billions of brain cells linked by trillions of synaptic connections, the brain is the most complicated structure on the planet. That's why disorders of the brain and spinal cord (i.e., the central nervous system) are so devastating and the most difficult to treat of all human diseases.

It's for this reason that Krembil Research Institute investigators are focused on better understanding how the brain and spine function. Krembil also has extensive programs investigating arthritis and disorders of vision, and research in these areas will be the subject of subsequent magazines in this series.

The Krembil Research Institute is one of the principal research institutes of University Health Network – the largest research hospital in Canada. Krembil is also one of the top research institutes in Canada focusing on neurological diseases from both a basic science and clinical research perspective. Research at Krembil is directed at the development of management strategies and treatments for neurodegenerative diseases (Alzheimer's disease, Parkinson's disease), epilepsy, stroke, concussions, spinal cord injuries and disorders of the central nervous system. The Krembil magazine you hold in your hands today is one of three in a series that will be featured in *The Globe and Mail* this spring and highlights the cutting-edge research taking place at Krembil each and every day.

The need for pioneering curative therapies for these diseases is an immense medical, societal and economic priority worldwide. When a father suffers a major stroke or a mother with dementia loses cherished memories – and is unable to recognize her spouse or children – it is devastating for families and heart-wrenching for us. We, as a caring society, must address these life-robbing diseases. And we must take up this challenge sooner than later. Brain diseases are among the fastest-growing medical problems confronting society. As we age – and we now have more senior citizens than at any other time in human history – the burden of brain disease increases.

Curing brains is a lengthy, costly and exhausting pursuit. We thank the Krembil family and the many other patrons and donors who give so generously to support this important work. We also thank our patients for their trust and inspiration and for the privilege of working with them. Solving the riddle of the human brain and these diseases is a puzzle that fascinates and motivates us.

Researchers at Krembil are working relentlessly to understand and cure various neurological diseases. There are many exciting stories of progress and success emerging from our laboratories. Some of these stories are told in this magazine. But there are many more on the road ahead. This is only a sampling of what we do and what we are capable of. To learn more, please visit us online at DiscoverKrembil.ca.

Thank you for letting us share our passions and compassions with you.

Yours,

Donald F. Weaver,
MD, PhD, FRCPC,
*Director, Krembil Research Institute*


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# An iconoclast thrives in pursuit of knowledge

While exploring inflammation in the brain, Dr. Lyanne Schlichter finds the art in science

*Judy Gerstel*

Even before you arrive at neuroscientist Dr. Lyanne Schlichter's lab on the seventh floor of the Krembil Research Institute at Toronto Western Hospital, you see her work – her artwork, that is.

It's showcased on banners and elevator doors throughout the Krembil lobby.

One of the banners welcoming visitors to the three-year-old, ultramodern building reads, *Relentless*.

That succinctly sums up what the institute is all about in its pursuit of knowledge about the brain and how that can translate into cutting-edge health care.

But it's also a perfect description of Dr. Schlichter.

She's a Krembil senior scientist investigating the role of inflammation in the brain and is supervising research teams focusing on stroke, brain cells and electrophysiology, which is the field where she began her science career.

And she's relentless in going wherever her curious mind and honed instincts lead her, whether or not that makes her an iconoclast, which it almost always does.

The artwork is just one example of where her fertile mind takes her.

About six years ago, she was choosing images her trainees had captured on the microscope to include in papers they were publishing.

"What I suddenly realized was that these were so beautiful, it was a shame to just file away the ones we didn't use. So I thought, 'Why not have an art show?'"

She hung 36 very large pictures in a show she called *The Brain and Its Glue* at a coffee shop in Toronto's Cabbagetown neighbourhood, where she occasionally went to write papers, near her home.

Both her brain cell and spinal tissue art has been used in the corridors and elevator panels of the Krembil building.

Inflammation, the result of injury to the spinal cord and the brain, including stroke, is what occupies Dr. Schlichter's mind much of the time.

"I decided to start working on brain immune cells, the microglia," she says, "because almost nothing was known about them. And there was huge resistance to recognizing their role. They were considered the garbage collectors of the brain, clearing out dead cells and debris. So I received zero support and a lot of backlash," she says. "At first, granting agencies weren't interested in supporting the research. Some had never heard of microglia. But I persisted. What a battle! But we've done very well since then."

Now, she notes, 25 years later, "there's immense interest in microglia. They're implicated in every acute disorder of the brain."

It's the confounding aspect of immune cells and the inflammation they can cause in the brain that intrigues and challenges her. Is the inflammation helpful or harmful?

"The immune cells are double-faced," she explains. "They can go terribly wrong and attack the body. The question is, 'Why are these cells doing bad things in the body when the immune system is there to protect you?'"

That question is driving Dr. Schlichter's research, which also touches on diseases such as arthritis and cancer in which inflammation is, more and more, regarded as a key factor.

"There's not a simple explanation," she says. "But I believe there are two flavours of immune cells."

"The innate cells, like microglia, respond instantly; they're sensitive to any invader or damage (for example, bacteria) and they're ready to attack at once," says Dr. Schlichter.

"The adaptive cells, including lymphocytes," she explains, "are slower to act. They need to talk a lot back and forth." Lymphocytes are small white blood cells that play a large role in defending the body against disease. Dr. Schlichter and her team are exploring how these immune cells work in the brain: "How they function, how active they are, how they eat debris, how they interact with neurons and other cells in the petri dish."

She's also researching preclinical models of stroke, both brain hemorrhages and ischemic strokes.

"I'm looking at how inflammation develops in time and space from the site of the damage, what the cells are experiencing and how they are reacting."

Her job, as she sees it, is "to characterize the inflammation, so we have a better idea of how people can design treatment for the harmful effects of brain inflammation such as killing neurons or damaging the blood-brain barrier."

Understanding of stroke and inflammation has "boomed in the last 25 years," she says, "but hemorrhagic stroke is still grim. Fifty per cent of people die within the first year."

"This," she says, referring to her lab, her work and possibly what possesses her, "is about reducing damage and aiding recovery after stroke." ■

# Dr. James Eubanks is driven to find a cure for a disorder that afflicts young girls

Abby Congram, 17, has Rett syndrome, a rare neurological and developmental disorder that necessitates 24-7 assistance

*Shelley White*

In many ways, Abby Congram is a typical 17-year-old. She likes socializing with her friends, and she's interested in boys and music (Great Big Sea and Meghan Trainor are her favourite artists). Abby also loves horses – there are pictures of horses all over her room, and she rides them near her home in Stratford, Ont.

But unlike most of her peers, Abby is unable to speak. She can't use her hands to type or hold a pencil or eat. She needs 24-7 assistance for all the activities of daily living. Abby has Rett syndrome, a rare neurological and developmental disorder that affects girls almost exclusively.

One in 10,000 females around the world is born with Rett syndrome, a genetic disorder whose cause wasn't even known until 1999. Because it's neurologically based, symptoms vary greatly, but they can include seizures, the inability to speak, irregular breathing, poor thermoregulation (maintaining proper body temperature), an irregular heart rate, problems walking and the loss of purposeful hand use. Abby suffers from painful gastrointestinal problems and muscle weakness, which are also symptoms typical of Rett syndrome.

"Abby's muscle tone will suddenly go low one day and she can't walk, when yesterday she could," says Karen Congram, Abby's mother. "She has a lot of difficulty with what's called the autonomic nervous system, which controls her digestive system and her heart rate and her bladder, and so when the nervous system decides it's not working today, that creates a lot of pain."

Though Abby has been able to adapt to life with Rett syndrome – she attends classes with her peers at her local high school, and she's been learning to express her thoughts by using a special "eye gaze" communication device – Ms. Congram explains that kids with Rett syndrome often spend years unable to tell the world how they feel.

"These girls spend so many days in pain, and it's trying to manage that pain without having really specific communication about where it's hurting," she says. Ms. Congram and Abby have met many families of girls with Rett syndrome through her work on the board of the Ontario Rett Syndrome Association.

"For a lot of our girls, there are seizures or breathing problems. We have friends with kids in hospital on respirators because the breathing is controlled by your nervous system."

Rett syndrome is a disorder without a cure or any effective treatments to curb its debilitating and painful symptoms. But Dr. James Eubanks is working to change that.

Dr. Eubanks is a senior scientist at the Krembil Research Institute, and he's dedicated the last 15 years of his career to unravelling the mysteries of Rett syndrome. He recently received a research grant from the Ontario Rett Syndrome Association to aid in his team's hunt for drugs that can overcome the genetic mutations found in Rett syndrome. While the ultimate goal of research is to find a cure, Dr. Eubanks says, he and his team are also investigating whether drugs can be identified that could reduce or eliminate specific symptoms.

"Can we do something that will get rid of their epilepsy? Can we make their breathing better? Can we make their gastrointestinal difficulties better?" says Dr. Eubanks. "Can we find something that will make them speak again? We think these are achievable goals."

Dr. Eubanks met Abby more than a decade ago at a Run for Rett fundraiser when Abby was six years old. It was the first time Dr. Eubanks had met someone with Rett syndrome, and he invited Abby and her family to come to his lab. In the years since, she and her mother – along with other Rett syndrome kids and families – have visited Krembil multiple times.

"Abby definitely has a special bond with Dr. Eubanks; she recognizes him every time she comes back," says Ms. Congram.

Dr. Eubanks says that getting to know people like Abby is highly motivating for him and his team at Krembil.

"If you're working on a condition, it's important to know people who have the condition," he says.

"One of my students was [working on a drug] and one day she came in really, really excited and said, 'I got the [drug] to work.' And I said, 'Very good. But are you sure enough that you'll be willing to give that drug to Abby?' And she said, 'Not yet.' And I said, 'Come back when you're sure. There's still a long way to go.' And that's why it's so important," explains Dr. Eubanks. "It's one thing to find a drug and say, 'This is great,' but then when you actually know the person that the drug is going into, it gives you a little bit more impetus to get it right."

The search for disease-improving strategies stems from a groundbreaking discovery that showed even the worst neurological problems seen in Rett syndrome can be rescued in experimental genetic models. These genetic models have the same mutation of the gene called methyl-CpG binding protein 2 (MECP2) that causes Rett syndrome in 90 per cent of the people who have the disorder. The MECP2 gene is important because it provides instructions for creating a protein that is critical for normal brain function. Mutations of this gene prevent the protein from being made, and this causes problems in the brain.

*Karen Congram, right, helps her daughter Abby adapt to life with Rett syndrome, a genetic disorder that affects one in 10,000 girls around the world. Dr. James Eubanks, left page, has dedicated the last 15 years of his life to finding a cure.*

Using these genetic models, Dr. Eubanks' group showed clearly that if the missing or non-functional MECP2 gene is reintroduced, many of the existing neurological problems can not only be improved, but also in some cases completely returned to normal. "The experimental results show unequivocally that the condition, even at its most severe stages, can be reversed," explains Dr. Eubanks. "We weren't the first to show improvement could be attained – groups in Scotland had shown some positive outcomes before, but we were the first to show that the problems associated with several neural systems could be rescued. We showed that their epilepsy can be reversed, their thermoregulation can be dramatically improved, and [we showed] that their daily activity patterns can be restored to normal. These are each cardinal features seen in most Rett syndrome patients."

Unfortunately, the genetic model used for these studies was a product of a molecular genetic trickery that doesn't have applicability for humans. However, the crucial thing the experiment shows is that these symptoms of Rett syndrome are reversible, says Dr. Eubanks.

"For a lot of the other conditions that people are trying to cure, you actually don't know that they can be cured," he says. "You think they can, but there isn't any clear, concrete evidence that it can go from terrible to quite good. Here we have that evidence. We know it can happen; we just have to find a way that's clinically relevant."

Drug therapy is one potential curative method and gene editing is another. Dr. Eubanks notes that gene editing could possibly provide a more permanent fix (and it is an area his team is investigating), "but a drug is something that, in theory, could come quicker than genetic corrections," he says. Though a drug wouldn't permanently change the mutated MECP2 gene in Rett syndrome (patients would need to take it for life), a drug could reverse, even eliminate, the disorder's debilitating neurological symptoms, from seizures to motor difficulties to breathing regulation.

There are many different types of genetic mutations in girls with Rett syndrome, but Dr. Eubanks' current drug study is focusing on one particular type – "nonsense" mutations – which account for about one-third of all Rett syndrome cases. In nonsense mutations, a "termination code" is erroneously introduced into the MECP2 gene, which prevents the cell's machinery from making a functional protein. Without those critical proteins, the brain is unable to develop normally, and this results in Rett syndrome's many neurological abnormalities.

"These mutations put an errant stop sign where it shouldn't be," explains Dr. Eubanks. "But there are drugs that can help the cell's system say, 'This is a stop sign that doesn't belong; go past it.'"

In other words, the team is looking for a drug that will stimulate the cell to "read through" the mutation and reach the end of the normal protein coding sequence, so the correct proteins will be made. "By making a drug that will allow the read-through to proceed, we can actually make a functional protein, and allow the brain to regain proper function" he says.

## A DRUG TO REMOVE A GENETIC 'STOP SIGN'

Dr. Eubanks' research team is in the lab, looking at individual cells magnified hundreds of times. Dr. Eubanks points to a normal cell and then to an MECP2-deficient "mutant" cell.

The team has engineered the MECP2 protein so that when it binds to beacon sites in normal cells, you can see bright fluorescent dots that indicate a properly functioning protein. In the mutated cell, these green dots are absent. If the mutant cells are corrected, the bright fluorescence dots reappear. "We're trying to fix the molecular deficits of the mutant, so this is one of the ways we can see directly if it works," says Dr. Eubanks. "We will only see the fluorescence if the drug worked, and we make the correct protein."

In partnership with a medicinal chemist based in Chicago, Dr. Eubanks says they are testing both novel compounds and already-existing drugs that are used to treat other ailments.

"It's still got a few stages before we get into the clinical trials, but ultimately that's where we want to go," says Dr. Eubanks. ■

# How a repurposed drug is helping patients with spinal cord injuries

Dr. Michael Fehlings and his team have discovered that the drug named riluzole has a protective effect, and they have launched a large-scale North American clinical trial

*Renee Sylvestre-Williams*

If your brain is the computer that runs your body, then your spine is the cable that delivers the operating orders. So if your spine is damaged via injury or compression, then the entire communications network is compromised and in disarray.

