nova scotia health authority
Research Services

Research Focus

ophthalmology

With its aging population and rising rates of diabetes, Nova Scotia carries a growing burden of age-and diabetes-related eye disease. Researchers in the NSHA/Dalhousie Department of Ophthalmology & Visual Sciences are tackling the challenge with high-impact research. Together with their colleagues and with collaborators around the world, they are transforming the understanding, diagnosis, monitoring and treatment of eye diseases.

Research strengths include: world-leading work to understand glaucoma through long-term clinical studies and the development of powerful imaging technologies; identifying genes and treatments for inherited eye diseases; testing novel therapeutics for macular degeneration and diabetic retinopathy, and developing a new generation of safe and effective treatments for pain and inflammation in the eye.

The department is deeply committed to fostering the next generation of eye researchers and has developed extensive supports for trainee research.

Study Participant Enjoys Recurrence-Free Recovery

"I was lucky... I received monthly injections and, within three months, my vision had started to improve. By the end of one year of treatment, my vision was almost normal."

Patient Vic Lewis' retina is scanned using equipment purchased with funds that he, the Masonic Foundation and the QEII Foundation raised.

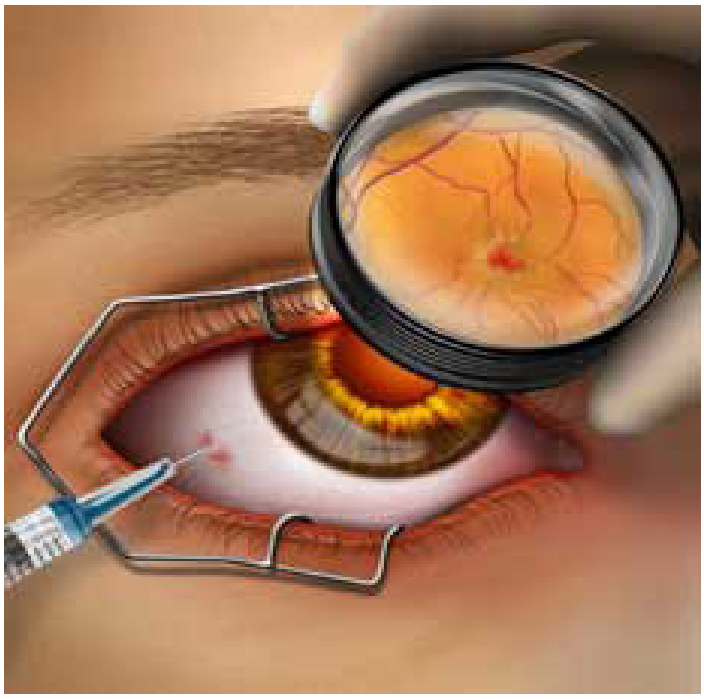
The loss of central vision came on suddenly for Vic Lewis. In 2009, the former high school teacher and website developer noticed a black area in the middle of his left-eye visual field. It grew so quickly, soon he could scarcely see out of that eye. An ophthalmologist in his Prospect-area community promptly referred him to a retina specialist at the QEII Health Sciences Centre, Dr. Ann Hoskin-Mott.

"Dr. Hoskin-Mott diagnosed wet AMD, a type of age-related macular degeneration that can progress quickly to total blindness," says Mr. Lewis, now 75. "I was lucky… she put me on a trial of a new drug, Eylea. I received monthly injections and, within three months, my vision had started to improve. By the end of one year of treatment, my vision was almost normal. It's been fine ever since!"

Mr. Lewis is now one of the longest recurrence-free wet AMD patients in the world. "The team at the Eye Care Centre is exceptional," he says, noting that staff like Trina MacDonnell and Andrea Dean (pictured above) have been a steady support since the beginning. "I come back every three months for a thorough check-up with Dr. Alan Cruess; I know my eyes are in excellent hands."

In an effort to show his gratitude to the Eye Care Centre for its diligent care, Mr. Lewis, a freemason, teamed up with Dr. Cruess, the QEII Foundation and the Masonic Foundation to raise funds for a sophisticated clinical retina scanner. Now his eyes are scanned using equipment he helped fund: "I owe them so much, it was the least I could do."

Retina Researchers Bring Sight-Saving Treatments to Maritimes



Treatments for AMD are injected directly into the eye
Image source: www.allaboutvision.com

NSHA researchers are key players in worldwide efforts to introduce powerful new treatments for degenerative retinal diseases that, until 2007, were simply unstoppable.

"We enrolled some of the first patients in the world to receive Lucentis, the breakthrough treatment that has reversed vision loss and preserved years of sight for millions of people with age-related macular degeneration," says Dr. Alan Cruess, a senior ophthalmologist, former department head and professor who specializes in retinal disease. "Since then, we've continued to test new treatments for AMD and expand the uses of approved medications."

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Age-related macular degeneration (AMD) is the leading cause of blindness in people over the age of 50, and affects as many as 15 per cent of people over the age of 80. It is caused by the progressive breakdown of the macula, a small area in the centre of the retina that allows us to see details in front of us so we can recognize faces, read, drive and perform other functions of daily life. Lucentis and newer treatments like Eylea work only on the "wet" form of AMD, by interfering with the overgrowth of leaky blood vessels behind the retina that damages the delicate nerves of this light-sensitive tissue.

"We're currently involved in a trial of a new agent for 'dry' AMD," notes Dr. Cruess. "In another year or two, we may have an effective treatment for this devastating form of macular degeneration as well."

The same treatments that have preserved vision for so many people with wet AMD are also showing promise against diabetes-induced retinal damage.

"We enrolled some of the first patients in the world to receive the breakthrough treatment that has reversed vision loss and preserved years of sight for millions of people."

