A VIRTUAL CHECK FOR EARLY SIGNS OF GLAUCOMA

BREAKTHROUGH COULD MAKE RETINAL REATTACHMENT EASIER

NATIONAL NETWORK COMBATS VISION LOSS FROM DIABETES

CLASSICAL MUSICIAN SOARS, THANKS TO THESE DOCTORS

KREMBIL

Krembil Research Institute | Vision

On the front-lines of the battle to save our vision

Researchers like Dr. Valerie Wallace want to do more than stop blindness – they want to bring back vision altogether

Toronto Western Hospital UHN

Krembil is dedicated to finding answers for eye diseases

Every 12 minutes, someone in Canada joins the list of the visually impaired. The total number of people living with significant vision issues now tops 500,000 – and it continues to grow, thanks in part to our aging population.

So chances are, if you live in Canada, you know someone struggling with vision issues. In addition to blindness, vision impairment can cause a host of other problems, from loss of sharpness or clarity of vision to a narrowed visual field or a loss of depth perception. People experiencing these problems may be living with any one of a number of diseases, including age-related macular degeneration, diabetic retinopathy, glaucoma or retinitis pigmentosa.

At the Krembil Research Institute, we are determined to unlock the secrets of these diseases. In recent years, we've assembled a top-notch team of research scientists who are committed to finding answers to fundamental questions about the retina, the brain and disease function.

Many of the causes of these diseases remain unknown. But what is known is that living with these conditions can affect a person's family life and relationships, their finances and mental health, but most of all, vision loss can have a negative impact on an individual's overall quality of life. That's why it's essential for us to make a long-term commitment to high-calibre basic research. We were fortunate to receive a tremendously generous philanthropic gift in 2015, which led to the establishment of the Donald K. Johnson Eye Institute in 2016. In less than a year, this entity – the largest vision program in Canada – has already helped foster a culture of collaboration between our clinicians and our vision scientists.

When it comes to finding a cure to these conditions, no one lab can do so on its own. It will take many incremental discoveries over a number of years. But gifts like this – and the many others that come from the community – allow us to recruit some of the brightest minds in the field, carve out a unique and diverse culture and move closer to our collective goal of becoming one of the top five vision institutions in the world.

In the pages to come, you will read about the significant advancements our scientists have made in recent years, and the new frontiers we are exploring to diagnose diseases of the eye and restore vision. If you care about joining the search for answers about how the eye works, then we are more than happy to have you on our team. In the end, that's the only way these problems get solved – by supporting innovative research pursuits like those currently underway at Krembil.

Sincerely,

Dr. Valerie Wallace

Co-Director, Donald K. Johnson Eye Institute;

Senior Scientist, Krembil Research Institute;

Donald K. Johnson Chair in Vision Research

Dr. Robert Devenyi

Co-Director, Donald K. Johnson Eye Institute;

Clinician Investigator, Krembil Research Institute;

Karen and William Barnett Chair in Ophthalmology

KREMBIL
JUNE 2017 • ISSUE 2
VISION

EDITOR
Steve Tustin

ART DIRECTOR
Frank Perito

CONTRIBUTORS
Chris Atchison
Jennifer D. Foster
Mary Gooderham
David Israelson
Marjo Johne
Shannon Moneo
Renee Sylvestre-Williams
Shelley White

PHOTOGRAPHY
Tim Fraser

THE GLOBE EDGE TEAM

Jon Banack
MANAGING DIRECTOR

Sean Stanleigh
MANAGING EDITOR

Liz Massicotte
PROGRAM MANAGER

Isabelle Cabral
PRODUCTION CO-ORDINATOR, THE GLOBE AND MAIL

KREMBIL is designed and produced by The Globe and Mail Custom Content Group on behalf of the Krembil Research Institute, University Health Network.

Printing and prepress by Metagraphic Network

Switching to a cure

Renowned scientist Dr. Philippe Monnier and his team at Krembil are developing an injection that could dramatically improve the lives of patients

Marjo Johne

What if, with one injection, doctors could turn off the molecular switch that triggers the death of the eye's photoreceptors – those neuron cells in the retina that enable vision by processing and transmitting visual information to the brain?

"It would significantly improve the lives of patients with conditions such as retinitis pigmentosa, glaucoma and age-related macular degeneration," says Dr. Philippe Monnier, a senior scientist at the Krembil Research Institute. "Eye diseases dramatically impact quality of life, and the older you get, the higher your chances of developing an eye disease such as glaucoma."

More than a decade ago, Dr. Monnier led a research team that made an intriguing discovery: when the eye's photoreceptor cells are stressed – usually because of a malfunction caused by an injury or a gene mutation – proteins known as neogenins activate a pathway that leads to the death of these cells.

"These are proteins that will tell your eye how to connect with the brain, and dictate where to establish and stop the connection," explains Dr. Monnier. "What we discovered was a higher presence of neogenin in diseased photoreceptor cells, and we believe that these neogenin proteins are basically telling the cells, 'No, you cannot regenerate – you're going to die.'"

Today, Dr. Monnier and his team of researchers at Krembil are working on a therapy that they hope can stop neogenin proteins from activating photoreceptor cell death. The scientists have developed a peptide called 4IG that, when injected into the retina, successfully blocked the death-inducing function of neogenin proteins in photoreceptor cells that are diseased with retinitis pigmentosa. Peptides are fundamental components of cells that carry out important biological functions.

Laboratory tests show that effects

could be detected in as little as two weeks, says Dr. Monnier. An injection with 4IG improved photoreceptor cell survival and structure, and led to better vision.

"The improvement was very dramatic," says Dr. Monnier. "The peptides, which are these small protein fragments, blocked the neogenin pathway that would normally lead to photoreceptor cell death."

While the lab tests have focused primarily on retinitis pigmentosa, the findings may also be relevant for other eye conditions.

"We could have well identified a molecular switch that is critical for cell death in multiple eye diseases," says Dr. Monnier. "We have a lot of indications which tell us that by targeting this specific pathway, we can not only protect photoreceptors, but also other cell types in the eye that are important for diseases such as glaucoma and age-related macular degeneration."

Jason Charish, a project lead in Dr. Monnier's research into neogenin blockers for retinitis pigmentosa, notes that the study findings – and, most importantly, the potential for a cure – also have implications that go beyond the eyes.

"Eye diseases dramatically impact quality of life, and the older you get, the higher your chances of developing an eye disease like glaucoma."

– Dr. Philippe Monnier

Krembil scientists believe neogenins may also play a critical role in multiple sclerosis (MS) and in stroke, says Mr. Charish, a PhD student at the University of Toronto.

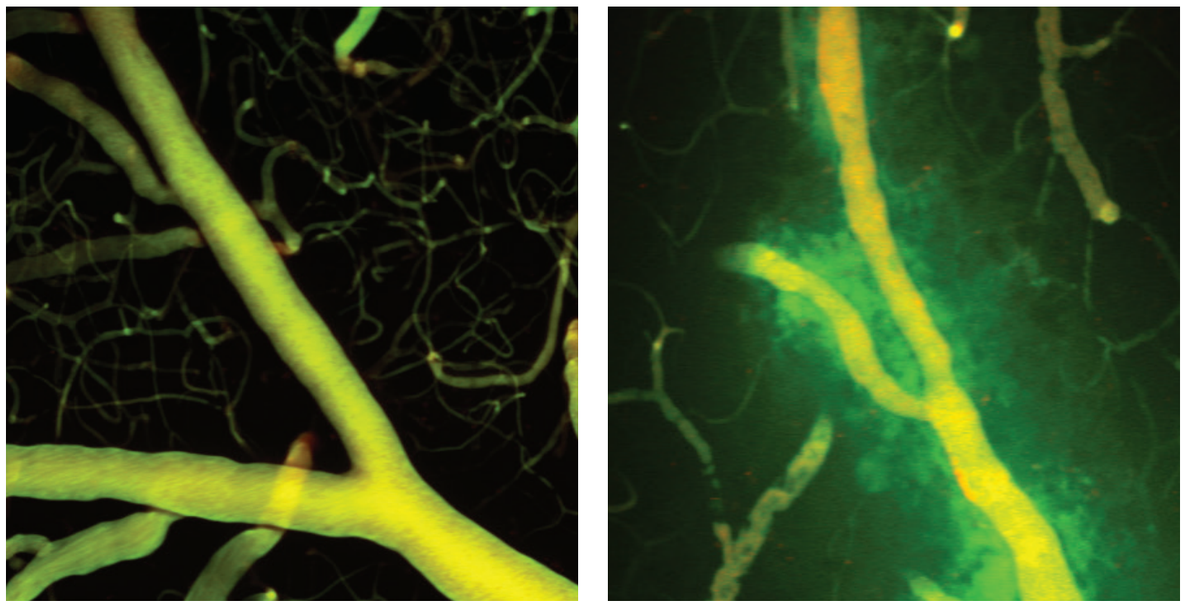
"Other members of the lab have also looked at MS and stroke models, and we see potential applications of the therapy in these diseases as well," he says.

Dr. Monnier says the application of 4IG produced an unexpected finding: neogenins were also responsible for maintaining the blood-brain barrier – a protective membrane that prevents harmful substances from entering the brain.