"The outflow of the brain is through the spinal cord, so if you think of the spinal cord as being like part of a computer, then having a spinal cord injury is like disconnecting the cable from the computer," says Dr. Michael Fehlings, senior scientist at the Krembil Research Institute, vice-chair of research in the surgery department and head of the spinal program at Toronto Western Hospital and holder of the Gerry and Tootsie Halbert Chair in Neural Repair and Regeneration. Spinal cord injury (SCI) and its treatment is still a relatively new area of research. When the spine is damaged, says Dr. Fehlings, it affects every single organ system in the body.

Spinal cord compression is caused by injuries from accidents or conditions such as tumours that put pressure on the spinal cord, preventing messages from moving through the network cable. Spinal decompression is the term used for a variety of procedures that relieve the pressure placed on the spinal cord. Dr. Fehlings and his team have been able to determine why spine decompression surgeries can lead to neurological complications, and that a drug, riluzole, can have a protective effect. Based on these findings, the team has launched a large-scale North American clinical trial.

If you had an SCI, there weren't many treatment options 30 years ago.

"SCI will result in motor dysfunction, so, paralysis," Dr. Fehlings says. "It will result in sensory dysfunction. It will cause disordered sensory signalling, so you get neuropathic pain [chronic pain resulting from damaged nerve fibres]. It will cause autonomic changes [the unconscious control system that regulates bodily functions], so these are the changes that can occur in your cardiovascular control."

He also notes that "there can be immunological consequences, and patients will become immunosuppressed. It can affect your kidney function. It can affect your bladder function, your bowel function, your sexual functions. It essentially affects all parts of your body."

SCI typically is a two-step process, says Dr. Fehlings. The first is the original mechanical injury to the spinal cord, which he says commonly involves a fracture of the spine or a dislocation of the spine. "Then there are fractured bone elements that are putting compression on the spinal cord, and the vertical column is unstable. Then this initiates a process called secondary injury, which is a complex array of secondary molecular pathways that further exacerbate the extent of the injury."

He discovered in the 1990s that there was secondary degeneration of neurons around the injury, which often resulted from the surgery done to relieve spinal cord compression. He and his team theorized that surgery increased blood flow in the region, and this may cause further injury to the area – known as neuronal oxidative damage – from excessive sodium glutamate, an amino acid in the body. The theory was that this damage was most likely the cause for the neurological complications seen in SCI patients. This led Dr. Fehlings toward finding an agent that would protect these neurons from decline. Enter riluzole.

He was familiar with the drug, as it had been developed and marketed as an anti-epileptic to help treat seizures. The problem was, it just wasn't very good. "It's not a very good anti-epileptic, but it turns out that it's a dynamite neuroprotective agent," he says. "It blocks the right kind of sodium channels at the right dose."

The team started doing research with models of acute spinal cord injury, and later with models of non-traumatic injury. What they found is quite dramatic evidence of nerve protection in these models. Their work was subsequently validated in other laboratories.

The next step was conducting a Phase 1/2A clinical trial with 36 subjects with an acute spinal cord injury and 36 controls. They found significant improvement in the rates of neurological recovery and the extent of neurological recovery when riluzole is combined with surgery. Their current trial has some very promising results.

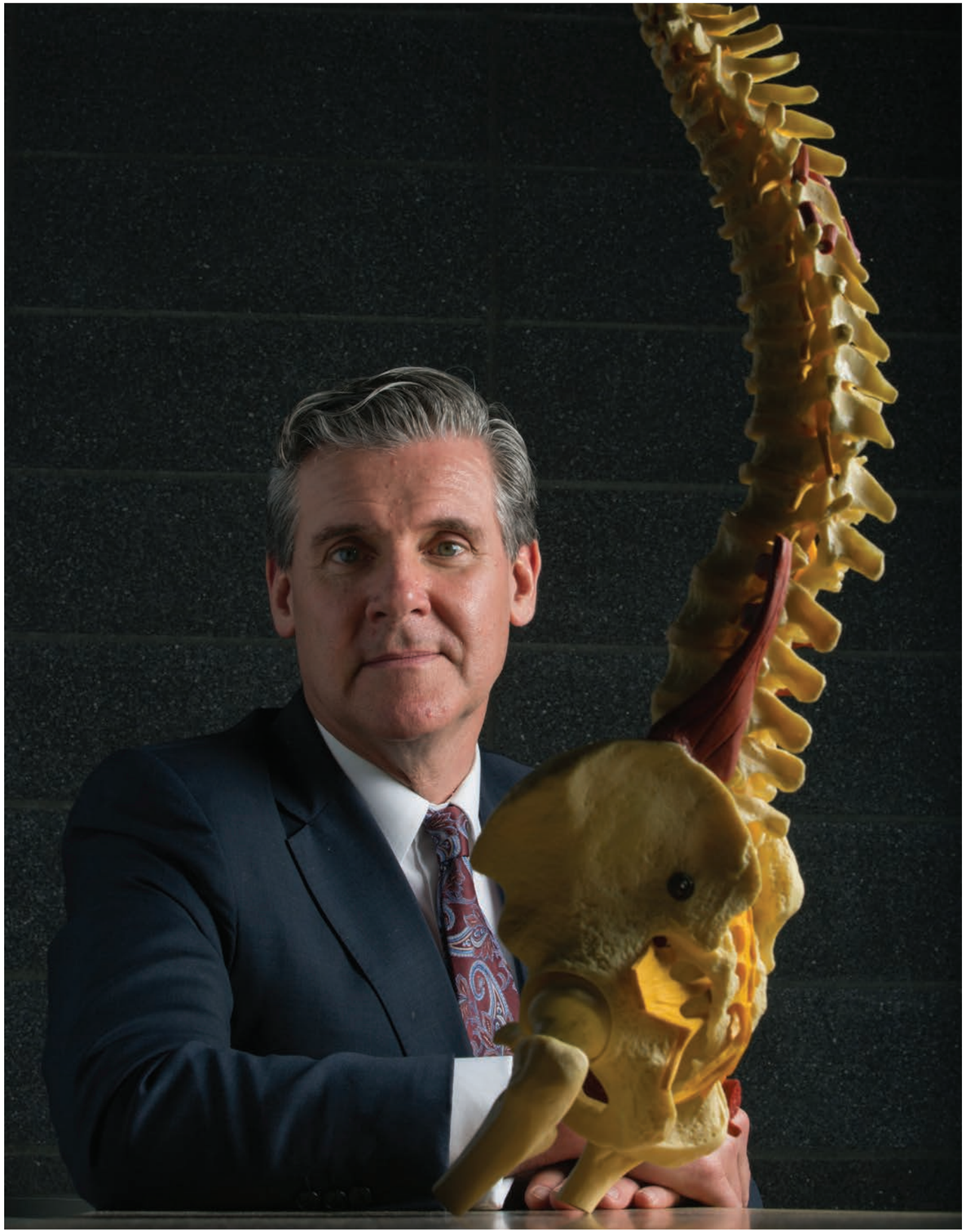
**"In the mid-1980s, the mortality rate for severe cervical spinal cord injuries was as high as 30 to 40 per cent. That's now been reduced to around 5 per cent."**

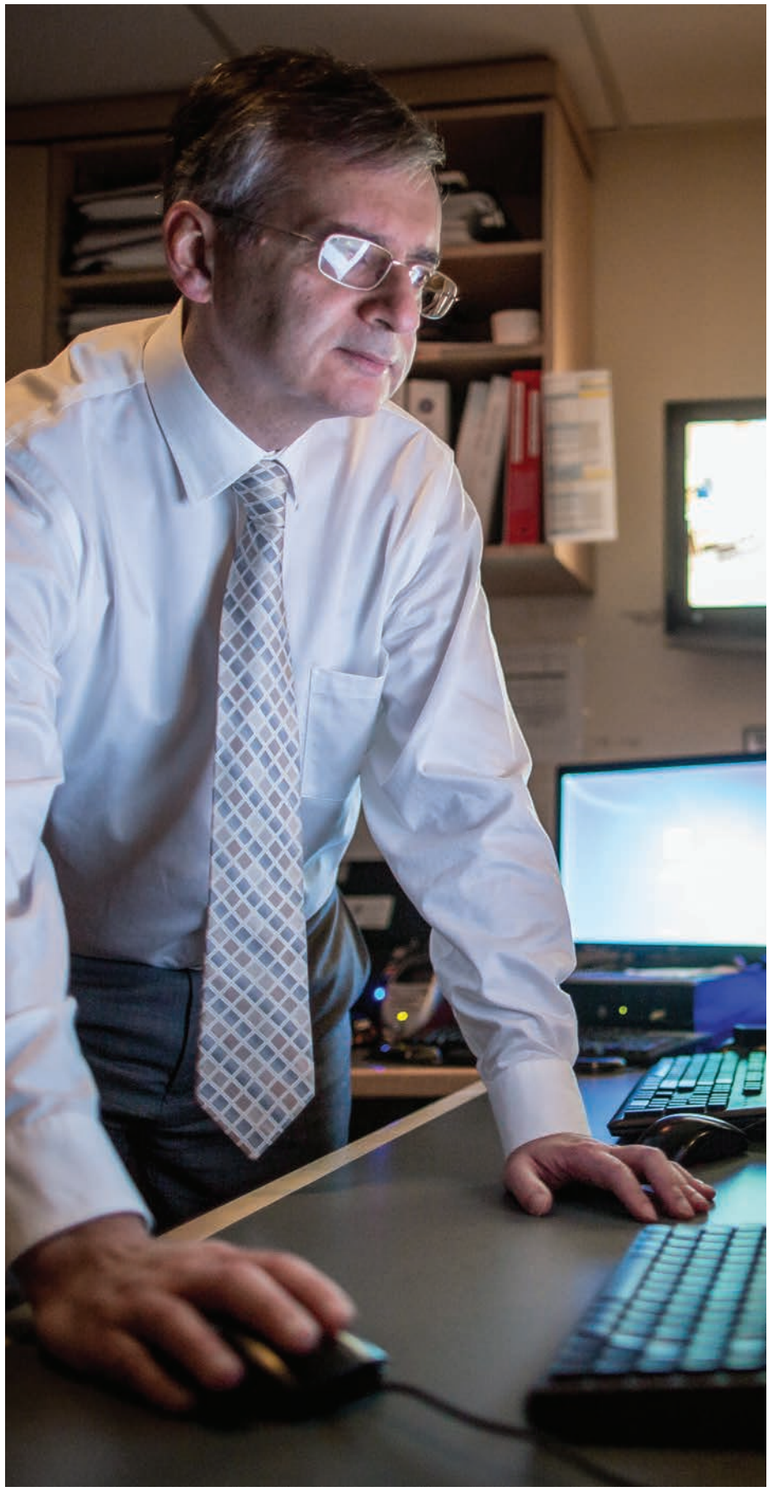
– Dr. Michael Fehlings

"We're focused on patients with an acute cervical spinal cord injury," says Dr. Fehlings. "The neurological levels are between C4 and the C8 levels of the spinal cord [the lowest levels of the cervical spine, near the base of the neck and affect the arms and hands]. Patients have to have evidence of a severe spinal cord injury."

This means that patients who have an acute spinal cord injury can now see better outcomes in treatment versus 30 years ago.

"In the mid-1980s, the mortality rate for severe cervical spinal cord injuries was as high as 30 to 40 per cent. That's now been reduced to around 5 per cent. The outcomes for patients are much better. We're seeing far more incomplete injuries as a result of improved safety measures and prevention, but also in terms of improved medical and surgical treatment," says Dr. Fehlings. "There are more patients who are walking away from injuries. We have made strides, so the outcomes are dramatically better." ■





# For Dr. Andres Lozano, it's back to the future via ultrasound

A researcher who helped pioneer the new helmet-like device creates major brain surgery breakthroughs that control tremor

*Bryan Borzykowski*

Dr. Andres Lozano has been fixing people's brains for about 25 years. And while he's one of the best neurosurgeons in the world, working on someone's brain always comes with risks, even for him. However, a recent game-changing breakthrough is dramatically reducing complications to the point where patients will be able to visit the hospital in the morning for non-invasive brain surgery and then go home that same day.

In some ways, the breakthrough isn't much of a breakthrough at all. Decades ago, researchers realized that ultrasound technology could be used to penetrate the human skull and destroy pathological tissue in the brain. The skull, though, is so strong that a normal jolt of soundwaves is essentially useless. "The skull tends to block ultrasounds," says Dr. Lozano, a senior scientist at the Krembil Research Institute and a surgeon at Toronto Western Hospital.

He and his colleagues knew, however, that ultrasound waves could make it through the skull if enough beams were used. Most would bounce off the bones, but a small fraction of the ultrasound energy would make it through. The problem? There wasn't a machine that could produce enough waves to bypass the skull.

That changed four years ago, when a medical device company, working with Dr. Lozano and others, developed a helmet-like apparatus, similar to an old salon hair dryer, which delivers 1,000 ultrasound beams into the brain. These beams can be focused on a single area of the brain and produce enough energy to destroy the problematic tissue. And it's all done without opening the skull. "It's really a technological advance," says Dr. Lozano. "And it's safer, effective and may reduce risk and costs."

For now, Dr. Lozano, who is a pioneering surgeon in treating Parkinson's, Huntington's and Alzheimer's diseases, is using this focused ultrasound technology to treat tremor, which causes people's hands to shake uncontrollably. It can be a severe problem, as the shaking can interfere with eating, washing, dressing and other daily necessities.

It is treatable, though. Typically, surgeons have to drill a hole in the skull and then put a needle into the brain to get rid of the problematic tissue. Another option is deep brain stimulation, where surgeons place an electrode on the brain, then connect it to a pacemaker in order to electrically modify the activity of the malfunctioning area. Naturally, any surgery requiring the brain to be touched, whether it's with a needle or an electrode, has a risk. Complications include hemorrhaging and infection.

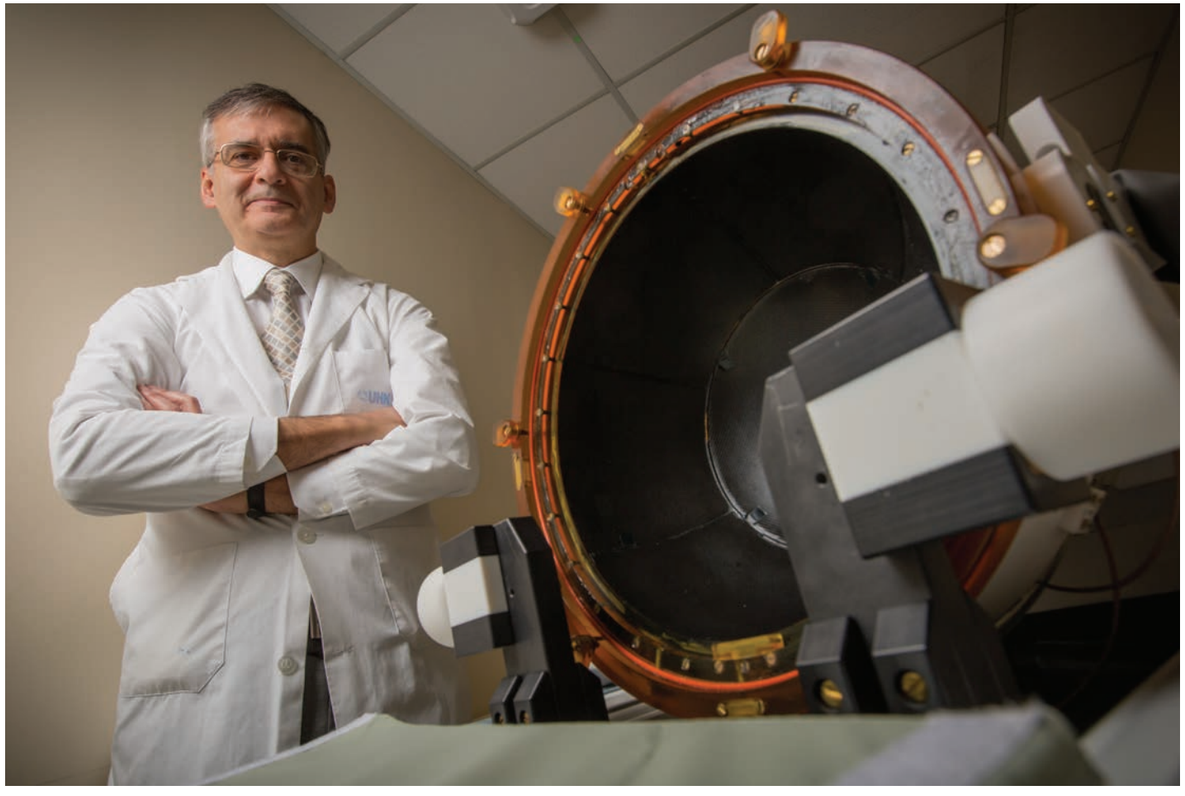
Using focused ultrasound technology eliminates these problems. Now, Dr. Lozano's patients are put through a magnetic resonance imaging (MRI) machine, while wearing the ultrasound helmet. The MRI allows him to pinpoint where on the brain ultrasound beams should be focused. The beams then burn the offending tissue. It's similar to using a magnifying glass used to burn a piece of paper with the sun on a hot summer day, he explains.

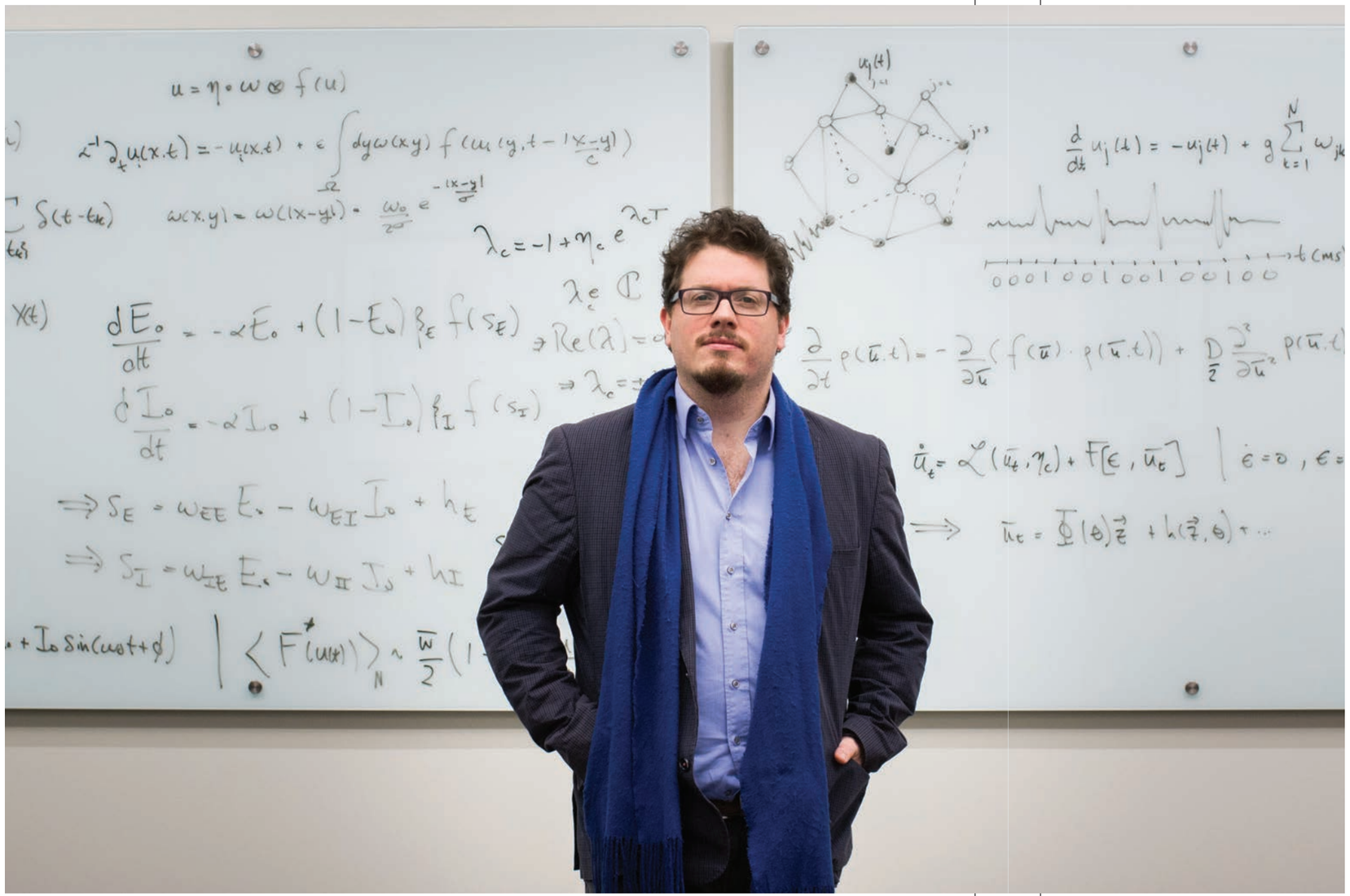
The zapping process takes about an hour, with two to three hours of preparation time beforehand. It works so effectively, and happens so quickly, that the patient, who is awake during the entire procedure, should have no tremors in the affected arm by the end of that hour. In fact, patients are kept awake because Dr. Lozano wants to see those tremors disappear, to make sure that he's focusing the beams in the right place. "As soon as we do these procedures, those tremors stop," he says. "And they appear to stay gone in most patients."

The technology is still in its early days, which is why Dr. Lozano only uses it to destroy tissue on one side of the brain. In many cases, there's bad tissue on both sides, which creates tremors in both hands. More testing needs to be done to ensure that using 1,000 beams twice, for both sides of the brain, is safe.

He does think the focused ultrasound technology will have much further reaching applications in the future, helping to eliminate epilepsy and treat Alzheimer's. With Alzheimer's, patients develop protein deposits in the brain that are thought to cause problems with memory and cognitive functions. In preclinical models of Alzheimer's, ultrasound can be used to clear those deposits. Dr. Lozano is currently collaborating with other neuroscience researchers in Toronto on an Alzheimer's-related ultrasound trial to see if this technique could be useful in patients.

Today, Dr. Lozano, who holds the R. R. Tasker Chair in Stereotactic and Functional Neurosurgery and the Dan Family Chair in Neurosurgery, can only do one or two procedures a month, as the procedure is not yet covered by the government. Once that changes, and he hopes it will soon, he'll likely be performing these daily. "We want to help more people," he says. "People see it as not as dangerous, and therefore those who may have not wanted to go through surgery before, [now] find this more appealing. It's potentially going to have a major impact on people's lives." ■





# How mathematicians are unlocking the secrets of the human brain

Dr. Jérémie Lefebvre combines computer and brain power to discover how our minds work

*David Israelson*

The mysteries of the mind may challenge philosophers, but to Dr. Jérémie Lefebvre the challenge is different – the brain is the ultimate computer math puzzle.

"Think of the brain itself as a computer – a biological computer. Instead of using software or hardware, it uses wetware," says Dr. Lefebvre, a neuroscientist and mathematician at the Krembil Research Institute in Toronto.

Dr. Lefebvre's lab at Krembil studies computational neuroscience and non-linear dynamics.

It's called the SYNC lab – it synchronizes studies and stimulates corroborative work around the world among researchers working in a variety of disciplines. Dr. Lefebvre and his team develop and analyze models of neural circuits to better understand the brain and how it is affected by neurodegenerative diseases.

"This is where mathematics and physics come in," he explains. "The neurons in the brain are actually doing computations and calculations, and we're trying to crack the code."

Using [data from] all the most up-to-date information-gathering techniques, such EEGs, scanners and fMRIs that are used by his colleagues and collaborators, Dr. Lefebvre and members of his SYNC lab team assemble data about what's actually going on in the brains they examine.

That's only the beginning of the research. He says it's "interesting" to see a part of the brain light up when, say, a patient raises an arm, but the SYNC lab is looking for more.

"This is where my work starts: we look at what the brain is doing and how it's doing it, as opposed to where in the brain it's going on," Dr. Lefebvre explains.

The goal of the one-year-old lab's clinical research is to develop mathematical and computational descriptions of neural systems. The SYNC team wants its work to continue to stimulate interdisciplinary work and collaboration among experimental, clinical and theoretical scholars in neuroscience and medicine.

"In particular, what I'm working on is brain stimulation. Right now, there's a resurgence of interest in the use of electrical fields to shape the activity of neurons in the brain," says Dr. Lefebvre. He's been interested in brain research since childhood, wondering why the brain patterns of his sister, who has cerebral palsy, caused her severe disability.

"I combined my curiosity with my interest in math," he says. He cautions that research takes a long time to yield answers.

In July 2016, Dr. Lefebvre and the SYNC lab announced what their computational model is revealing so far. It shows that in addition to sustained and recurring stimulation, exposure to intense, high-frequency brain stimulation can cause brain waves to accelerate – a sign of improved information processing and awareness.

"These results open new perspectives. Information gleaned from our model lays the groundwork for future studies investigating how temporary treatment with brain stimulation can cause lasting effects in neuropsychiatric diseases with unbalanced brain activity, including major depression, Parkinson's disease and schizophrenia," he says.

"Neurons are using electricity to communicate, so the idea is to use electricity to manipulate or control those neurons, [to] tell them what to do. Maybe we'll be able to tell those neurons to do things differently, to restore healthy function."

While deep brain stimulation is already a form of treatment for Parkinson's, SYNC's research hopes to yield more comprehensive understanding, to improve its precision and effectiveness.

"We actually don't know how it works yet. We don't know how the electrical stimulation patterns interact with the different networks of the brain."

Another aspect of the computational science at the SYNC lab is to analyze neural data gathered from patients, to find the "signature" elements common to particular brain diseases. This information is shared with researchers around the world.

> **"This is where mathematics and physics come in. The neurons in the brain are actually doing computations and calculations, and we're trying to crack the code."**
>
> – Dr. Jérémie Lefebvre

"We're developing models of diseases and how they work, to go beyond just applying some form of drug. If we understand the mechanics of the disease, we can be more efficient," Dr. Lefebvre says.

As part of their groundbreaking study, Dr. Lefebvre and his team build computer models of neural networks, which they can mix and manipulate on screen.

"We can see what happens if we take one component of a model out – is it similar to what we see in human data?" It's a less risky and potentially more accurate way of pinpointing what parts of the brain are linked to neural disorders.

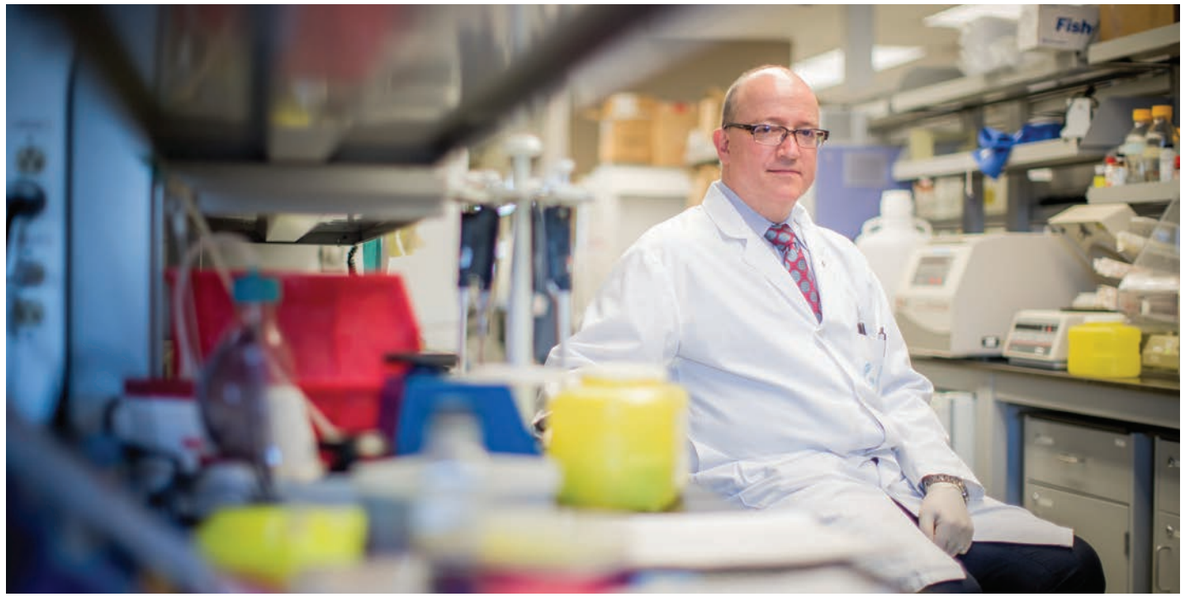
The SYNC lab has the ability to tap into the most high-powered supercomputers and the latest state-of-the-art software.