"The blood-brain barrier prevents a lot of bad things from happening. For example, it prevents the immune system from going into your brain," he says. "In multiple sclerosis, the immune system is somehow able to cross the barrier and attack the brain. So if we can restore the barrier, then we prevent immune system cells from [targeting] the brain."

Krembil is now working to take 4IG from the lab into clinical practice. Dr. Monnier and his team are preparing to test 4IG for preclinical safety. They have also partnered with a pharmaceutical company to eventually produce and market 4IG as a drug.

"Our goal is, in four to five years, to be able to turn 4IG into a drug that can be administered to patients," says Dr. Monnier. ■



Left: blood vessels in the brain. The blood-brain barrier is functioning well. Right: a cloud around the blood vessels indicating that the blood-brain barrier is no longer functional. This is seen in a model for MS, where the blood-brain barrier stops working.

Are your eyes also the windows to your brain?

Dr. Efrem Mandelcorn is exploring whether a simple eye test could help detect Alzheimer's earlier

Shelley White

The test takes about a minute ... two minutes, tops.

Perched on a stool, face supported on a chinrest, the patient looks into the optical coherence tomography (OCT) machine. A white cross on a black background is in her field of vision, with red lines that move up and down, back and forth. Dr. Efrem Mandelcorn, clinician investigator at the Krembil Research Institute and a retinal surgeon at the Donald K. Johnson Eye Institute's Retina Clinic, directs a laser into the patient's eye. He's using light waves to take cross-sectional pictures of the patient's retina and optic nerve. It's painless, it's simple and it's over very quickly.

OCT has been used in optometrist's and ophthalmologist's offices to diagnose eye diseases like glaucoma for years. But researchers like Dr. Mandelcorn are hoping this simple test could be used someday to help doctors diagnose neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS), even before patients show symptoms.

"We have very good technology to look at the eye," explains Dr. Mandelcorn. "You can look at what's called the retinal nerve fibre layer, which goes right to the optic nerve. It is a direct connection from the eye to the brain – a window to the brain."

Dr. Mandelcorn says that some smaller studies showed that when looking at images of the optic nerve head, the upper or "superior" portion of the nerve is thinner in late Alzheimer's, more so than in a control group of subjects the same age.

If this nerve fibre layer loss could be proven to be a biomarker – an accurate early indicator of Alzheimer's – then a simple eye test could become a valuable diagnostic tool for neurologists.

"The idea is that if you can find a pattern of nerve fibre layer loss on an OCT scan, which is exquisitely detailed, you

can then maybe say this person is at risk [for Alzheimer's]," says Dr. Mandelcorn.

The prospect of an eye test to predict the onset of Alzheimer's is, so far, still a theory, but it's one of the exciting avenues being explored by the Ontario Neurodegenerative Disease Research Initiative (ONDRI). ONDRI is an Ontario-wide, large-scale, collaborative study that could lead to major breakthroughs when it comes to the diagnosis and treatment of neurodegenerative diseases.

As our population ages, dementia is becoming the single greatest cause of disability in Canada's senior population. More than 500,000 Canadians have dementia, and more than 100,000 will develop dementia in the coming year.

By investigating early predictors of dementia in many forms, the study endeavours to identify tools to diagnose and treat these diseases to soften the impact on patients and their families.

Dr. Barry Greenberg is the director of strategy for the Toronto Dementia Research Alliance and the director of neuroscience drug discovery and development at University Health Network (UHN). He's the ocular co-lead for ONDRI and says the overarching goal is to do "deep characterization" of the people who have the neurodegenerative diseases included in the study. ONDRI will study close to 600 participants enrolled for up to three years – people who have been clinically identified as having these diseases.

"It's to get an idea of the features, the phenotypes of these individuals and how they change from year to year [as the disease progresses]," says Dr. Greenberg.

In partnership with the Ontario Brain Institute, ONDRI will employ more than 50 investigators at 13 sites around the province to study five neurodegenerative diseases. These are some of the most pervasive and debilitating diseases that humans can face: Alzheimer's disease, Parkinson's disease, ALS, frontotemporal lobar degeneration (a group of neurodegenerative diseases that cause dementia) and vascular cognitive impairment (resulting from stroke). Each of these diseases has one symptom in common: dementia. (Although not everyone with Parkinson's or ALS gets dementia, it is associated with these diseases.)

As part of the study, researchers will do eight assessments with each participant. One is gait and balance; another is neuroimaging. Other tests include neuropsychology (measuring cognitive skills such as attention and memory) and genomics (blood samples taken to compare all participants genetically). There are two ocular tests. One involves eye tracking or measuring eye movements while people follow a light. Dr. Mandelcorn is an investigator for the other ocular test, the OCT imaging described earlier.

"If you really want to be sure about it, you have to wait until the patient dies and [then] look into an autopsy ... so if an eye test works, this is great."

– Dr. David Tang-Wai

He likens ONDRI to a Rubik's Cube – each row of colours represents a different assessment or a different disease or a different period of time in the study. As you move the squares and mix up the colours, it's like the researchers detecting patterns in how the factors intersect and interact.

"Each investigator has his/her own platform," he explains. "If you get all this rich data from all these different platforms, you can then tease out what happens over time, what happens between diseases, what happens within the same disease."

But the question could be asked: "If a doctor were able to predict if someone was going to develop Alzheimer's, ALS or Parkinson's before it happens, how could that help someone?" After all, there are no cures for any of these diseases as of yet.

"From a basic science perspective, you want to catch something early while the brain is still normal," says Dr. Mandelcorn. "If you catch it late, then those brain cells are gone. Theoretically, if you catch something early, then you can preserve cells. And what that means for patients is, instead of getting dementia or Alzheimer's now, they get it five or 10 years later. For them, for their families and for the health system, it could be very significant."

Dr. David Tang-Wai is a neurologist, co-director at the UHN Memory Clinic, clinician investigator at Krembil Research Institute and one of the recruiting physicians with the study. His job is to recruit patients with early Alzheimer's disease or mild cognitive impairment to participate in the study. He says that finding a cheaper, faster way to diagnose Alzheimer's would be a boon to both patients and researchers. The currently methodology used to diagnose the disease (physical examinations, MRI or positron emission tomography (PET) scans) is not always accurate.

"If you really want to be sure about it, you have to wait until the patient dies and [then] look into an autopsy," he says. "We can do a spinal fluid exam and measure Alzheimer's proteins in the spinal fluid, but it's a needle in the back, and not too many people enjoy that particular test. So, if an eye test works, this is great. If it complements what we do now and improves our accuracy, that will just be a step forward."

An ocular test could also be a way to detect whether a trial Alzheimer's medication is working to prevent, or slow, the disease. Normally, doctors need to take a "wait-and-see" approach when testing an Alzheimer's drug, employing cognitive tests over years to measure impairment. Having a method that could accurately measure the progression of Alzheimer's would be a major step forward when it comes to drug research, says Dr. Mandelcorn.

"We use OCT scanning in ophthalmology all the time in the case of glaucoma to see how people respond to medication when they're asymptomatic, and if that worked in other types of diseases, it would be very interesting," he says.

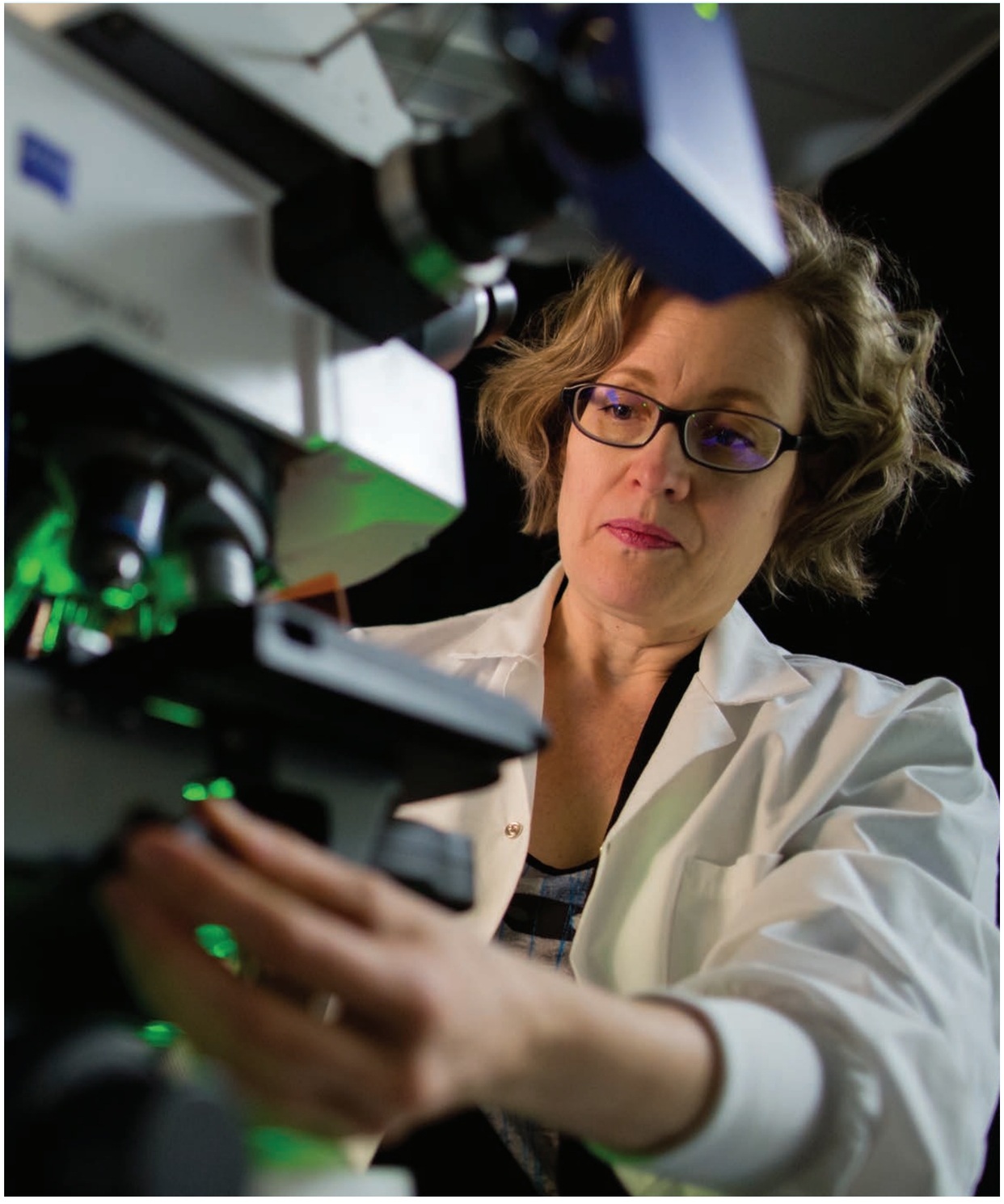
Another intriguing avenue the study is pursuing is the connection between vascular disease (an abnormal condition of the blood vessels) and dementia. Dr. Greenberg says that studies in the United States and Europe are showing that vascular abnormalities may be part of the very early stages of neurodegenerative disease.

If scientists are able to prove that the same lifestyle changes that can ward off vascular disease (like diet, exercise and quitting smoking) could also prevent Alzheimer's, it would be a major breakthrough.

"Studies have shown that good cardiovascular health on a population statistic level depresses the prevalence of dementia at any given age," Dr. Greenberg notes. "Cardiovascular health, lifestyle, diet, intellectual engagement – all these things contribute to activity in the brain, to oxygenation to the brain. So it makes a great deal of sense."

As the investigators continue their research, there are already plans in place to extend the study.

"Unfortunately, Alzheimer's and Parkinson's are not diseases that last one or two years," says Dr. Tang-Wai. "The longer we can study people, the better we get at it, and the better we can answer questions." ■



Searching for a way to bring back the light

Through research, Dr. Valerie Wallace hopes to show that cell transplants can help restore vision for those with retinal disease

Renee Sylvestre-Williams

When the photoreceptor cells in your retina die, the light vanishes. For good. But recent exciting work by Krembil's Dr. Valerie Wallace, when studying cone photoreceptor transplants to the eye, has uncovered a novel and surprising property of material exchange between cells.

Now, she and her dedicated team are evaluating whether this exchange process could help restore vision.

Dr. Wallace, co-director of the Donald K. Johnson Eye Institute within the Krembil Research Institute and holder of the Donald K. Johnson Chair in Vision Research, is primarily interested in blindness as a result of retinal disease. "My lab in particular is focused on diseases that impair the function or cause the death of the photoreceptors," she says. "The photoreceptors are the cells in the retina that you need to sense light. If you lose them, your retina does not work," says Dr. Wallace.

"Because there are no treatments to restore vision after photoreceptors die, we are taking this very conceptually simple approach, and that is: 'Can we circumvent all of this cell loss by just putting in healthy photoreceptors, and would they behave like normal photoreceptors and hook up to the rest of the retina and restore the ability to respond to light?' It's really, really simple." Dr. Wallace laughs, "Well, the idea is simple."

We still do not have a deep understanding of why photoreceptors die, even in inherited diseases such as retinitis pigmentosa. Dr. Wallace says that there is a huge body of research over the last 25 years that has discovered many genetic mutations that cause photoreceptor disease, but there is significant variability in how vision loss manifests in these conditions. In some instances, the problem manifests at birth but can also emerge in adulthood. Furthermore, there are other conditions, such as age-related macular degeneration (AMD), which cause the death of cone photoreceptors. The cause of AMD is multifactorial and includes inflammation, genetic susceptibility and other age-related components that can lead to blindness. Currently, there is no cure for retina-related blindness.

Dr. Wallace's lab has been targeting cone photoreceptors for transplantation, due to their high clinical relevance. Cone cells die when a patient has AMD or in late-stage retinitis pigmentosa, robbing patients of central vision. Ultimately, this means that these people can't read, see fine detail or discriminate colours. People, says Dr. Wallace, have been transplanting cells to replace bone marrow and skin for years, and those two procedures are relatively common. Everything else related to cell transplantation is still experimental. "Years ago, people started transplanting photoreceptor cells to the eye and used a green fluorescent protein, which comes from jellyfish, to track the cells. When you transplanted those cells, what people found was that they got these really beautiful green photoreceptor cells in the eyes of recipients. Photoreceptor cells are a very complicated cell type and are structurally very specific to the retina," says Dr. Wallace. "Detecting green photoreceptors was very exciting, because what people thought at the time was that their immature cells were going in and setting up shop in the recipient retina."

Except the cells weren't setting up shop. Instead, they were transferring material. Specifically, they were donating their green fluorescent protein to the remaining photoreceptors, and in some cases, also the missing proteins that were lost due to retina-related diseases. Researchers were finding that this material exchange could create modest improvements in vision. "It has to be really formally proven, but it raises the possibility that just transferring the missing proteins may be enough. Somehow [the recipients] were acquiring the normal proteins from the normal donor cells that were transplanted – at least that is what the interpretation is now," says Dr. Wallace.

> **"The photoreceptors are the cells in the retina that you need to sense light. If you lose them, your retina does not work."**
>
> – Dr. Valerie Wallace

It's too early to tell whether material exchange could be a treatment or a cure for blindness. But it is deeply interesting and has raised even more questions such as: "How do the donor proteins know where to go? What happens to the donor cells after the material exchange? How long after donor cells die can you still detect this exchange? How long can you keep donor cells alive to mediate this transfer? Do the donor proteins integrate fully within the recipient's retina with the photoreceptors?" The short answer? There are no definite answers.

"It's just so impossible to say how this will all pan out," says Dr. Wallace. "It may be that we can harvest material from photoreceptors and use that to repair retinas, like a drug therapy, which is speculation at this point." Adds Dr. Wallace: "We're really asking these fundamental questions, but we would really need to have enough answers [in order] to support any kind of cell transplantation to the eye." ■

Retinal detachment surgery revolution

Groundbreaking new treatment promises speedier recovery and less discomfort

Chris Atchison

Dr. Robert Devenyi has pioneered a new treatment for vision-saving vitrectomies. Patients like North Bay's Phil Rauch, right, urge others not to delay assessment.

It typically starts with a small, dark spot, light flashes or blurred vision at the corner of one's peripheral vision. The symptoms typically intensify and spread, sometimes even emerging in multiple parts of one eye – or both.

It's a frightening condition known as a retinal detachment, when the retina – which sits at the back of the eye and captures light much like camera film, before triggering nerve impulses that create an image for the brain to process – detaches from the eyeball due to small tears or holes, or due to a separation of the vitreous, a gel-like fluid inside the eye.

Phil Rauch knows these symptoms all too well.

Since 2013, the 55-year-old production manager from North Bay, Ont., has experienced five separate retinal detachments in multiple areas of each of his eyes.

"The very first time it caught me off guard because I started seeing a dark spot on my eye; it was like having something on the side of your nose, but nothing was there," he recalls.

According to the Canadian National Institute for the Blind, about half of the population experience vitreous separation by age 50. Nearsightedness, trauma, a family history of retinal detachment and eye diseases, tumours or diabetes can all cause a detachment.

The condition occurs in roughly one person out of every 10,000 in the general population, but is far more common following cataract surgery, when that rate jumps dramatically to one in 100 patients. The condition will eventually lead to blindness, if untreated.

Phil had no idea what was happening the first time he experienced his symptoms. A retinal detachment can permanently impair vision in a matter of days. Indeed, Phil has lost some vision in his left eye, simply because he was unaware of the symptoms.

"I left it for a day before I saw my optometrist, and they told me I had a retinal detachment. They sent me to Toronto right away, to start the process."

According to Dr. Robert Devenyi, a clinician investigator at the Krembil Research Institute and co-director of the Donald K. Johnson Eye Institute – and the doctor who performed Phil's surgeries – that process is called a vitrectomy, a procedure in which the vitreous jelly is removed from a patient's affected eye. In its place, a liquid called perfluorocarbon is injected.

As he explains, the liquid flattens the retina like a steamroller, at which point a laser is used to seal the tear. A reattachment can involve multiple steps, including removing the perfluorocarbon liquid, replacing it with a gas and injecting a silicone oil into the gas-filled eye to help keep the retina in place. Because that oil can only stay in the eye for about three months, a subsequent surgery is required to remove it.