"And we use the most sophisticated tool – mathematics," Dr. Lefebvre says.

"We devise equations by hand, and we use the computer to see if we can't solve them analytically. We collect the data that's gathered throughout various clinical labs and try to compress it and chunk it into something that makes sense."

Unlike research that relies on ultra-expensive technology, "here we can do a lot with little resources. We can go quite far with moderate investments, because math does not require expensive equipment. Most of the funding we require goes into recruiting the best people," he says.

"The brain is the most complicated object in the known universe. Being able to crack that device is most satisfactory and using mathematics to do it is something that I find profoundly elegant." ■



# The stakes are high for an acclaimed cerebrovascular surgeon searching for a stroke drug

Surgeon and entrepreneur Dr. Michael Tymianski is developing a drug that reduces brain damage associated with stroke

*Shannon Moneo*

In Canada, stroke is the third-leading cause of death, after cancer and heart disease, striking down more than 13,000 people each year and leaving thousands with life-changing disabilities. In 2012, the World Health Organization reported that strokes killed 6.7 million people worldwide.

And yet, with more than 1,000 drugs tested in preclinical models, with more than 200 drugs tested in human trials and with billions spent by multinational pharmaceutical companies, a drug to mitigate the effects of stroke remains elusive. Only the clot-busting medication, tPA, is currently approved – but under highly restricted conditions. But that could be old news soon.

Since 2002, Dr. Michael Tymianski, head of the Division of Neurosurgery at University Health Network and a senior scientist at the Krembil Research Institute, who also holds the Harold & Esther Halpern Chair in Neurosurgical Stroke Research and the Chair in Innovations for the Head of Division of Neurosurgery, has been testing the drug he has named NA-1. In ongoing human trials, the drug has reduced the amount of brain damage incurred during a stroke by about half, without serious side effects.

"We already have data to show that the drug is effective," Dr. Tymianski says. "I've seen it work in lab models and in people."

NA-1 is what's known as a neuroprotectant, a substance that can preserve brain neuron function and structure under conditions of stress, such as in a stroke.

When a stroke occurs, brain cells die at a rate of 1.9 million per minute. NA-1 can prevent that, but the drug must be administered before the stroke damage is completed.

A physician since 1987, Dr. Tymianski entered the neurosurgery training program at the University of Toronto in 1988 and completed clinical fellowship training in cerebrovascular surgery at Toronto Western Hospital in 1995 and then for a further year in Phoenix, under renowned neurosurgeon, Robert Spetzler. As a specialist in cerebrovascular surgery, Dr. Tymianski went on to conduct the world's first outpatient surgery for aneurysms, and he is one of the few surgeons, anywhere, who uses laser surgery to control the brain's blood flow to prevent stroke. In December, Dr. Tymianski was made a Member of the Order of Canada by Governor General David Johnston. Dr. Tymianski was cited, "For his contributions to neuroscience, particularly through his leadership in investigating new mechanisms to protect the brain following a stroke."

"As a cerebrovascular surgeon, I treat conditions that lead to stroke. We all know someone who's been touched by stroke. It's a devastating disease," he says.

Stroke targets a Canadian every nine minutes; 405,000 Canadians are living with the effects of stroke, be it loss of memory, speech or mobility. The costs of treating stroke and poststroke care are approximately $3.7 billion each year in Canada. As well, a recent Canadian report on strokes revealed that having a stroke more than doubles the risk of developing dementia. One in three Canadians will develop stroke, dementia, or both, the study says.

**"As a cerebrovascular surgeon, I treat conditions that lead to stroke. We all know someone who's been touched by stroke. It's a devastating disease."**

**– Dr. Michael Tymianski**

Dr. Tymianski's challenge has been that although stroke drugs appear to work in lab models, decades of research by major pharmaceutical companies have not yielded a drug that helps people. Therefore, in 2003, he started his company NoNO Inc., operating within Krembil, to develop NA-1 so that patients may benefit. He continues his unflagging mission to secure funding that would enable the conduct of new and original clinical trials that will succeed, where the major pharmaceutical companies haven't. He does this while still saving lives as a surgeon.

"Developing a drug for stroke is an enormous challenge. Everyone else has failed, and therefore the roadmap to success has not yet been travelled," he says.

If someone is developing a new blood pressure medicine, or even new software, they can get advice from someone who's done it successfully, Dr. Tymianski notes. When it comes to the challenge of stroke, there is no playbook.

But for this surgeon-scientist-entrepreneur, known for his deft skills with a scalpel or a laser, the importance of creating a stroke drug cannot be overstated. "It [NA-1] would help a lot more people than I ever could as a surgeon," he says.

Around 300 people have been given NA-1 in various clinical trials in Canada and the United States since 2007. Results have been encouraging, and since last year the Tymianski team has stepped up to final clinical trials to enable them to apply to Health Canada and the U.S.'s Food and Drug Administration (FDA) for approval to get NA-1 on the market as a stroke treatment.

NA-1 is particularly important in a country like Canada, where the time it takes to transport patients from small or isolated communities to larger hospitals with stroke centres can be longer than a 20-minute ambulance ride in the city. "NA-1 will give more time," Dr. Tymianski says.

In 2015, one of Dr. Tymianski's trials began. It will run until sometime in 2019, with the aim of treating more than 500 patients. Those experiencing stroke will receive NA-1 from paramedics via intravenous bags in an ambulance or on-site in the double-blind experiment. Double-blind means that the paramedics, hospital staff and patients don't know who is receiving the drug or a placebo. The gold standard when it comes to trials, the double-blind method prevents the placebo effect or observer bias from influencing outcomes. After the stroke patient is brought to the hospital, the hope is that NA-1 has preserved their brain cells. "The trials are proceeding smoothly. So far there have been no serious safety concerns," Dr. Tymianski says.

Dr. Tymianski's team is embarking on a second even more ambitious trial, which has just started, and is taking place in 35 hospitals across Canada, the U.S., Europe, South Korea and Australia. It also has a 2019 finish date and is being led by Dr. Michael Hill, a neurology professor and director of the Calgary Stroke Program, and Dr. Mayank Goyal, a professor of radiology at the University of Calgary.

Drs. Hill and Goyal were part of the Alberta team that led a recent and very promising trial, where endovascular therapy was used on more than 300 patients in 22 sites worldwide to remove blood clots in the brain, thus restoring blood flow to the vital organ.

The three doctors have known each another since the mid-1990s, and all have dedicated their professional lives to the treatment of stroke.

In this second trial, NA-1 will be used in patients undergoing endovascular thrombectomy, once again in a double-blind trial. The first patient to be enrolled was planned in Calgary.

The stakes are high. "If we win this, it's a big win, not just for stroke but for neuroscience," Dr. Hill says.

"One thing that some scientists do, they're overly exuberant about their pet projects. But some conditions are so challenging to deal with. They're humbling. My cautious tone doesn't mean I'm lacking conviction. It's an appreciation that the road is still fraught with challenges," Dr. Tymianski says.

If the destination is reached, Dr. Tymianski notes that NA-1 has a very fundamental method of action and because of that may also be effective with traumatic brain injuries, epilepsy and, as related to stroke, Alzheimer's disease.

"We have something that we truly believe in," Dr. Tymianski says. "We have a social responsibility not to let go."

Based on the already very promising results, combined with his great desire to tame the damage strokes have wrought, Dr. Tymianski expects that results from the two trials will be life-changing and life-saving. ■

## Understanding how the breakthrough drug NA-1 works

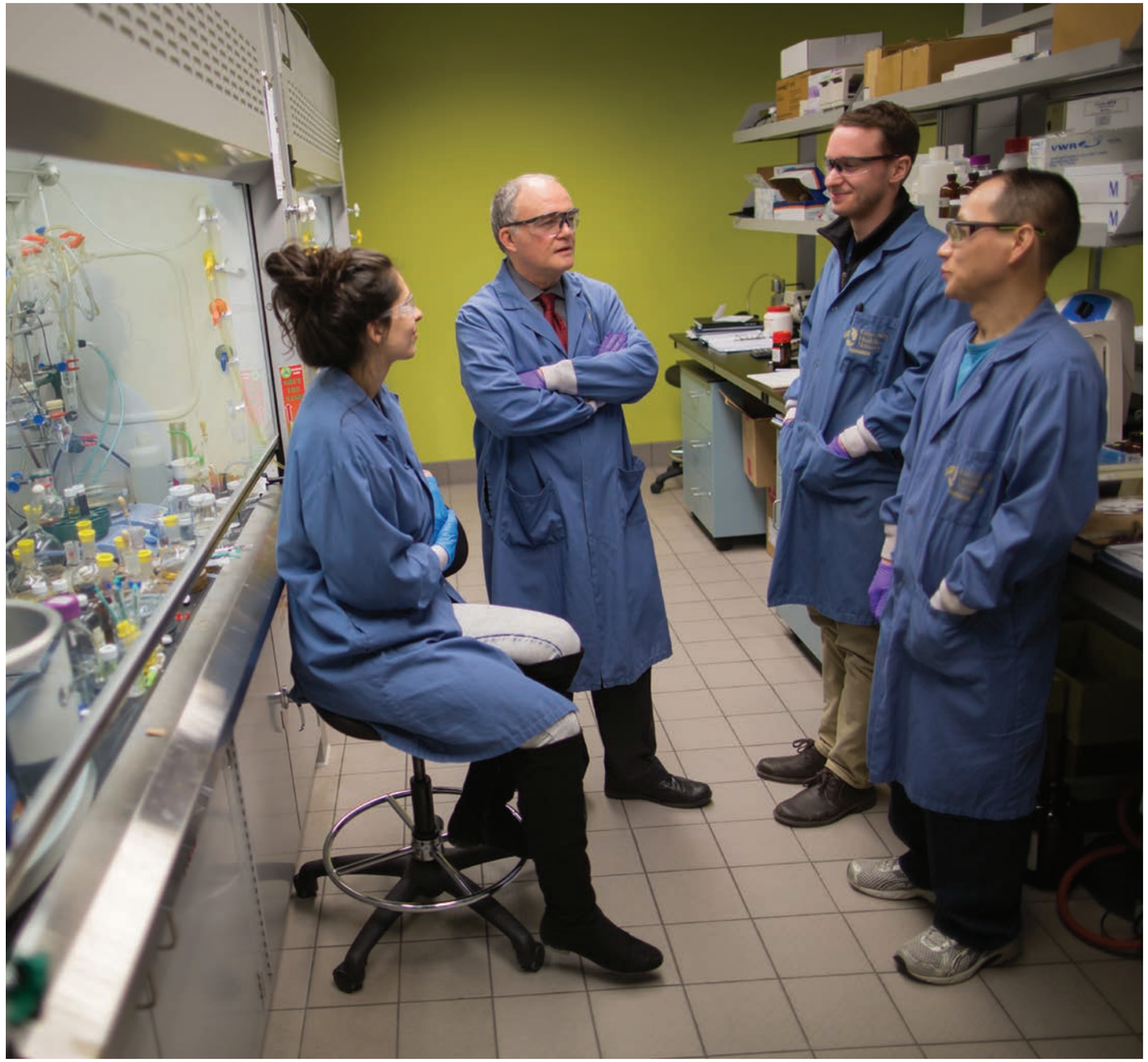
Strokes come in two types:

- In North America, 85 per cent are ischemic and occur when a blood vessel supplying blood to a region of the brain suddenly becomes obstructed.
- The other 15 per cent are hemorrhagic and happen when a weakened vessel ruptures and bleeds into surrounding brain.
- NA-1 is being tested for efficacy on ischemic strokes. The average adult brain has about 86 billion neurons (the "grey matter"), with more than 60 trillion connections (synapses) joining them together. After a stroke, brain cells die at a rate of 1.9 million per minute. Every 30 minutes, a favourable outcome diminishes by 10 to 20 per cent, which is why stroke victims can be left blind or paralyzed. What NA-1 does is keep brain cells alive for a number of hours, until hospital treatment is available.

Dr. Michael Tymianski began his NA-1 odyssey in the early 1990s. By 1999, he and his team identified a protein found in neurons called PSD-95. When a stroke happens:

- Neurons release a lethal amount of neurotransmitters, one of them being glutamic acid.
- A blocked brain artery prevents necessary nutrients (like glucose and oxygen) from reaching the brain cell, nutrients which are critical for preventing damage induced by a massive dose of glutamate.
- The glutamate binds to the neurons' receptors, opening the door to cell-killing reactions. One such chemical is nitric oxide (NO), which kills neurons.

Dr. Tymianski's team determined that PSD-95 was the mediator between glutamate receptors and the manufacturer of nitric oxide, known as nNOS (neuronal nitric oxide synthase). If PSD-95 was stifled, glutamate receptors couldn't then activate nNOS. So, if the nNOS isn't activated, the brain cell destroyer NO cannot be produced. NA-1 removes PSD-95.



# A relentless research quest to end Alzheimer's disease

The pioneering work of Dr. Donald Weaver and his team on a groundbreaking drug offers hope to Canadians

*Shelley White*

Dr. Donald Weaver's goal in life is to never have to give bad news to an Alzheimer's patient and their family again.

Over the 30 years he's been a neurologist and Alzheimer's disease (AD) researcher, Dr. Weaver has grown accustomed to informing patients and their families about AD's grim prognosis.

"Last week I met yet another family that I really felt badly for," says Dr. Weaver, sitting in his office at the Krembil Research Institute in Toronto, where he's director.

"This family brought in a loved one who is 53 years old, well-advanced in AD. They had seen their general practitioner, who told them, 'Go see a neurologist, now.' So the family comes in, and they ask, 'Do you have a pill that's going to make this all better?' And you have to say, 'No, I don't.' I tell them what they have and I tell them what the prognosis is. And the room is filled with tears," says Dr. Weaver.

"I've been doing this for decades, and I'm tired of doing it. Someone needs to come up with a drug," he says.

Alzheimer's is a disease that strikes fear into people's hearts, largely because its progression cannot be stopped. No matter when someone is diagnosed, there is no escaping the fact that a patient's memory loss and cognitive decline will continue until the patient passes away.

Currently, there are no disease-modifying drugs for Alzheimer's available, and yet it's one of the fastest-growing diseases. There are more than 550,000 Canadians living with AD or other forms of dementia today, and it's estimated that in 15 years, that number will jump to more than 900,000.

But what if there were a drug that could stop AD in its tracks and prevent the disease from progressing?

It's a prospect that could be a reality in only a few years, thanks to the pioneering work of Dr. Weaver and his team at Krembil. They are working on a groundbreaking, disease-modifying Alzheimer's drug that could profoundly affect the lives of hundreds of thousands of Canadians and millions worldwide. Finding that drug is Dr. Weaver's mission in life.

"When we hire new people, I say, 'We only have one goal: getting a drug that works for Alzheimer's,'" says Dr. Weaver. "It's not producing a pretty paper in a journal. To me, that's just a stepping stone. Our goal is the drug. Our goal is helping people."

## UNLOCKING THE SECRETS OF MISSHAPEN PROTEINS

Dr. Weaver and his team began their research by analyzing the abnormal proteins implicated in Alzheimer's disease – beta-amyloid and tau. The shape of a protein is controlled by a process called "folding," but in patients with AD, these folds are misshapen.

"Proteins are dynamic. Proteins move. They flex," explains Dr. Weaver, who as a medicinal chemist and a neurologist has a unique skill set. "And for reasons that are unclear, they twist into a particular shape, and that's the 'bad-news' shape. When proteins get into that shape, an aggregation or 'clumping' process starts."

This clumping creates the signature plaques and tangles found in the brains of AD patients. Although scientists aren't absolutely sure what causes the cell death and tissue loss that leads to progressive cognitive decline, these misshapen aggregates are the prime suspects.

Dr. Weaver notes that everyone may have some beta-amyloid or tau, but "as long as it's sitting there and it's by itself, you're good," he says. "But for some people, there are just a lot of them. They clump."

Why the misshapen proteins aggregate in one person and not another is one of the mysteries of the disease, he adds.

"There are certain risk factors – family history, repetitive head trauma – but on average, it's just bad luck."

The first major breakthrough in Dr. Weaver's lab came when the team was able to identify a shape found in both beta-amyloid and tau proteins that predisposes them to misfold, which they called the Common Conformational Motif. This particular shape appears to trigger the "cascade" of clumping proteins found in AD.

> **"When we hire new people, I say, 'We only have one goal: getting a drug that works for Alzheimer's.'"**
>
> – Dr. Donald Weaver

Having studied and modelled the folds that predicate the clumping process, the team began work on the next step: finding a drug that would impede the clumping process.

Dr. Weaver's lab is split in half – an academic half and a commercial half. The commercial half is called Treventis, and this is where the drug is being developed.

The key to developing a disease-modifying drug is to find a drug-like chemical that binds to the misshapen protein when in its singular or "monomeric" form, preventing clumping from happening in the first place.

To illustrate, Dr. Weaver gives the example of building a log cabin:

"When you stack logs, you have a log and then you put on the next layer and the next layer. But if I put a bump on the log, the next one doesn't sit correctly, and I can't stack it," he says. "I always tell people we're trying to invent a molecule that's a bump on a log. We're trying to come up with a molecule that's a bump on beta-amyloid and tau."

By identifying a compound that will act as a physical barrier preventing the clumping process, the team could then create a drug that would halt the progression of Alzheimer's.

"If it's given preclinically, so before the person has symptoms, then we would be curative. If it's given after you actually have symptoms, then we are disease-stabilizing," says Dr. Weaver.

"A drug that targets both beta-amyloid and tau, and prevents their misfolding should be disease-modifying at any stage in the disease, right from presymptomatic to full-blown."

## THE SEARCH FOR THE ELUSIVE 'BUMP ON A LOG'

Down the hall from Dr. Weaver's office, chemist Dr. Christopher Barden clicks open a file. It's a 3-D model of the "bad-news" shape of a misfolded beta-amyloid protein. The model is an intricate network of matchstick-like molecular bonds in white, red and blue, standing out vividly from the black background. Nestled right in the middle of the protein is a rectangular cluster of grey and red spheres, looking a bit like a spaceship stuck in a spider's web.

That cluster is a model of a new chemical entity, and it's one of the promising compounds that could be the elusive "bump on a log," binding with the protein to stop the progression of AD.

Computer modelling technology has enabled the team to test millions of chemical compounds to see which ones will bind best with beta-amyloid and tau, says Dr. Barden. Doing testing on that scale with real proteins and compounds would be next to impossible.

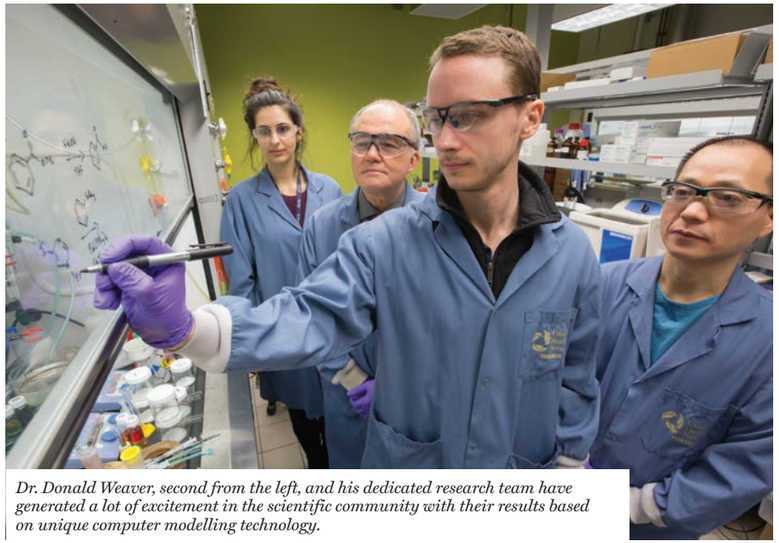
"The problem with diseases like Alzheimer's is that this misfolded protein is by its very nature not going to stay in one place in that particular shape," he says. "It's intrinsically disordered, and so it's hard to get a picture of that. What we've done instead is to create these computer models to stand in for the picture we would otherwise have for drug design."

Since identifying the misshapen proteins, Dr. Weaver says the team has done an "in-silico," or in-computer, screening of 11.8 million compounds to see what would stick.

"We basically threw everything at it, saying, 'We've got to find something that binds to this shape,'" says Dr. Weaver. "We got 130 hits. We looked at them and then once we got one that really bound well, we synthesized analogues of it. We probably did a thousand variants on the first lead."

As the computer model narrowed the options down, the discovery process went from virtual to physical. Promising chemical compositions were created in the lab, so they could be tested in vitro to see if they really would bind to beta-amyloid and tau.

"We have to make the compound and then test the compound. If it doesn't work, it's back to the drawing board," says Dr. Weaver.



*Dr. Donald Weaver, second from the left, and his dedicated research team have generated a lot of excitement in the scientific community with their results based on unique computer modelling technology.*

"If something fails, you get knowledge from it."

After 11 million compounds tested in silico and dozens of compounds tested in the lab, Dr. Weaver says they are down to a final 20 to 30 promising compounds.

"We hope to say, 'This is our molecule' and do the preclinical work in 2017 and then be in a human trial by 2018."

The team's innovative research has generated a lot of excitement in the scientific community and beyond. They've been invited to present their findings at the Alzheimer's Association International Conference for two years in a row and garnered media attention worldwide.

Dr. Weaver notes that researchers in other parts of the country (and the world) are also in the race to solve the Alzheimer's riddle, with some taking different approaches. But for Dr. Weaver, that proliferation of ideas can only be a positive.

"There are other people working on other avenues, and so I would like to think that in five to 10 years, someone – maybe not us, but hopefully us – will have a disease-modifying drug out there. And that would be huge."

Dr. Bradly Wouters, executive vice-president, science and research at University Health Network (UHN), says that Dr. Weaver's research is important because Alzheimer's affects such a large percentage of the Canadian population and will continue to grow as the population ages.

"Currently, there are no effective treatments to either stop or reverse its progression," says Dr. Wouters. "Dr. Weaver's research is aimed directly at identifying novel therapies that can stop the progression of Alzheimer's."

**"Dr. Weaver's research is aimed directly at identifying novel therapies that can stop the progression of Alzheimer's."**

**– Dr. Bradly Wouters,**
Executive Vice-President,
Science and Research, UHN

### GETTING THE DRUG FROM LAB TO PATIENT

Dr. Weaver acknowledges that the road to a potentially disease-modifying Alzheimer's drug can be long, and the challenges are many. Financial support is always an issue because testing and trials can cost millions of dollars. Plus, there are numerous safety and efficacy issues to work out.

"Compounds need to be chemically stable and affordable to make," he points out. "There are lots of beautiful molecules out there, but once you swallow them they could be destroyed either by the stomach or the liver and thus can't go from the gums to the brain. So, we have to engineer both safety and efficacy in the molecule. Then you have to worry about your toxicology because this is not something that you're taking for five to 10 days. This is something that you're taking for 10 to 20 years."

Another issue is how often a patient has to take the drug, he points out.

"If you have a memory problem, four times a day is not a good idea," says Dr. Weaver. "And so then we have to engineer into the molecule the capacity for once a day."

Dr. Weaver's interaction with his AD patients means he's constantly reminded of these kinds of real-life challenges. This connection to patients is an important element of his success as a researcher, says Dr. Wouters.

"At UHN, our purpose is to transform the lives of patients and communities through excellence in care, discovery and learning. Dr. Weaver represents an individual who embodies all three elements of this approach. He is a clinician who sees and cares for his patients and understands the devastation of the disease and our limited ability to treat it effectively. This focuses his own research efforts to identify therapeutic approaches that can impact the lives of patients with Alzheimer's and their families."

Dr. Albert Jin is an associate professor of neurology at Queen's University in Kingston, Ont., with a cross-appointment to the Department of Biomedical and Molecular Sciences. He's known Dr. Weaver since he was one of his graduate students in the early 1990s.

"He's someone who can bring together the knowledge and the experience from two very different areas of inquiry," says Dr. Jin. "He's a neurologist and he's also a chemist, and to marry those two fields is very difficult. And he's the only person I know who can do that as successfully as he has."

Dr. Jin agrees that unlike many academic researchers, Dr. Weaver is able to go beyond the thrill of the science and really understand what kind of impact his discoveries could have on the world.

"He has no illusions about how difficult it is to make a difference as a chemist to the world, but the world makes a difference to him," he says. "So what he sees with patients and the sometimes awful things that people go through, that's what drives him."

In addition to his cutting-edge work as a scientist and the care he provides for his patients, Dr. Weaver finds a creative outlet in writing poetry in his spare time.

"A number of years ago I started writing what I call therapeutic poems, and I give them to patients," he says. "And some patients, they really like it."

One of his poems about Alzheimer's disease was published in the July 2016 issue of *Neurology*, the journal of the American Academy of Neurology. The last two lines seem to sum up his goal as a researcher and a doctor:

"To cure AD... the mind, the brain,
With scientific hand humane." ■





# Identifying genetic biomarkers is the key to better and faster treatment for depression

Discovering the causes of Canada's most prevalent type of mental illness and selecting the best treatment for each patient is Dr. Sidney Kennedy's mission

*David Israelson*

Seeking to solve one of modern medicine's most complicated puzzles, Dr. Sidney Kennedy is putting down markers. Dr. Kennedy, senior scientist at Toronto's Krembil Research Institute, is working to discover what causes people to become depressed, and how to select the best treatment for each individual patient. Dr. Kennedy is working with biomarkers – biological measures that are used to detect the presence or risk of a disease or to identify subgroups that could help clinicians select the most appropriate treatment. "We're particularly interested in identifying clusters of markers that distinguish subtypes of depression and help to predict response to treatments, such as medication, psychotherapy and brain stimulation."

Through his research, Dr. Kennedy hopes to find important clues to unlock the science of one of the most prevalent and burdensome types of mental illnesses in Canada. Although it is gradually becoming better understood, mental illness is a leading cause of disability in Canada. Nearly 4,000 people die by suicide each year – almost 11 people each day. In a 2016 survey about mental health, 40 per cent of respondents agreed they have experienced anxiety or depression, but have not sought medical help.

Dr. Kennedy and his team at Krembil are expanding upon the growing knowledge of the neurobiological and environmental factors associated with depression and suicidal behaviour. "We don't have the exact biomarkers yet, though we do see individual variants," he says. In 2014, *The Lancet* medical journal reported that roughly half the risk for suicide could be hereditary. "There has been a quest, for example, through the Human Genome Project, to associate specific genes with different psychiatric disorders," Dr. Kennedy explains. "While I'm not a geneticist, I think it's fair to say that no single gene is specifically linked to depression."

The search for biomarkers is more complicated than simply identifying a group of genes. "We do have different clinical profiles that distinguish patients with depression. For example, some are anxious, others are slowed down with fatigue and extreme hopelessness, while others gain weight, oversleep and are overly sensitive in their interactions with others," says Dr. Kennedy. "Unfortunately, the individual biomarkers that have been studied are not consistently linked to any one clinical type and do not help to predict which treatment is best for an individual patient."

Those with unusually high cortisol levels "may be constantly in a fight-or-flight stress mode, even when there isn't a threat at that moment. Their systems aren't sensitive to normal 'on' and 'off' signals. Within the brain, the hippocampus – the long ridge on each side of the bottom of our brains – is a possible biomarker of depression. It forms part of our emotional and cognitive brain circuitry. It helps with memory function and emotional responses," Dr. Kennedy says. "You would find that overall, among the general population, the brains of those with depression have smaller hippocampi than those who don't have depression."

Another challenge is identifying people

who are likely to become depressed. "We still can't do a quick MRI [magnetic resonance imaging] on you and say that, based on the size of your hippocampus, you're likely to get depressed in the next year. We don't have those kinds of biomarkers yet," Dr. Kennedy says.

The real question he and his team are trying to solve is: "Do different antecedents of depression result in different brain disturbances?" For example, people who experienced emotional or sexual abuse in childhood; offspring of parents with a history of depression; and individuals being treated with an antiviral therapy are all at an increased risk of becoming depressed – but are there different brain mechanisms underlying each of these pathways to depression, and should different treatments be used?