It's a time-consuming process that compromises the patient's vision in the affected eye until the oil is removed. In Phil's case, that meant missing about six weeks of work on more than one occasion during the recovery period.

But if a revolutionary new treatment pioneered by Dr. Devenyi and his Toronto Western Hospital colleagues is approved, the vision-saving vitrectomies of today could soon become obsolete.

While he conducts multiple vitrectomies each week, Dr. Devenyi, who is also the Karen and William Barnett Chair in Ophthalmology, has long been troubled by the discomfort and inconvenience the procedure can cause.

So about three years ago, he began looking for ways to streamline the process. He contacted University of Toronto biomedical engineer Dr. Molly Shoichet, and the two began working on a vitreous substitute.

The result is a groundbreaking hydrocarbon gel, still in experimental trials, that essentially replaces the multiple, complex stages of a vitrectomy with a one-step process.

Here's how it works: When a patient has a retinal detachment, doctors conduct a vitrectomy to remove the vitreous in the individual's eye. But instead of using silicone oil, they inject hydrocarbon gel into the eye to help reattach the retina.

That gel remains in the patient's eye for several months and dissolves on its own, negating the need for a gas injection, the use of silicone oil or subsequent operations.

Perhaps most importantly, the hydrocarbon gel is made with the same optical density as the human eye, so patients maintain their vision while healing. Another benefit: postoperative patients with gas in their eye wouldn't be forced to lie in awkward positions as they recover.

"If they have a gas in their eye, and the tear is in the lower portion of their retina, they'd have to lie with their feet above their heads often for days, a week or more," Dr. Devenyi explains. "But with our vitreous substitute, none of that is necessary. They can be in a normal position."

The promising new procedure would not only mean a more comfortable recovery for patients, but also markedly faster healing times, up to several months less than with the established vitrectomy procedure.

"It's really very exciting to think that if this pans out as we suspect it will, it will change how these procedures are done around the world," Dr. Devenyi says, adding that he's expecting an improvement on the 5 per cent failure rate and 10 to 20 per cent reoperation rate with current retinal detachment methods.

With the hydrocarbon gel now in its seventh (and likely final) laboratory trial version, Dr. Devenyi hopes the procedure will be put into widespread use in about a year.

That development would be welcome news for patients such as Phil, whose lives are temporarily upended by retinal reattachment surgery. In the meantime, he offers this advice to others: don't delay treatment.

"The vision I have lost in my left eye is minimal, but my recommendation is to get to the doctor as soon as you start experiencing something that doesn't look right," he says. "The other times I realized what it was, I reacted right away." ■

Finding new methods for detecting glaucoma

Patients like Stelth Ng know first-hand the impact of this rapidly growing disease

Renee Sylvestre-Williams

Eyes might be the windows to the soul, but they don't like to give up their own secrets, especially with diseases such as glaucoma. Musician and filmmaker Stelth Ng should know; he's spent a decade in and out of the hospital because of his eyes. Stelth, 26, has had more than 16 surgeries in both eyes as a result of various conditions, including cataracts, dislocation of his intraocular lenses, multiple retinal detachments, corneal edema and glaucoma. As a result, he is completely blind in his right eye and uses his left eye to see.

"When people talk about glaucoma, they're usually talking about primary open-angle glaucoma," says Dr. Graham Trope, senior scientist at the Krembil Research Institute and co-director of Glaucoma Service at the Donald K. Johnson Eye Institute. He is also Stelth's ophthalmologist and has been treating him for the past six years. "[Primary open-angle glaucoma is] the most common form of glaucoma in North America. It affects about 65 million people in the world. That's projected to increase to about 76 million or so in 2020. With the aging boomers, glaucoma is becoming more and more common."

Glaucoma results in a buildup of pressure in the eye, which can lead to irreversible vision loss. That does happen, but when you speak with research scientist Dr. Jeremy Sivak, a scientist at the Krembil Research Institute and the Chair in Glaucoma Research at the Donald K. Johnson Eye Institute, you discover that it's more than just a pressure disease – and it can have many causes, as in Stelth's case.

"Glaucoma," he says, "is a chronic degeneration of the optic nerve and the cells that make up the optic nerve, which are called retinal ganglion cells. But they're a particular type of nerve cell in the retina, which is the light-receptive tissue at the back of your eye, like the film in a camera, if you will." All of our visual input, he says, goes through this one thread of the optic nerve that comes out the back of the eyeball. In glaucoma, that thread is damaged, and messages can't reach the brain.

So, glaucoma is actually a neurodegenerative disease. While treatment has focused on lowering eye pressure, research is looking at what causes the nerve damage. There is no definite answer, but there are a lot of options, including looking at the role of glial cells, which are support cells in the central nervous system, or as Dr. Sivak describes them, the pit crew for the specialized nerve cells.

When these specialized cells suffer damage, this can trigger a switch in how the glial support cells work, according to Dr. Sivak. The glial cells go to deal with the injury and don't do their regular work. "The dysfunction of those glial cells is linked as one of the earliest pathological signs that happens in a glaucoma eye. The broad hypothesis underlying this aspect of the lab is, if we can selectively target the right enzymes or the right proteins in those glial cells, then we could encourage them to do their job better again."

Dr. Trope is also working on new methods for detecting glaucoma. His current work with engineer Dr. Moshe Eizenman at the University of Toronto (who is also an affiliate scientist at the Krembil Research Institute) explores the possibility of completing a visual field test on a cellphone. "Patients who may have glaucoma have to do a vision test called a visual field test. This is a very complicated test and expensive," he says. "Patients have to come to the hospital and sit in the machine for 10 or 15 minutes. We check their peripheral vision. It's expensive and hard work, and it requires a skilled technician to run the test."

Stelth says that while his medical odyssey was at times stressful, he was inspired by Dr. Trope and other members of the Glaucoma Service at Toronto Western Hospital.

"I have always felt sincere concern for the well-being of my eyes and vision. My experiences with the doctors here have led me to feel that my vision is a priority, and that I'm not just another name that goes in and out of the hospital. I really owe all of them so much for my ability to still see today."

"My experiences with the doctors here have led me to feel that my vision is a priority ... I really owe all of them so much for my ability to still see today."

– Musician Stelth Ng

And Stelth, who approached music with great intensity because he feared he might go blind, has used that inspiration from these very experiences to influence his current career path. This past March, he organized and initiated a music concert and lecture demonstration series for the visually impaired.

"There were many young children there who were completely blind – some of them had cancer from the age of two that robbed them of their vision. Playing piano, violin and ballet music to them during the concert showed me how much of a difference music can make in their lives. Their enthusiasm alone was touching."

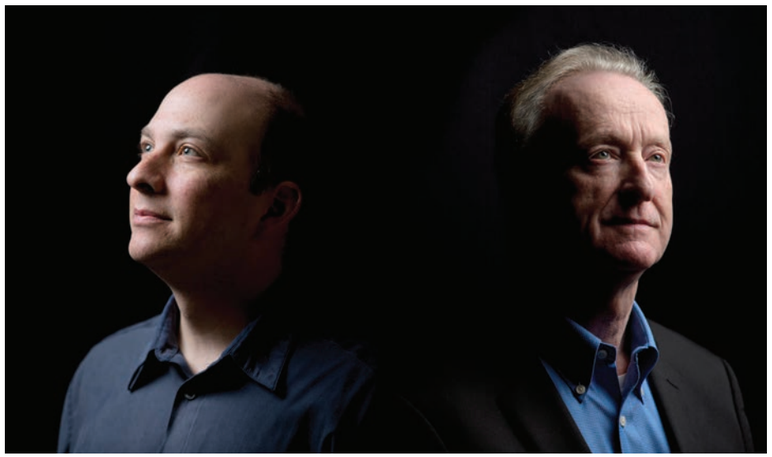
Stelth says he hopes to continue his work with visually impaired children.

Outside of his busy teaching and ballet accompaniment schedule, Stelth works with cinematographers, dancers and musicians in Toronto and New York City to create choreographed short films that combine the two art forms.

"When I was 18, subsequent surgeries on my eyes resulted in total blindness for three months. During those months, I turned to the violin and piano whenever I lost faith and became depressed. Not being able to see sheet music actually gave me the chance to envision visual images in my head while I practised. Several years later, when I regained my vision and saw Charlotte Ballet Dancers perform in Chautauqua, [N.Y.,] the connection with visualizing music came full circle back to me."

Meanwhile, until a cure is found, Dr. Trope says the best treatment for glaucoma is early detection.

He compares it to hypertension, where there are no symptoms, and people aren't aware they have it. People, especially those under age 65, don't get their eyes checked because they have to pay out of pocket. Once there is a glaucoma diagnosis, treatment is free, but unless people get their eyes checked, there's no means for early detection. ■



Because of vision loss, Stelth Ng, opposite page, has had more than 16 surgeries in both eyes. Dr. Jeremy Sivak, above left, and Dr. Graham Trope, above right, are searching for answers.

The miracle of corneal transplants

Researchers at Krembil are striving to be world leaders in ocular regeneration

Shannon Moneo

Patients like Tom Tsokas say that after having corneal transplant surgery, it's "unreal" how much they can now see.

About 10 years ago, Tom Tsokas had to stop driving. He was diagnosed with keratoconus in his right eye during high school, and by his late 40s, it had suddenly gotten worse. "It was like a curtain in front of my eye," says Tom, 56, a Stouffville, Ont., resident who works as an attendant at Toronto General Hospital. "I didn't have pain, but if I was reading a book I had to hold it really close to my face."

Keratoconus is a disease characterized by thinning and protrusion of the cornea, causing an irregular, conical shape and leading to blurred vision. Approximately 50 to 200 out of every 100,000 people develop keratoconus. One possible cause is a decrease in protective antioxidants in the cornea.

Enter Dr. Allan Slomovic, clinician investigator at the Krembil Research Institute and an ophthalmologist specializing in corneal surgery at the Donald K. Johnson Eye Institute. With more than three decades of study and experience, the former clinical psychologist focused on the cornea, the clear window at the front of the eye where surgery results in the highest rates of success, he says. Since completing two prestigious fellowships at Miami's Bascom Palmer Eye Institute, Dr. Slomovic has conducted research into conditions and procedures ranging from penetrating keratoplasty and corneal sensitivity to corneal transplantation and the effects of eye rubbing.

Dr. Slomovic has studied penetrating keratoplasty since 1986, striving to perfect the treatment along the way.

In Tom's case, after a referral by his optometrist in 2011, Dr. Slomovic and his team performed a penetrating keratoplasty. They removed a circular, full-thickness section of Tom's damaged cornea and replaced it with healthy donor tissue that was held in place with stitches.

Following the one-hour, pain-free procedure, Tom wore a patch over his eye for 24 hours. He had the stitches (one-fifth the diameter of a single human hair in size) removed after one year, and gradually the curtain over Tom's eye lifted. "Now I can see, at the bottom of my TV, the scrolling headlines," he says. "It's unreal how much I can see. Before, I couldn't even notice people. Life's gotten better."

Life has also brightened for Harold Keevil, 71. Considered legally blind, he received a new cornea for his left eye, also via penetrating keratoplasty surgery, in February 2017 at Toronto Western Hospital with Dr. Slomovic. The retired stockbroker, who lives in Bracebridge, Ont., had a viral eye infection when he was six. While his right eye did all the heavy lifting, allowing him to be a hockey goalie when younger, Harold had reached the point where he could only see the "E" on the vision chart.

After surgery, like Tom, Harold wore an eye patch, and he has noticed his vision is improving each day. Some of his stitches will be removed after one year, with the remainder taken out months later. Because of his childhood infection, Harold has to take anti-viral drugs for the rest of his life, and he must also take steroids to prevent rejection. But that's all worth it.

"I can now read the eye chart down seven lines," Harold says. "I'm quite delighted. I look forward to getting the vision I had when I was six. And I love photography. This [transplant] should help a lot."

A few centuries ago, the ability to restore someone's vision would have been likened to a miracle. Today, Dr. Slomovic, who is also the Owen and Marta Boris Chair in Stem Cell Vision Research, performs almost 100 corneal transplants each year, bringing light to where there once was darkness.

"I love what I do," says Dr. Slomovic. "But you have to have dedication. There are always improved techniques. You have to stay abreast of the growing technology."

As further proof of how his research has led to pioneering work, in 2010 Dr. Slomovic performed the first successful limbal stem cell transplant for the new ocular stem cell program at University Health Network (UHN). He used cells from Tori Binns's left eye, which were removed and attached to her brother Taylor's left eye. Taylor, 23 at the time, had stem cell deficiency, a rare condition where stem cells that had kept his cornea clear and healthy had been damaged and then destroyed due to wearing contact lenses. Following surgery, Taylor could see well enough to drive, and his eye pain substantially diminished. Dr. Slomovic has since completed several limbal stem cell transplants and is working to make UHN the hands-down leader in ocular regeneration.

One thing that has remained constant is the cornea itself, likened to a three-layer cookie. "It's the only tissue in your body that is perfectly clear, that has no blood vessels," says Dr. Slomovic.

Dr. David Rootman recalls that when he began performing corneal surgery in 1988, there was only one corneal transplant method. "We cut all three layers and replaced them [with a donor's eye tissue]. It worked relatively well, but there was a long healing time." The outermost layer of the cornea is the epithelium, the middle layer is the stroma and the bottom layer is the endothelium.

Also a Krembil scientist, clinician investigator and an ophthalmologist specializing in corneal surgery at the Donald K. Johnson Eye Institute, Dr. Rootman says it could take many months before the transplant stabilized. During that time, and up to many years later, a 10 to 30 per cent rejection rate was possible. "And after the stitches are removed, the only thing holding it in place is scar tissue, which is not terribly strong," he says. People who fell and hit their eye could undo the transplant.

But in 2002, Dr. Rootman became the first Canadian surgeon to perform the Posterior Lamellar Keratoplasty (PLK) procedure, which eventually evolved into the Descemet's Membrane Endothelial Keratoplasty (DMEK) procedure, a revolutionary technique in which only the diseased layers in the cornea are replaced, leaving healthy areas intact.

"I only take the inner 2 per cent – 10 to 15 microns versus 100 microns. Ten microns are the equivalent of two red blood cells stacked on top of one another," Dr. Rootman says.

Like Dr. Slomovic, Dr. Rootman has been honing procedures that were once cutting edge. "There's always progress. We've studied our results and continue to improve our techniques," he says.

First he makes a very small incision where the cornea and the white part of the eye (sclera) meet. Looking through a 100-pound microscope that provides 20 to 40 times magnification, Dr. Rootman peels off the endothelium and Descemet's membrane from the donor tissue, a very exacting procedure. The same thing is done to the patient's cornea. "It's like peeling a very thin postage stamp," Dr. Rootman says. He then injects what he calls the "scroll" of the endothelium through a tiny glass tube, and he unfurls it inside the eye.

DMEK has proven very successful. The single, small incision either self-seals or requires only one or two sutures, making the procedure safer. As well, the rejection rate is a mere 1 per cent, compared to donor rejection rates that can reach 30 per cent. DMEK is a great choice for those patients who have rejected previous transplants. "Within one or two months, patients recover and can see remarkably [well]. It's really solved a lot of issues around corneal transplantations," Dr. Rootman says.

Having performed more than 400 DMEKs, Dr. Rootman now travels the world. He was recently in Israel, teaching other surgeons how to perform the meticulous surgery targeted at the back of the cornea. "I love to work with my hands and spread these techniques, and microsurgery gives me the chance," he

Dr. David Rootman, left, and Dr. Allan Slomovic, right, are relentless in their pursuit of new techniques and technologies.

"I love what I do. But you have to have dedication. There are always improved techniques."

– Dr. Allan Slomovic

says. "I get a kick out of showing people how to do surgery."

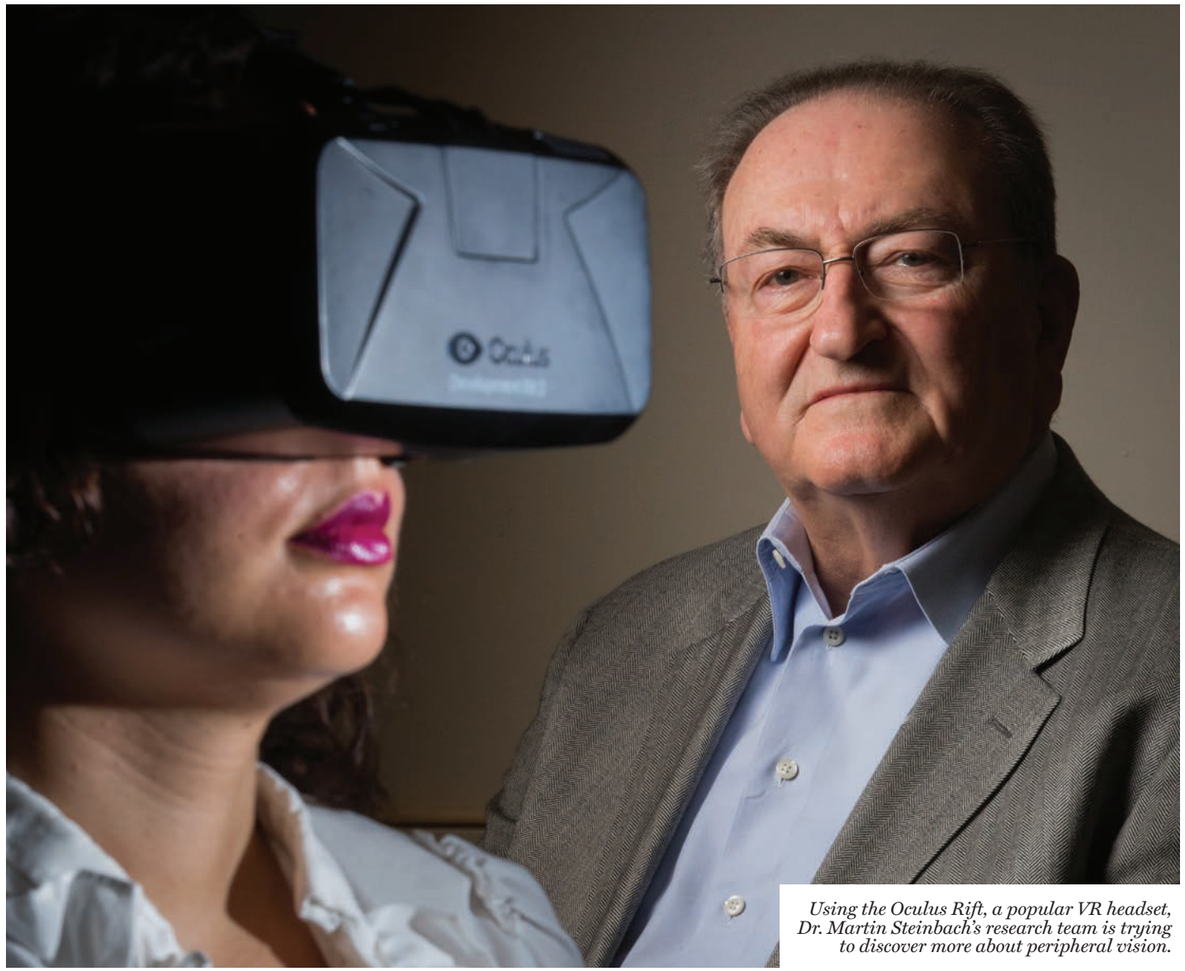
When the front of the cornea is scarred or diseased, a different procedure called deep anterior lamellar keratoplasty may be used. "It's definitely harder. You have to separate the internal membrane without having it rip," says Dr. Rootman, who has performed hundreds of these transplants. "You remove the top and middle layers and preserve the inner layer." Healthy donor tissue replaces what was removed. Because the inner layer (endothelium) is left intact, the integrity of the cornea is maintained, healing is relatively fast, rejection is unlikely and the transplant may last a lifetime.