"In each case the end point is the same," says Dr. Kennedy. "Each of these individuals may be sad, hopeless, with no sex drive, no interest in anything, perhaps wanting to [end their lives]. Are there different pathways to this disorder? If we identify those pathways, could we predict the correct treatment more accurately?"

Dr. Kennedy's research team works with other investigators across Canada – at the University of British Columbia, University of Calgary, Western University and McGill University – and in Ontario with McMaster University, Queen's University, University of Guelph, Brock University and the University of Ottawa, CAMH and St. Michael's Hospital.

"We are an extensive network implementing a broad range of treatment trials. We try to use overlapping and constant biomarkers," he says. The scientists use fMRI (functional magnetic resonance imaging) to look at changes in specific regions of the brain, and they take blood samples. They are also applying augmented intelligence ("machine learning," as Dr. Kennedy calls it) and big data methods to combine and analyze the information from brain imaging, clinical and genetic data. "The ultimate goal is to be able to come up with profiles that can predict responses." Already, over a four-year period, 300 patients have gone through brain scans and provided blood samples, including 100 healthy patients whose data can be compared.

In the summer of 2016, Dr. Kennedy and fellow researchers met to plan the next stage of study – how to apply what they've been learning from biomarkers related to depression into the development of viable treatments. "We're still hampered by lack of understanding of depression. If I went to see a respirologist and was told, 'You have a bad cough,' I wouldn't be satisfied with that diagnosis," he says. "We have to learn from these tests and use them to development treatments that are affordable and accessible." ■

# Hard work is paying off for Canada's foremost concussion researcher

## Matching treatment with the injury through lab tests could lead to a speedier recovery

*David Israelson*

Dr. Charles Tator says that Canadians understand the seriousness of concussions better than ever before, and now he wants doctors to have better ways to diagnose them.

"There is not a good enough method. Right now, the diagnosis of concussion is a clinical diagnosis," says Dr. Tator, founder of the Krembil Research Institute's Canadian Concussion Centre.

A clinical diagnosis means that doctors can determine whether someone has suffered a concussion only by looking at the symptoms. For example: Is the patient dizzy?

Dr. Tator and his colleagues are currently working on the next step. It would be a breakthrough to diagnose concussions "through a combination of imaging, blood tests, EEGs (electroencephalograms) or any of the 20 to 30 other methods that have been tried," he says.

Pinpointing concussions through laboratory tests would make it easier to prescribe treatment that more closely matches the injury – and that could lead to a speedier recovery.

Annually, as many as 200,000 Canadians suffer from concussions. The causes can range from a fall on the ice or a blow on the head from an accident at home, at work or in a car mishap, to a hard hit to an athlete in sport. "Not all of these people get better," Dr. Tator says. "A large number of people are walking around with residual symptoms."

And although not every bump on the head means a concussion, there are some 60 different symptoms that may indicate an injury. They range from aversion to light, persistent headaches, insomnia and an inability to concentrate. It can also lead to mental health issues such as anxiety, depression or even suicidal thoughts.

One brain condition, called chronic traumatic encephalopathy (CTE), resembles Alzheimer's disease, and it can lead to premature death. Yet its diagnosis is difficult to distinguish from a concussion.

The problem is, right now the only way doctors can be 100 per cent sure whether the condition is CTE or concussion-related is by examining the patient after death.

"Can you imagine that in 2017 you have to do an autopsy to make a correct diagnosis? We don't have an in-life method yet to diagnose CTE, but we're close," Dr. Tator says.

Along with colleagues such as Dr. Carmela Tartaglia, who was recently awarded the Marion and Gerald Soloway Professorship in Brain Injury and Concussion Research, Dr. Tator has been instrumental in building greater awareness and understanding of concussions and their consequences.

His July 2013 paper in the *Canadian Medical Association Journal*, "Concussions and their consequences: current diagnosis, management and prevention," has helped inform and focus public discussion about concussions.

The Canadian Concussion Centre's four-pronged approach includes education and treatment, as well as research and diagnosis. The centre is making a difference among athletes, too, working with players and coaches to make them more aware of the steps for preventing concussions.

"Athletes are smart, and they respond to the necessity for prevention," Dr. Tator says. In rugby, for example, there used to be a lot of broken necks from a play that called for collapsing the scrum, when opposing teams scrape and paw for the ball.

"They have changed the way they play. They don't collapse during scrums anymore," Dr. Tator says.

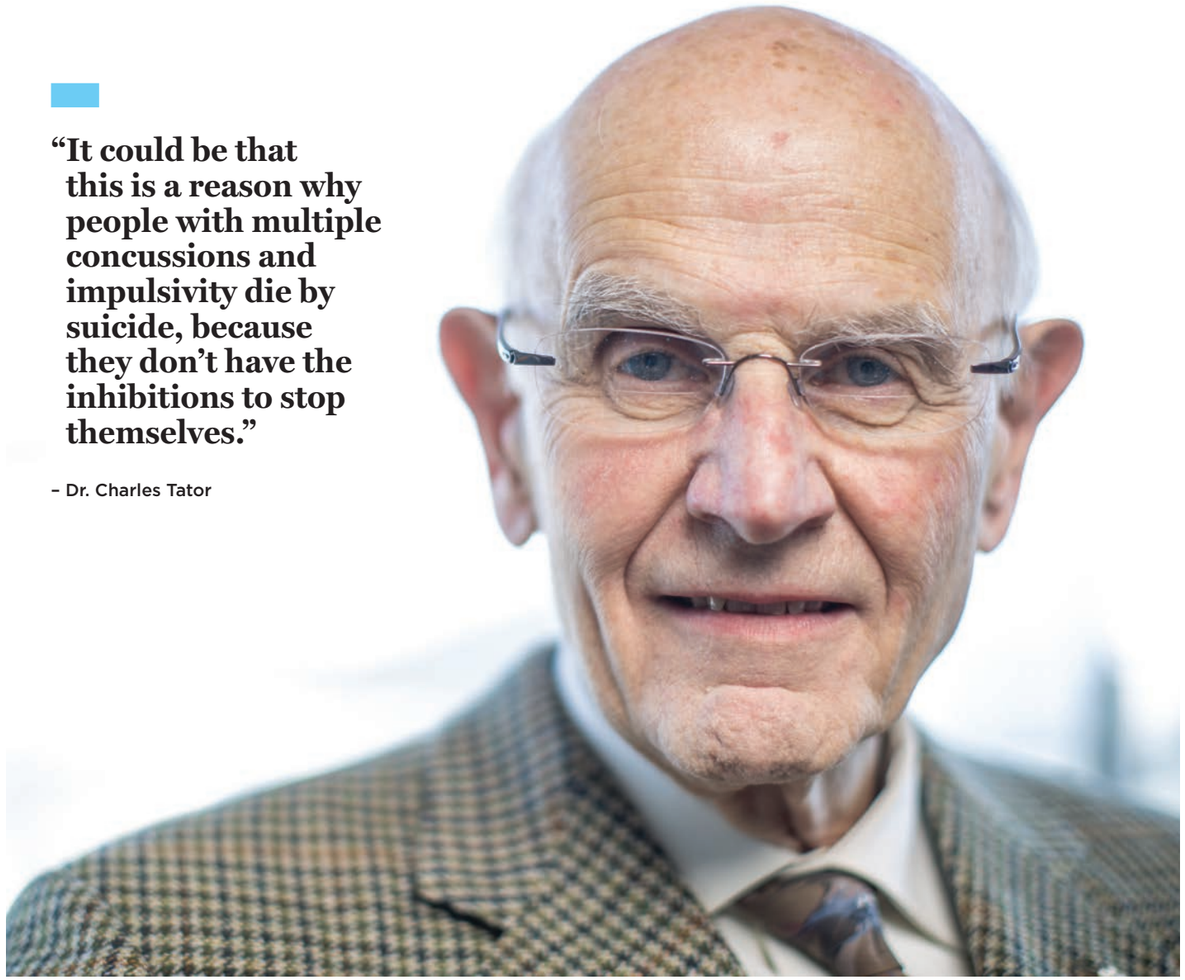
Similarly, he says the days seem to be numbered for the single-purpose "enforcer" in hockey, whose role was simply to fight and instigate the opposing team. Players are now hitting each other from behind less frequently – a blindsiding move that can often cause concussions.

Concussion research at Krembil is wide ranging, with scientists also working toward a number of diagnostic breakthroughs. For example, they have located a particular white matter tract in the brain of concussed patients that when damaged seems to trigger impulsive behaviour, Dr. Tator says.

"It could be that this is a reason why people with multiple concussions and impulsivity die by suicide, because they don't have the inhibitions to stop themselves," he explains.

**"It could be that this is a reason why people with multiple concussions and impulsivity die by suicide, because they don't have the inhibitions to stop themselves."**

– Dr. Charles Tator



Dr. Tator works extensively with schools to help them design programs to reintegrate kids who have had concussions back into the classroom, with accommodations for their injuries.

The project has also developed its own educational support program, which has patients come to the hospital for two-hour sessions twice a month to learn more about concussions and get answers to some of their questions about concussions.

"These sessions will be made available on YouTube, so people who aren't nearby can benefit, too," Dr. Tator says.

While there's still much work to be done, Dr. Tator is pleased with the progress so far. "We have one of the most multidisciplinary concussion research teams in the world, and we are starting to get the answers," he says. ■

*Athletes are smart, says Dr. Tator, and they respond to the necessity for prevention.*


# Unlocking the secrets of the brain's connection to pain

Advanced brain imaging, led by doctors like Karen Davis, is bringing patients one step closer to personalized precision pain solutions

*Judy Gerstel*

Dr. Karen Davis has devoted her life to learning about something no one wants.

And there's still so much to learn, she says, about pain.

She was turned on to the topic by her North York, Ont., high-school biology teacher, Marty Greenberg.

"He was excited because they'd just discovered opiate receptors," she recalls. "It was a cool idea that we have mechanisms in the brain to not only feel pain, but also to modulate pain."

"That really got me hooked on the whole topic of pain and pain control."

Now, many years later, Dr. Davis is an eminent neuroscientist and author of more than 150 published papers. Many have been cited hundreds of times by other scholars. She's a senior scientist and division head at the Krembil Research Institute and a professor in the Department of Surgery at the University of Toronto.

Her highly informative TED-Ed video entitled "How Does Your Brain Respond to Pain?" has been viewed more than 1.1 million times.

Dr. Davis still finds the work of the brain and how it relates to pain fascinating. For example, she references "making a small lesion in the brain to target a specific area of pain."

Early results of a research study of the treatment for trigeminal neuralgia (a facial pain syndrome) were extremely promising in some patients, she reports.

"The patients who responded showed reversal of abnormalities in one part of the brain. That's [exciting that] treatment is reversing abnormality."

Innovative research in neuroscience, Dr. Davis explains, "is not only about what is not working, but also about what parts of the brain have the capacity to bring about change."

She'll be studying exactly that as one of the principal investigators of the Chronic Pain Network.

It's one of five new national research networks in a $62.5-million federal program called Canada's Strategy for Patient-Oriented Research.

"Chronic pain is so widespread in our society," says Dr. Davis. "Studies have shown how prevalent it is. But society just wants you to grin and bear it."

One in three Canadians experiences chronic pain, and the cost for health care, wages and lost productivity is more than $40 billion annually.

"Society tends to focus research dollars and attention on diseases that can kill you, and rightly so," she says, "but chronic pain is an enormous, silent societal issue."

Discussion about medical assistance in dying brought the issue "out of the closet," Dr. Davis says, "because pain and suffering can be so severe that people want to end their lives."

She's met many patients with chronic pain conditions who weren't believed. "They were told it's psychological, all in their head, and this influenced how their employers and family members regarded them."

But with scanning technology, she explains, "we were able to show that their brains were functioning abnormally (in response) to pain originating, for example, in the gut from IBS (irritable bowel syndrome)."

"These patients were thankful to know that it was real, that it's not a psychiatric condition, not malingering. The brain response is abnormal. There are many chronic pain conditions where patients are told they're making it up or exaggerating," Dr. Davis says.

**"Chronic pain is so widespread in our society. Studies have shown how prevalent it is. But society just wants you to grin and bear it."**

– Dr. Karen Davis

"But you can see on the scans that their brains are not normal."

This, says Dr. Davis, "is the first step in not only helping patients understand what's going on, but also showing physicians and the world that they need to take these patients more seriously and look at treatments that tap into abnormality."

Investigating and making known those abnormalities has motivated Dr. Davis from the beginning.

"When I started university," she recalls, "I sought out and was lucky to have opportunities to work in the labs of leading pain researchers."

One of her mentors was Dr. Jonathan Dostrovsky, now retired from the University of Toronto.

Normally, says Dr. Dostrovsky, "when students apply to do grad work with me, they don't really know what they would like to do. She was different. She already had a lot of her own ideas and a project she thought out entirely on her own, investigating the mechanism of signals in the brain linked to migraine. It hadn't been investigated before."

He lists her strong points: "motivation, creativity, innovation, organization skills, leadership."

As part of her training, including post-doctoral work at Johns Hopkins University in Baltimore, she spent 15 years in operating rooms.

"I wanted to figure out what's going on by recording brain activity while patients were awake and could tell us what is happening," she explains.

And then a sea change happened in the field of neuroscience.

"Brain imaging came along. It was a huge leap in looking at the whole brain, including the brains of healthy people, to create a normal database."

While the availability of magnetic resonance imaging (MRI) was "a major, major advance," says Dr. Davis, "where we are going now, the next major advance is MEG (magnetoencephalography)."

MEG records magnetic fields produced by electrical currents in the brain, just as electrocardiogram (ECG) does in the heart.

"I'm confident that in my lifetime, we are going to get close to personalized and precision pain management," she says.

"We've had all these treatments for chronic pain that did a great job at helping a very small subset of patients. There's something different in these patients' brains that makes them respond to treatment while others don't. Not every treatment or drug works for everybody in same way," says Dr. Davis.

"With advanced brain imaging, we'll be able to non-invasively figure out brain circuits in people with conditions that look the same and find out why some are responsive to treatment and some are not."

Figuring out the variability to target, she explains, could reduce healthcare costs and "the agony of patients having to shop around for something that may or may not work."

People with end-of-life pain would benefit, as well as those with chronic disease pain.

Dr. Davis also insists that we shouldn't have to accept the aches and pains of aging.

"We should be able to figure out a way to live through our middle age years without aches and pains," she says. "A lot of people don't experience them. So we need to look at why some people are resilient or have a high pain threshold or respond well. They're going to give us clues."