One area Dr. Rootman would like to further target relates to work being done in Japan, where cells from living or deceased donors are taken. The cornea cells are then mixed with an enzyme that makes them float on the surface of a petri dish, where the cells grow over a number of days. They are then injected into a patient's eye. "I would like to start trials," he says.

Dr. Slomovic, meanwhile, has been enhancing his artificial corneal transplant skills at Toronto Western Hospital over the last decade. He does about 15 each year, compared to the 75 non-artificial transplants he performs. "It's sort of like a last-ditch effort. When they come to this point, there's nothing else," he says. For patients who have rejected donor tissues or had three or more transplants, the acrylic and titanium cornea becomes the ultimate solution.

While both researchers are approaching retirement, they are not ready to hang up their lab coats just yet. Plus, there's much work yet to be done. "I'm having too much fun to stop now," says Dr. Slomovic, 65.

Dr. Rootman, 61, says: "I feel like I'm the luckiest person in the world. I'm doing what I love and helping people. The work is beautiful." ■



Using the Oculus Rift, a popular VR headset, Dr. Martin Steinbach's research team is trying to discover more about peripheral vision.

Using virtual reality to spot glaucoma

A Krembil researcher is deploying digital VR to find early signs of disease

David Israelson

To safeguard our vision, eye experts usually recommend putting aside virtual reality (VR) devices and looking away from computer screens, but Dr. Martin Steinbach has his patients doing just the opposite.

Dr. Steinbach's vision tests started with the use of a large projector screen measuring about two square metres – the size of a TV monitor in an upscale sports bar. The viewing sensation, he says, would be similar to watching an IMAX movie.

At the Krembil Research Institute, his research team (Dr. Esther Gonzalez, Dr. Lumi Tarita-Nistor and students Taylor Brin, Saba Samet and Henry Liu) now has test participants wearing the Oculus Rift, a popular VR headset that immerses its users in their own personal movie. The Rift is not being used for entertainment here, though. The purpose is to find new ways to detect glaucoma in its early stages by measuring "vection" – the sensation viewers experience when a large part of their field of vision is moving and they feel like they too are moving, even though they are not. In patients with mild glaucoma, vection is impaired or absent.

Dr. Steinbach has been trying to find out more about peripheral vision by putting patients into these virtual reality situations and showing them a moving stimulus that makes them feel like they are also in motion. "We did this study called 'Vection in Patients with Glaucoma' in 2014," he says. "We found, by using that big field of vision, that glaucoma patients responded differently than people with

normal vision."

While more work needs to be done, such tests measuring vection in early-stage glaucoma patients could be done in doctors' offices.

"The challenge is that most physicians won't have a giant screen in their office," Dr. Steinbach says. "[But] with a virtual reality device, you can put on a pair of goggles and create a large moving field quite well. That's the project now – to replicate what we've done using a device [that] we can [recreate] in a clinical setting."

Dr. Steinbach's team hopes that the findings of its vection research will make it easier to detect the early signs of glaucoma before too many physical changes have occurred in the eyes of patients with the disease, which is the second most common cause of vision loss in seniors in the country. In someone with glaucoma, the optic nerve is damaged (associated with, but not caused) by high pressure in the eye due to a buildup of excess fluid. More than 250,000 Canadians have chronic open-angle glaucoma.

Other research at Krembil focuses on potential new drug therapies. "All of the current treatments are focused on reducing that pressure [in the eye]," says Dr. Jeremy Sivak, a scientist at Krembil. "It's great to have that option to delay progression of the disease, but what about a treatment that can actually improve things by using drugs? I feel that glaucoma is ready for that kind of change."

According to Dr. Steinbach, detecting the signs of glaucoma early is important because the condition can sneak up on people. Unlike with central vision deterioration – known as macular degeneration – many early-stage glaucoma patients do not experience pain or vision loss.

"Macular degeneration affects fine vision – the part that you use for reading, fine detail and watching television," Dr. Steinbach notes. "That's what gets wrecked, but the periphery still works. [For macular patients], we find out what part of the retina is still working, and [we] retrain people to use that."

People can help preserve their vision by limiting the amount of time spent staring at computer screens. "There are studies that show that a lot of close work affects the development of nearsightness and myopia," he says. "The guidelines say [that] every now and then, [we should] look off into the distance."

Says Dr. Steinbach: "Treating peripheral vision loss due to glaucoma can be more complicated than central vision loss, though. [In glaucoma cases], the centre of the retina works fine. It's the periphery of the retina where the damage is taking place. The problem is that people don't notice it."

If late-stage glaucoma is left untreated, the patient's loss of peripheral vision can develop into tunnel vision or blindness. Dr. Steinbach's research using visual fields is making it possible to detect changes in glaucoma patients earlier, before eye damage occurs.

"Vision is a rich area for study," Dr. Steinbach says. "There is so much you can learn about the brain from patients whose vision is compromised." ■

"Macular degeneration affects fine vision – the part that you use for reading, fine detail and watching television."

– Dr. Martin Steinbach

Bright blue light test sheds light on glaucoma

Glaucoma – an eye disease that is difficult to diagnose and is often without symptoms early on – is one of the top three causes of blindness in the world, affecting hundreds of thousands of Canadians.

At the Krembil Research Institute, Dr. Agnes Wong is leading a study that uses a new procedure to measure changes in the eyes of those with glaucoma, a condition that develops when damage occurs to the optic nerve (the cable that connects the eyeball to the brain), with increased eye pressure being a major risk factor.

An ophthalmologist at Toronto Western Hospital and the Hospital for Sick Children, as well as a scientist, Dr. Wong is employing the chromatic pupillometry technique on the recently discovered intrinsically photosensitive retinal ganglion cells (ipRGCs).

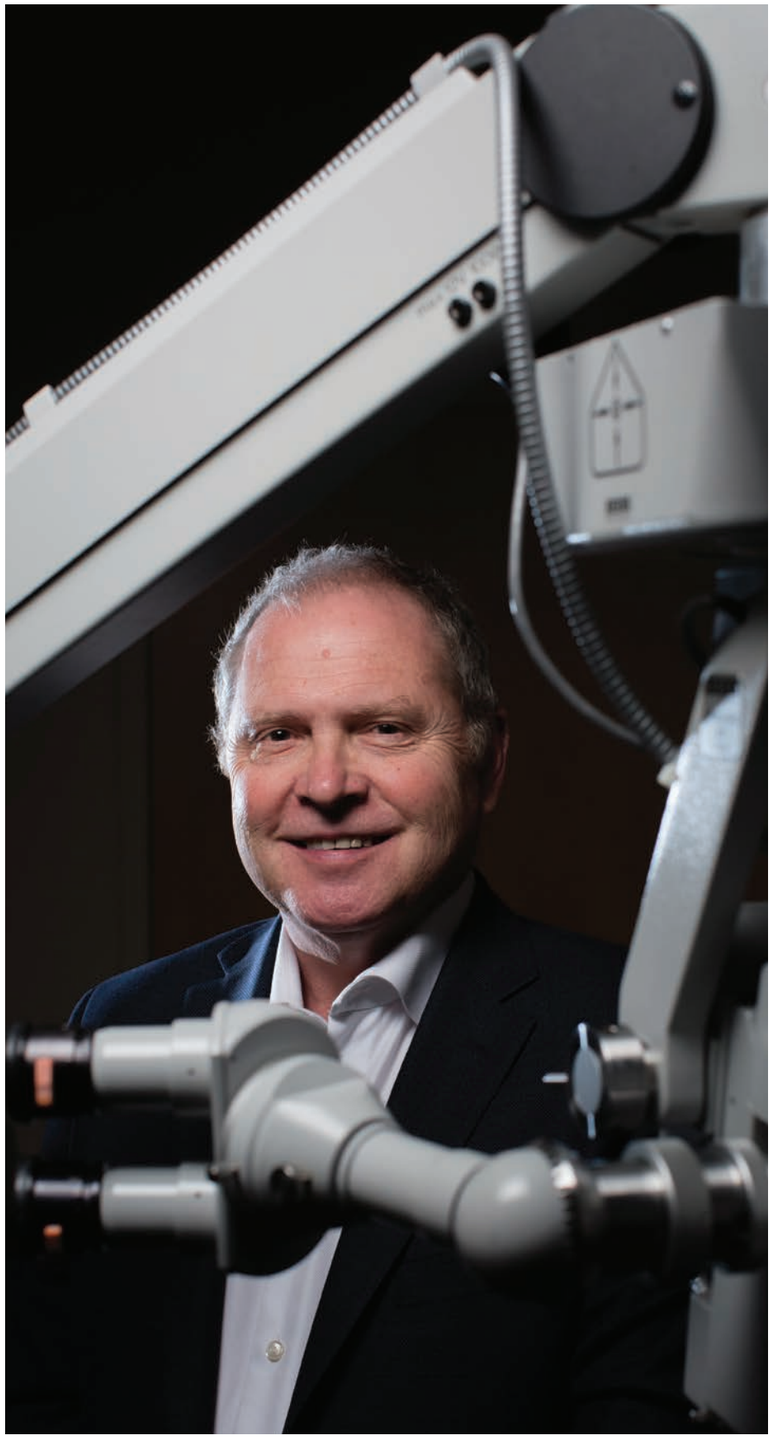
IpRGCs are found in the retina and are now the third type of cells that detect light (photoreceptors), joining rods and cones, which have long been known as the two-unit light traffic team in the eyes.