It's very likely that some of those breakthroughs will come in Dr. Davis' lab and those of her colleagues at Krembil.

"In terms of pain research," she says, "Canadians are definitely known internationally as world leaders. We have a long history of tremendous research. Many of us are involved in a lot of international societies. We punch above our weight. It's something we should be proud of." ■

## Should brain scans be used to measure pain?

Being able to scan the brain with advanced imaging technology provides huge benefits to pain researchers like Krembil Research Institute senior scientist Dr. Karen Davis, to clinicians and to patients.

But there's also a dark side to brain imaging.

For example, using it to prove that someone does or does not have pain, usually in legal and insurance cases, is an ethical issue that's of great concern to Dr. Davis and many colleagues.

She's spearheading an international effort to explore the ethics of using information from brain scans, how it should or shouldn't be used and by whom and for what purposes.

Dr. Davis cites the privacy issue, comparing brain scans to genetic screening, and she believes the information should be used solely for treatment that benefits the patient.

"Using brain scans to diagnose pain is something I'm against," she says firmly. "It's essentially like a lie detector test, mostly for legal cases. I've been fighting against that."

She says judges tell her they're dealing with this every day in court. "It's an issue in Canada," she adds. "People come to me that work for insurance companies."

"Can Brain Imaging Be a Pain-o-Meter?" was the title of her presentation last year at a Harvard Law School conference titled "How Neuroimaging Helps Law Re-Envision Pain."

Her answer to the pain-o-meter question is a clear "No!"

Says Dr. Davis: "It's not what the technology should be used for."

She says people with chronic pain are constantly being asked to prove they're in pain.

She now serves as Chair of the Special Presidential Task Force on "The Use of Brain-Based Diagnostic Tests for Chronic Pain." The task force is part of the International Association for the Study of Pain.

*Parkinson's patient Julie Wood and her husband Luke Mastin volunteered to help Dr. Anthony Lang with his Systemic Synuclien Sampling Study known as S4.*

# When patients join the fight against Parkinson's

Dr. Anthony Lang's research team hunts for biomarkers that could lead to early diagnosis and treatment

*Marjo Johne*

Over the last year, Julie Wood has given scientists at the Krembil Research Institute samples of skin from her neck and leg, blood, saliva and fluid from her spine, as well as tissue from her salivary glands and colon.

Ms. Wood, who lives in Toronto with her husband, also went last year for a brain scan to be used by the same group of Krembil scientists. The team is led by world-leading Parkinson's disease neurologist Dr. Anthony Lang, director of the Edmond J. Safra Program in Parkinson's Disease and holder of the Lily Safra Chair in Movement Disorders. Ms. Wood had to travel to Buffalo, N.Y., for the scan because the particular machine used in the study is not available in Canada.

It's a lot to give and do for research. But for Ms. Wood, it's a way of fighting back against the disease she was diagnosed with five years ago.

"It took about a year to find out what was wrong with me, but in the end, the conclusion – which I had already suspected myself – was that I have Parkinson's disease," says Ms. Wood, who is 56 years old and recently retired from an executive role in a national, not-for-profit land conservation organization.

The research project Ms. Wood contributed to last year – she's been involved in five other previous studies – is called the Systemic Synuclein Sampling Study or S4, for short.

The object of the study is to identify the best biological indicators for Parkinson's disease by tracking the levels of a protein called alpha-synuclein. This normally occurring protein, which is believed to play an important role in the development of Parkinson's, has been found in concentrated clumps in the brain cells of people with the disease, within substances called Lewy bodies.

"There are suggestions that Parkinson's disease doesn't begin in the brain at all, and that by the time patients present with the disease, we may be trying to treat them too late, because the disease is already well established," says Dr. Lang, the S4 lead investigator at Krembil. "So if we can define the presence of alpha-synuclein in peripheral systems where the disease might have started, then that could lead to an earlier diagnosis of Parkinson's, as well as the development of treatment to slow the progression of this disease."

**"There are suggestions that Parkinson's disease does not begin in the brain at all."**

– Dr. Anthony Lang

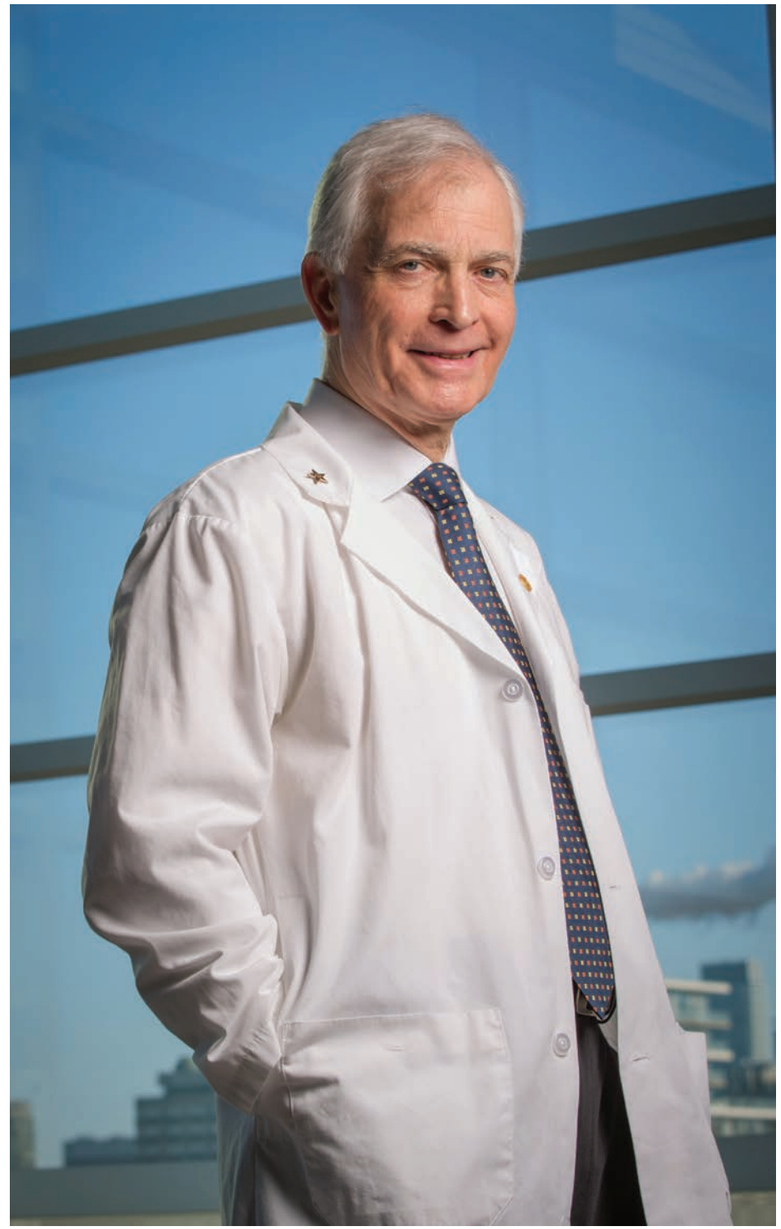
There are other studies focused on the presence of alpha-synuclein in a specific site of the body such as the colon or the skin. S4 is the first study to look at alpha-synuclein in multiple parts of the body. The study, which is enrolling 80 participants, including 20 for the control group without Parkinson's, is looking at patients across all stages of the disease.

At Krembil, S4 researchers are also experimenting with various imaging techniques and assays to figure out the best methods for spotting alpha-synuclein as a biomarker for Parkinson's disease.

"We are looking at all these different regions within a given individual for critical information about the distribution of alpha-synuclein throughout the body of somebody with Parkinson's disease, then we are correlating this information with the brain scan, which tells us how advanced the disease is," explains Dr. Naomi Visanji, who, along with Dr. Connie Marras, is working with Dr. Lang on S4. "By looking at patients with different stages of Parkinson's, we will have a clear picture of how alpha-synuclein in systems outside the brain changes, according to the progression of the disease."

There are currently no biomarkers for Parkinson's, and the disease is diagnosed based on a clinical assessment of symptoms such as trembling, stiffness in the limbs or neck and limited facial expressions. Some doctors confirm their diagnosis with a brain scan that looks at levels of dopamine, a neurotransmitter whose presence slowly diminishes in people with Parkinson's.

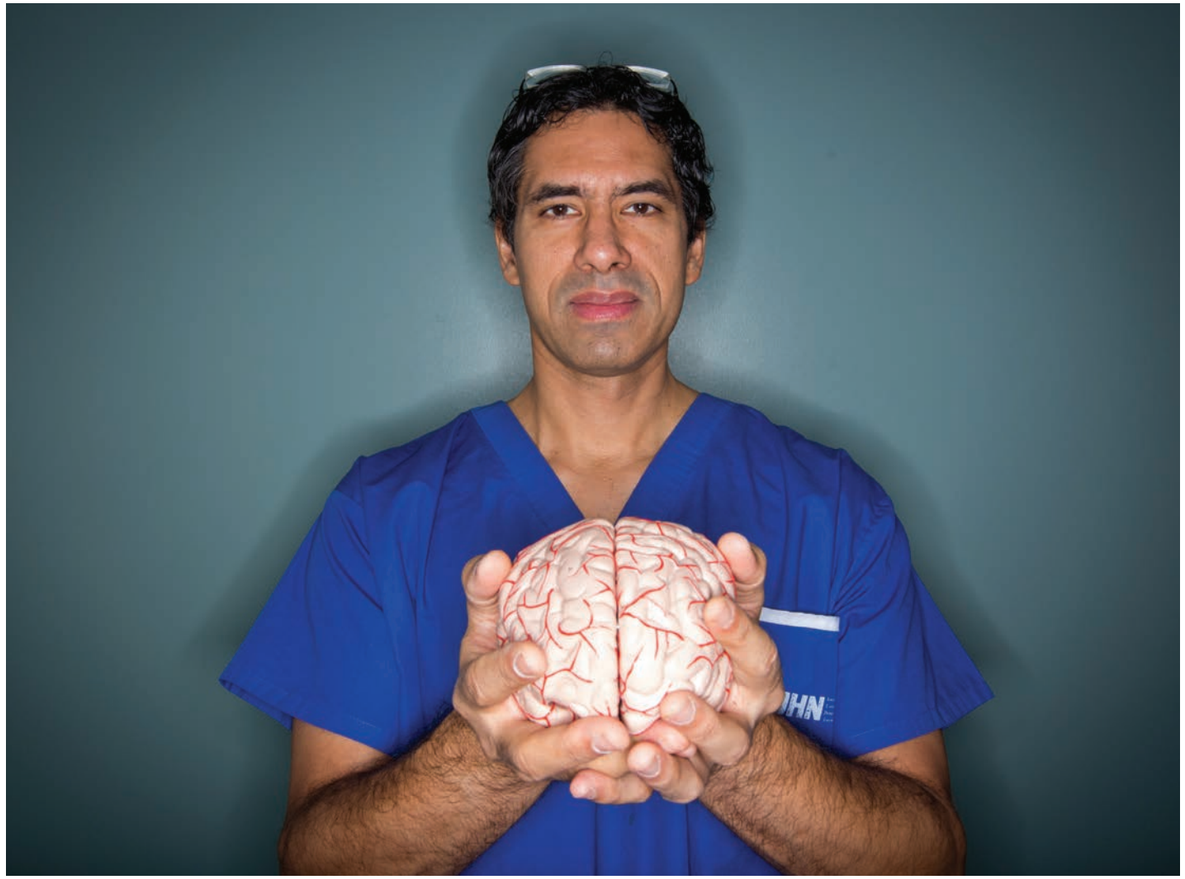
"The field is moving toward clinical trials of drugs that will stop the disease in its tracks," says Dr. Visanji. "It would be nice to see biomarkers that indicate if alpha-synuclein has stopped aggregating after a patient has taken a certain drug or if it's actually accumulating even more."



Krembil is looking to sign up 12 S4 participants. So far, six people have enrolled, including Mike Clare, a former high-school history teacher whose wife has Parkinson's disease.

Providing samples and travelling to Buffalo for a brain scan presented some inconvenience and discomfort, and the results of S4 are unlikely to yield direct benefits for him or his wife. But Mr. Clare, who like Ms. Wood lives in Toronto, says he's happy to be part of this novel – and hopefully groundbreaking – study into a disease that still remains a medical mystery.

"I could get really angry that my brilliant, gorgeous wife has this disease, but what good would that do?" he says. "Taking part in this and other studies gives [us] a way to give back and maybe help prevent future generations from getting this terrible disease." ■



# The ‘Holy Grail’ of epilepsy research

Neurosurgeon Dr. Taufik Valiante thinks an implanted electronic device could sense and stop seizures

*Shelley White*

As tech-savvy citizens of the world, we’ve become accustomed to the idea of a tiny computer chip controlling the functions of a sophisticated device, whether it’s a mobile phone, a laptop or an automobile. But what if an especially “smart” computer chip could control activity in the most sophisticated machine of all – the human brain?

Dr. Taufik Valiante, scientist at the Krembil Research Institute and neurosurgeon at Toronto Western Hospital, is working toward what he calls the “Holy Grail” of epilepsy research – an electronic device implanted in the brain that could monitor brain activity, sense a coming seizure and prevent it from happening, all without the patient’s awareness.

It’s an innovation that offers new hope for people living with epilepsy, a neurological condition that can be especially debilitating when seizures cannot be controlled by medication. For the 30 per cent of those who have an intractable (drug-resistant) form of epilepsy, brain surgery is often their only treatment option. But Dr. Valiante’s research could offer a less-invasive alternative. In collaboration with colleagues at the University of Toronto’s Faculty of Engineering, Dr. Valiante is building and testing an implanted electronic device that would reduce the need to remove a part of the brain.

“The idea is that can we actually change brain function, so that if a person is starting to have a seizure, we can push the brain out of that seizure state,” he says.

Dr. Valiante’s innovative device works through a process called neuromodulation – the targeted delivery of a stimulus to the brain. Electrodes on the device monitor electrical signals in the brain. That information is processed in real time with the purpose of detecting a developing seizure. Then the device delivers a pulse to influence the neurons that participate in seizure development in such a way that the seizure is avoided.



And while there are currently devices on the market that deliver electrical stimulation to the brain (to treat diseases like Parkinson’s, for example), they do so without a precise picture of what is going on in the brain, says Dr. Valiante.