Chromatic pupillometry uses coloured light that is shone into the eyes to measure pupil size and reaction. Because ipRGCs detect light, they control pupil function, Dr. Wong says. And as she discovered in a previous trial, ipRGCs are activated directly by bright blue light, but not directly by red light.

Using her scientist's palette, Dr. Wong is now applying this new knowledge to the detection of glaucoma, wondering if shining bright blue light into the eyes of those with the condition can provide valuable knowledge.

"Can we monitor ipRGC activity as a biological marker for disease progression in glaucoma?" she asks.

– *Shannon Moneo*



Krembil's Dr. Michael Brent is one of the leading forces behind the national network Diabetes Action Canada. Diabetes is the leading cause of blindness among working-age Canadians.

Breaking down the barriers to eye care

Krembil researchers tackling diabetes are constantly innovating to make retinal screening easier

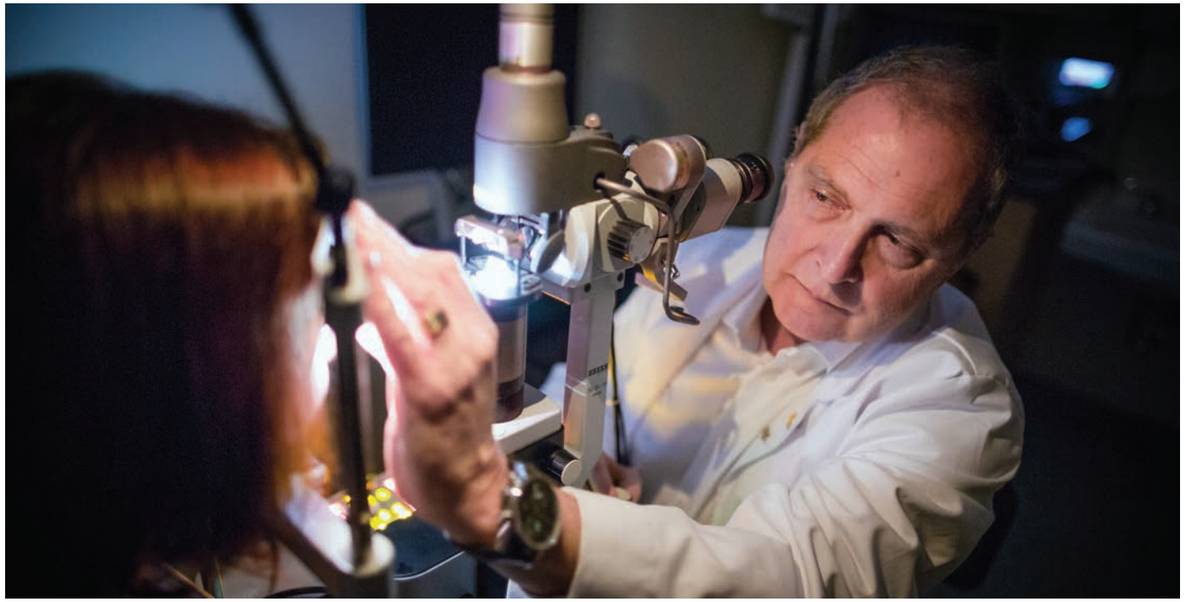
Mary Gooderham

Diabetes is the leading cause of blindness among working-age Canadians. Yet, many people living with the disease fail to get regular examinations that can detect changes in their eyes, signalling diabetes-related complications.

A national network has been set up to encourage earlier diagnoses of eye problems and ensure better health outcomes for more than three million Canadians with the disease.

Dr. Michael Brent, a clinician investigator at the Krembil Research Institute and ophthalmologist at the Donald K. Johnson Eye Institute, says that diabetes particularly affects the eyes. A disease called diabetic retinopathy, which can lead to hemorrhaging of the blood vessels in the retina, is present in up to two-thirds of patients who have had diabetes for 10 years or more, he notes. Yet, studies show that one-third of Canadians living with diabetes have not had an eye examination in the last two years or more.

"There are a number of barriers to care," says Dr. Brent, a retinal specialist who is the ophthalmology lead for Diabetes Action Canada, a national network on diabetes and its related complications that was set up under the Strategy for Patient-Oriented Research (SPOR) program, established by the Canadian



Institutes of Health Research. "Low screening rates can be found everywhere, from marginalized communities in inner cities to the most remote Aboriginal reserves."

The network is currently focused on studying why people don't get regular eye examinations, he says, while its goals include creating a national diabetic retinopathy screening program and developing new technologies that allow for better monitoring of eye diseases among diabetic patients.

"We know that having regular eye examinations is a critically important aspect of preventing blindness in people with diabetes," says Dr. Gary Lewis, endocrinologist and diabetes specialist at University Health Network, director of the Banting & Best Diabetes Centre at the University of Toronto and co-leader of Diabetes Action Canada. "Much of the vision loss associated with diabetes is preventable."

He says the key is to make retinal screening as easy to do as possible. One option is to establish a telephthalmology program, using mobile imaging units in places such as community centres that can take images of the retinas of people with diabetes and upload them for experts elsewhere to analyze. A number of provinces have piloted such programs, Dr. Lewis says. "It's a massive undertaking to do this kind of thing, and we're making huge headway."

Dr. Chris Hudson, a senior scientist at Krembil, says there are novel tests to look for changes in the blood vessels of retinas in patients with diabetes and other diseases such as macular degeneration, hypertension and atherosclerosis. His lab at Krembil has developed techniques to measure changes and differences in blood vessels that are as small as 0.1 of a millimetre thick. For example, the vessels can become stiffer and lose the ability to regulate the flow of blood.

Detecting these kinds of changes – or simply by looking at subtle differences between blood vessels – could help doctors diagnose diabetic retinopathy sooner, says Dr. Hudson. Meanwhile, interventions are possible to repair and restore the condition of the microscopic blood vessels themselves, including new drugs and laser surgery. "All of these treatments work better if you can flag the problem as early as possible," he cautions.

"People often don't get tested in the first place because screening can be expensive and involve long wait times," says Dr. Brent, who is also the Milton Harris Chair in Adult Macular Degeneration. "And this can particularly be an issue for new immigrants and indigenous people." The network's retina screening group, which he co-leads, involves physicians, scientists and patients working together toward solutions.

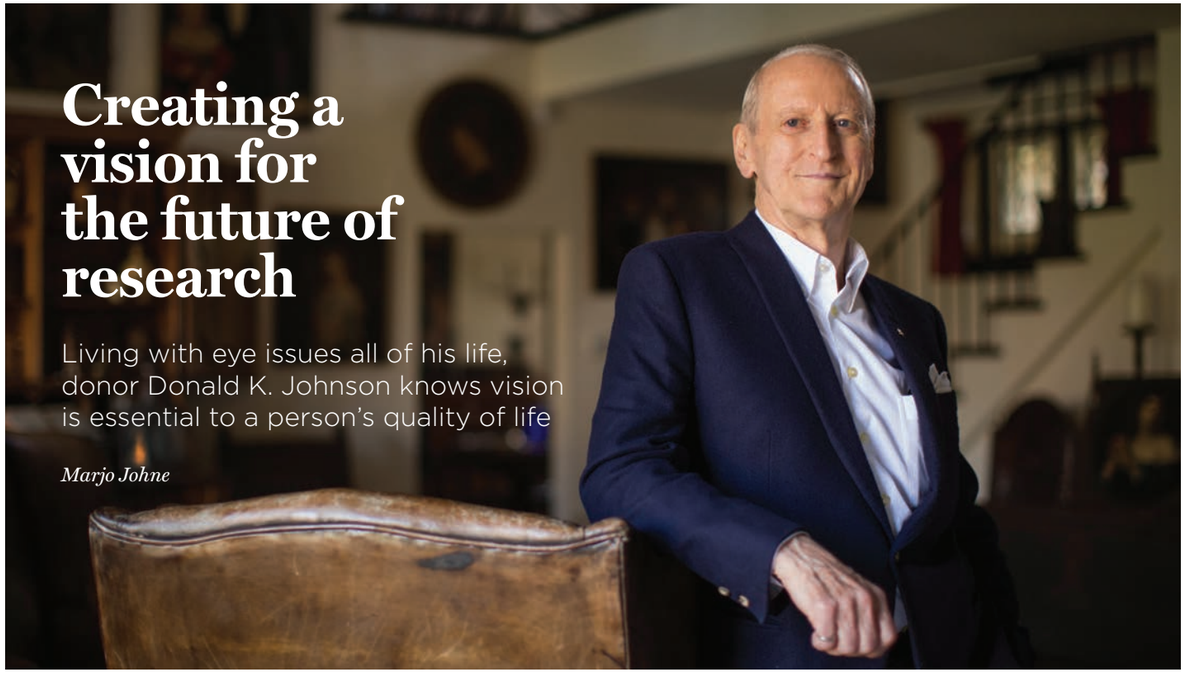
"Learning from each other is very important," he says. "We can change policy, scale up and take things to a national level, which someone working on their own can't do."

Dr. Lewis, who is also the Drucker Family Chair in Diabetes Research and the Sun Life Financial Chair in Diabetes, says the issue of retinal screening is getting an ever-higher profile, with the involvement of federal and provincial governments, as well as private companies. "And we have people living with diabetes advising us at every level of what we're doing."

He says that Diabetes Action Canada, which is one year into its five-year mandate, "has tremendous profile already," with vision as one of its flagship programs. "We have a real focus on innovation and healthcare delivery," Dr. Lewis says.

By developing a national diabetes database and taking a deep reach into marginalized communities, he expects that diabetic retinopathy can be diagnosed earlier, with fewer people experiencing vision loss.

"We're talking about blindness – that's a tremendous disability, and it's preventable in many cases. Let's screen more people and refer them for treatment," says Dr. Lewis. "We're talking about a very big, impactful thing we're doing here." ■



Creating a vision for the future of research

Living with eye issues all of his life, donor Donald K. Johnson knows vision is essential to a person's quality of life

Marjo Johne

Donald K. Johnson has had vision problems for most of his life. He was diagnosed with myopia – also known as short- or nearsightedness – when he was a child, and as an adult he developed glaucoma, cataracts and macular degeneration.

So in 2007, when he had an opportunity to help establish an eye centre at Toronto Western Hospital that would offer patients the latest treatments, Mr. Johnson stepped up – with a $5-million gift.

"Having good vision is key to experiencing a very productive and enjoyable life," says Mr. Johnson, a veteran investment banker who was named to the Investment Industry Association of Canada's Hall of Fame in 2013. "It's believed that 90 per cent of what we learn comes from vision – it's essential to a person's happy lifestyle."

The $5-million donation funded the launch of the Donald K. Johnson Eye Centre. That was just the beginning. On his 80th birthday, he and his wife, Anna McCowan-Johnson, donated another $10 million.

This enabled the Krembil Research Institute to merge its Vision Science Research Program with the Donald K. Johnson Eye Centre to create the Donald K. Johnson Eye Institute – a centre of excellence, where clinicians, researchers and educators can collaborate to advance the latest treatments for vision loss.

"That was the best birthday gift I received: the opportunity to top up my gift to create the leading eye institute in Canada and one of the best internationally," says Mr. Johnson, who was born in Lundar, Man., to parents of Icelandic descent. "I believe we all have a responsibility to give back to the communities and institutions that have touched and changed our lives."

Philanthropy like this has already helped support a number of groundbreaking achievements and is enabling Krembil researchers in their tireless quest for more.

Mr. Johnson says his life has certainly been changed by Krembil and Toronto Western Hospital.

"I wear contacts today," says Mr. Johnson. "I have cataracts and glaucoma, but I haven't needed surgery. I've had great treatment at Toronto Western."

Mr. Johnson's support for vision care and research dates back to the late 1980s – but his contributions to philanthropy go far beyond that. For 12 years, he lobbied for the removal of capital gains tax on listed securities donated to charity. The federal government lifted this tax in 2006. This has created more opportunities for people to be philanthropic and has had a major impact on many organizations.

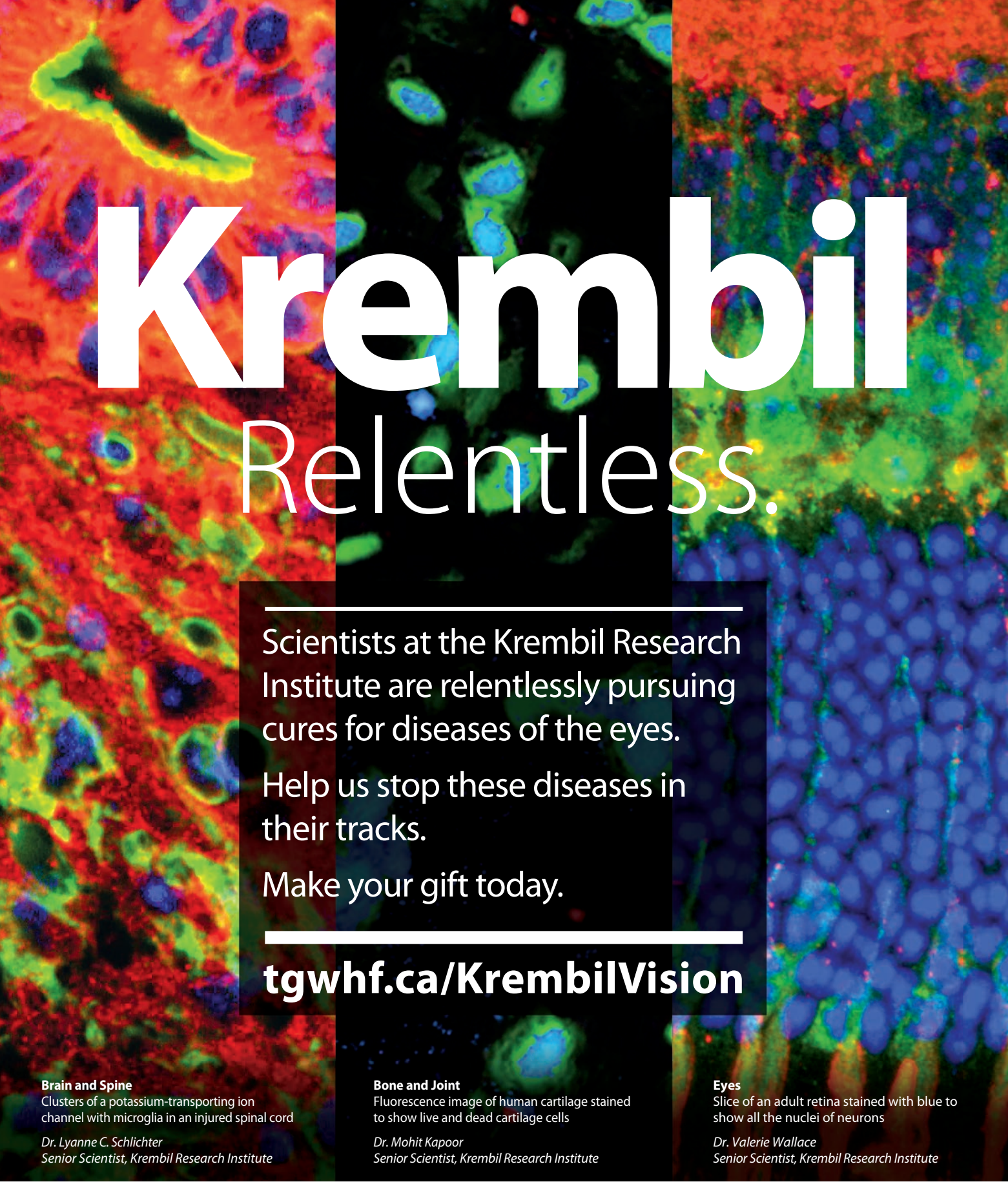
"Since then, charities have received more than $1 billion virtually every year," says Mr. Johnson.

But more needs to be done, he adds. Since 2006, Mr. Johnson has turned his lobbying efforts to capital gains tax on charitable donations of private company shares and real estate.

Such efforts are critical in the face of increasingly tight government budgets, he says.

"I think it's important for people to realize that all levels of government today are facing fiscal challenges and have a limited capacity to provide research funding for all diseases, including eyes," says Mr. Johnson. "Private sector donations are really key to enabling the purchase of the latest technology and equipment, and attracting star researchers to our institutions.

"Governments can provide funding to enable organizations to be good, but it's the donations from individuals and private sector companies that help research organizations go from being good to being great." ■



Toronto General & Western Hospital Foundation UHN