“When the device becomes sentient, when it’s measuring something, it [stimulates] meaningfully in the context of what it’s sensing,” he says. “It [becomes] a closed-loop system.”

The key to creating a platform that has the capacity to record, interpret and respond to an individual patient’s brain activity is machine-learning, says Professor Roman Genov, director of the Intelligent Sensory Microsystems Laboratory at the University of Toronto and a collaborator on Dr. Valiante’s neuromodulation project. Prof. Genov says that there is a class of algorithms that can be trained to learn as they function, so that the device can adapt to individual patients.

Brain activity data collected from patients with epilepsy would be used to develop a set of features that the chip could recognize and respond to.

“It would be patient-tailored, where depending on the signals that are generated by the brain of this given patient, the algorithm would, over time, learn to detect or anticipate seizures [in that individual] better than you could do otherwise,” says Prof. Genov. “What the device learns could indeed be different for every patient it’s used for.”

Another priority for the researchers is to create a system that can remain implanted, operating independently, for a significant amount of time.

“We study how we can implement machine-learning algorithms on a small electronic microchip that uses very little energy,” says Prof. Genov. “The reason it needs to be energy-efficient is because you would like the battery that powers it to run for the longest possible time, and that the heat that is generated as a by-product of its operation is minimal.”

**“The idea is that we can actually change brain function, so that if a person is starting to have a seizure, we can push the brain out of that seizure state.”**

**– Dr. Taufik Valiante**

The device wouldn’t have to be limited to delivering an electrical pulse to prevent a seizure, says Dr. Valiante. It could deliver a pharmacological agent to the brain at the right time or even deliver light.

Dr. Valiante is exploring the potential of optogenetics in neuromodulation – light-sensitive proteins that can be expressed in cells, so that they are turned on or off with light. Compared with using an electrical current, optogenetics allows for greater precision over which cell types are controlled, he says.

“It’s an incredible tool because you can turn on specific cells, depending on their genetic composition. So for example, you can turn on a pyramidal cell or turn it off; you can turn on an interneuron or turn it off.” Pyramidal neurons are found in regions of the forebrain (such as the cerebral cortex, hippocampus and amygdala) and are thought to play a key role in advanced cognitive functions; interneurons are nerve cells that connect sensory and motor pathways during a reflex response.

After successfully testing his neuromodulation platform on laboratory models in collaboration with Toronto’s Hospital for Sick Children, Dr. Valiante and his colleagues are starting clinical testing at Krembil involving human subjects. While the machine-learning aspect of the device is still in the development stage, they are currently evaluating the platform’s ability to monitor brain activity and prevent seizures with a well-timed electrical pulse.

The test subjects are patients with intractable epilepsy, and Dr. Valiante says he’s found they are more than willing to take part in the research. The patients, like him, are hopeful this work someday leads to a better quality of life for people with epilepsy.

“If you look at the statistics, people with epilepsy have the lowest quality of life among all people with self-reported chronic conditions in Ontario, so it’s devastating from a biological, physiological and social point of view,” says Dr. Valiante.

“When [patients] are asked about participating, they’ll say, ‘If this could help somebody else, absolutely,’ and that’s incredible to me. They hope nobody else would have to experience what they experience.” ■

## Genetic research leads to better treatment for epilepsy

For most people with epilepsy, medication is the primary mode of controlling seizures. But when someone is diagnosed, it can be a lengthy, difficult process to find the right medication.

“The way we treat epilepsy today is by using general guidelines for the use of the antiepileptic drugs. But we know each patient is different. So it often ends up being a matter of trial and error,” says Dr. Danielle Andrade, medical director of the epilepsy program at University Health Network (UHN).

While some medications may work, others may be ineffective or may even make seizures worse, which can be “distressing, tiring and anxiety-causing for the family and for the patient,” says Dr. Andrade. “[They wonder], ‘Why am I having this? What is going to be the next step?’”

Dr. Andrade is on the front-line of researchers identifying the genetic roots of different types of epilepsy and using that information to treat patients more effectively.

“Forty years ago, a small portion of epilepsies were thought to be genetic,” she says. “Now we know that around 70 per cent of epilepsies are genetic,” as opposed to epilepsy caused by brain tumours, injury or illness. “What we can do with genetics is tailor the treatment better.”

As an example, Dr. Andrade points to the discovery of the gene responsible for Dravet syndrome, a severe form of epilepsy that causes both generalized and partial onset seizures. It’s a condition that is normally treated by a combination of medications, with varying degrees of efficacy. But when researchers identified the Dravet syndrome gene as a “sodium channel” gene, they realized that certain commonly used medications that block that sort of channel were actually making the seizures worse.

Identifying genes can also help researchers repurpose drugs – find new medications for epilepsy that might already be on the market to treat other illnesses or conditions.

Although all the genes that cause epilepsy haven’t yet been identified, Dr. Andrade and her colleagues have already identified some. They are also working with the Ontario Brain Institute in the hopes of compiling the genetic data of epilepsy patients throughout the province to gain even more insight.

# Partners in the pursuit of discovery

## For Mark Krembil and family, giving back is a long-term investment

*David Israelson*

The Krembil Foundation was born out of a family's collective desire to help people.

Since 2001, it has focused almost exclusively on funding leading-edge medical research – research that will dramatically change people's lives in the long run.

To the entire Krembil family, research is key. They are passionate about it and they understand its impact on health care.

"This is a family affair," says Mark Krembil, President of the Krembil Foundation. "As a family, we've been philanthropic for many years. We had this concept of giving back to others, and investing in medical research was a logical way to do this."

In Mark's view, there is a critical and persistent lack of medical research funding, which does make a significant difference to health care and, ultimately, to society.

"Years ago, we started investing in neuroscience research, as it was severely underfunded," Mark says. "To maximize the Foundation's impact, we've decided to make brain research one of our priorities."

Research requires a long-term investment on all fronts. This is a familiar concept for the Krembil family: it's the core philosophy of the investment firm Trimark Financial, founded by Mark's father, Robert. The Foundation uses a similar methodology for analyzing equities as they do for deciding how to invest philanthropically.

"We take a long-term perspective, while continuing to do in-depth study and review," he says.

Focusing on complex medical research requires a great deal of due diligence. Expertise and a professional team are required to make sure that grant applications are properly assessed and that the funding gets to the doctors and scientists who will use it effectively.

The Foundation operates on a combination of scientifically based advice, but also on close-knit family decisions.

"While I manage the day-to-day operations, we really make decisions as a family," Mark says. "We meet a few times a year to review and update our granting portfolio."

Mark and his family members serve in all the board positions at the Foundation. This lean structure forces the Foundation to focus its funds on worthy research projects, rather than on office overhead.

"The major executive functions of the Foundation are performed by Michelle Tricarico, our grant administrator, and Dr. Kate Williams, our scientific director."

Dr. Williams, who holds a neuroscience PhD from McMaster University, helps bring scientific rigour to the Foundation and its decisions. She is responsible for overseeing the evaluation of research proposals submitted to the Foundation.

"We're looking for scientists with whom we can build long-term partnerships," Mark says. "We try to be strategic and identify projects that might have trouble finding funding elsewhere."

Research is about ideas that yield new information, he explains. "Sometimes the research doesn't always work out the way you expected, and that's okay. It leads to new opportunities."

The Foundation is always interested in new and exciting projects that have the potential to produce life-altering results. This was the major impetus behind the naming of the Krembil Research Institute (Krembil).

Krembil is relentless in its work directed at developing diagnostics, treatments and management strategies for brain and spine disorders such as Parkinson's disease and stroke, as well as bone, joint and eye disorders. The Foundation is one of many that continue to actively support the groundbreaking research projects that take place within Krembil.

The goal of Krembil is to be one of the top five research institutes in the world, and to that end, within five years it's seeking to increase its number of high-impact papers and citations by 10 per cent, recruit eight new researchers and establish a clinical research unit to add to its growing capacity and collaboration with other institutes.

It is the Krembil Foundation's expectation that its support will lead to the advancement of scientific understanding and breakthroughs at Krembil. The work is showing promising results. Krembil scientists are closer than ever to developing drugs that will stop the progression of Alzheimer's and minimize stroke damage, and to unlocking the mysteries of diseases that are not well understood such as Parkinson's and Rett syndrome.

Mark hopes more people will join his family in supporting Krembil, and he believes that anyone who does should be confident that the talent there will lead to new treatments and cures. ■



# NEUROLOGICAL FAST FACTS

Neurological conditions affect more than **3.6 million** Canadians of all ages.

By 2031, the number of Canadians living with Alzheimer's, dementia and Parkinson's disease is expected to **double**.

In Canada, someone is recognized as having dementia every **five minutes**.

There are about **86 billion neurons** in the human brain (the "grey matter"), with more than **60 trillion connections** (synapses) joining them together.

The financial cost of brain disease to the Canadian economy now exceeds **$61 billion** annually.

**564,000** Canadians are currently living with dementia.

# Krembil Relentless.

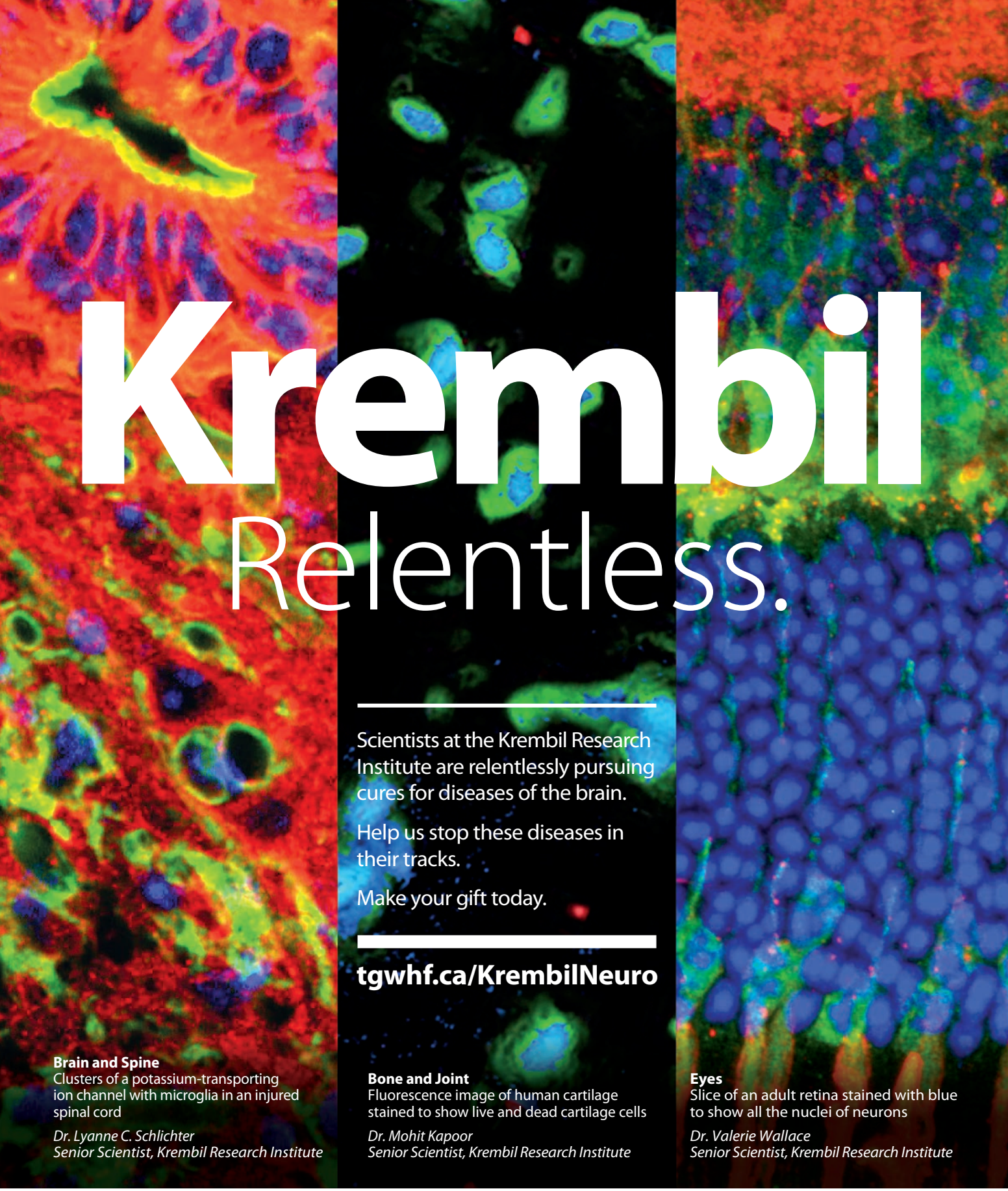
The Krembil Research Institute is one of the principal research institutes of University Health Network, Canada's largest research hospital. Scientists at Krembil are relentlessly pursuing cures for debilitating, chronic diseases in three main areas:

1. **Brain and spine disorders** such as epilepsy, stroke, dementia, depression, pain, spinal cord injury, concussion, Alzheimer's disease and Parkinson's disease.
2. **Bone and joint disorders** such as osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis.
3. **Eye disorders** such as glaucoma, macular degeneration and retinopathy.

## KREMBIL BY THE NUMBERS*

| | | | | |
|---|---|---|---|---|
| **219** researchers | **118** fellows and graduate student trainees | **275** staff members | **901** peer-reviewed publications produced** | **146,568 sq. ft.** of dedicated research space |

*Based on 2016 data **Publications from 2015 calendar year



# Krembil

## Relentless.

Scientists at the Krembil Research Institute are relentlessly pursuing cures for diseases of the brain.

Help us stop these diseases in their tracks.

Make your gift today.

**tgwhf.ca/KrembilNeuro**

**Brain and Spine**
Clusters of a potassium-transporting ion channel with microglia in an injured spinal cord

*Dr. Lyanne C. Schlichter*
*Senior Scientist, Krembil Research Institute*

**Bone and Joint**
Fluorescence image of human cartilage stained to show live and dead cartilage cells

*Dr. Mohit Kapoor*
*Senior Scientist, Krembil Research Institute*

**Eyes**
Slice of an adult retina stained with blue to show all the nuclei of neurons

*Dr. Valerie Wallace*
*Senior Scientist, Krembil Research Institute*

Toronto General & Western Hospital Foundation UHN