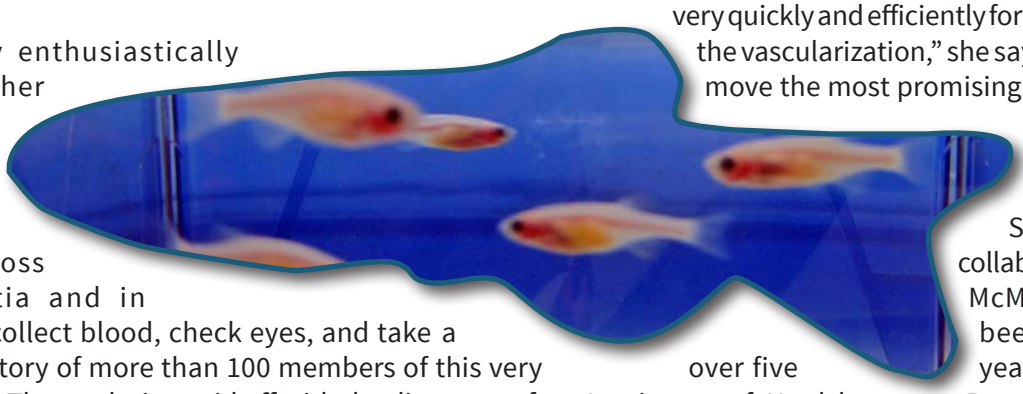
"We're involved in several trials to see if agents that work for wet AMD can also be used to protect vision in diabetic retinopathy," says Christine Morrison, a research coordinator in the Department of Ophthalmology & Visual Sciences. "With diabetes on the rise and affecting people at younger and younger ages, there's a serious need for treatment protocols to protect their eyesight."

The NSHA/Dalhousie retina research group is a member of the Diabetic Retinopathy Clinical Research Network, funded by the U.S. National Institutes of Health. "It's a feather in our cap to be invited to join this North American network of leading retina research centres," notes Dr. Cruess. "Whether in diabetic retinopathy, AMD, or other retinal diseases, our involvement in clinical trials provides patients with early access to the newest treatments and protocols, and physicians with a good working knowledge of the new treatments so they can be easily adopted for widespread use once they're approved."

From Gene to Therapy: Researchers Seek Solutions for FEVR

Researchers at NSHA, Dalhousie and the IWK are building on long-term genetic studies to identify and test potential therapies for FEVR, familial exudative vitreoretinopathy, a genetic disease that triggers disordered blood-vessel growth in the eye. This, in turn, can cause the retina to detach, often leading to visual impairment or blindness.

Nearly 20 years ago, pediatric ophthalmologist and NSHA-affiliated scientist Dr. Johane Robitaille encountered the worst case of FEVR in an infant she had ever seen. "The baby had a very severe form of FEVR, and her mother and other relatives were also affected," Dr. Robitaille recalls. "I saw the opportunity to identify the gene by studying this family."



The family enthusiastically embraced her proposal, welcoming her into their homes across Nova Scotia and in Ontario to collect blood, check eyes, and take a detailed history of more than 100 members of this very large family. The road trips paid off with the discovery of a key gene for FEVR, which Dr. Robitaille and her colleagues published in *Nature Genetics* in 2002.

Dr. Robitaille has been on the hunt for other genes involved in FEVR ever since, working with collaborators across Canada and in the United States, England, Finland, Saudi Arabia, Iran and Australia. Now, in Halifax, she is evaluating four new genes for FEVR in a zebrafish model developed by Dr. Jason Berman and his team in the Berman Zebrafish Laboratory.

"Zebrafish reproduce very quickly and are virtually transparent, so retina vessels tagged with a fluorescent protein are very easy to image," notes Dr. Robitaille. "This, and the fact they share many genes with humans, makes them an ideal proof-of-principle model."

Drs. Robitaille and Berman have already found that at least two of the genes, when mutated, affect blood-vessel development in the fish's eyes. "Once we know we have a valid zebrafish model, we can start testing candidate drugs very quickly and efficiently for their ability to regulate the vascularization," she says. "From there we will move the most promising agents along to more complex pre-clinical models."

She and another collaborator, Dr. Christopher McMaster, have recently been awarded $625,000 over five years from the Canadian Institutes of Health Research, and $4.5 million from ACOA's Atlantic Innovation Fund, for their promising efforts to identify and validate potential therapeutics for FEVR. This is on top of previous funding through the Genome Canada IGNITE project (a five-year project to identify genes and treatments for rare genetic diseases) and Canada Foundation for Innovation equipment funding in the amount of $7.5 million.

"Zebrafish reproduce very quickly and are virtually transparent, so retina vessels tagged with a fluorescent protein are very easy to image. This, and the fact they share many genes with humans, makes them an ideal proof-of-principle model."

The Berman Zebrafish lab currently houses 20,000 fish of its impressive 60,000-fish capacity. Left: Dr. Johane Robitaille and Dr. Jason Berman hold a small tank full of zebrafish that are part of Dr. Robitaille's research.

Studies Shed Light on Glaucoma and Potential New Treatments for "Tunnel Vision"

The term "tunnel vision" is usually used as a metaphor for a too-narrow focus of attention, but for many people with glaucoma, tunnel vision becomes a literal reality as they lose their peripheral vision.

"Glaucoma kills retinal ganglion cells which carry messages from the eye to the brain, leading in many cases to gradual loss of vision," explains Dr. Balwantray Chauhan, Mathers Chair, professor and research director in the Department of Ophthalmology & Visual Sciences. "But it can take years or decades to produce symptoms… many people are not even aware they have glaucoma until the damage is extensive and so detecting damage early is key."

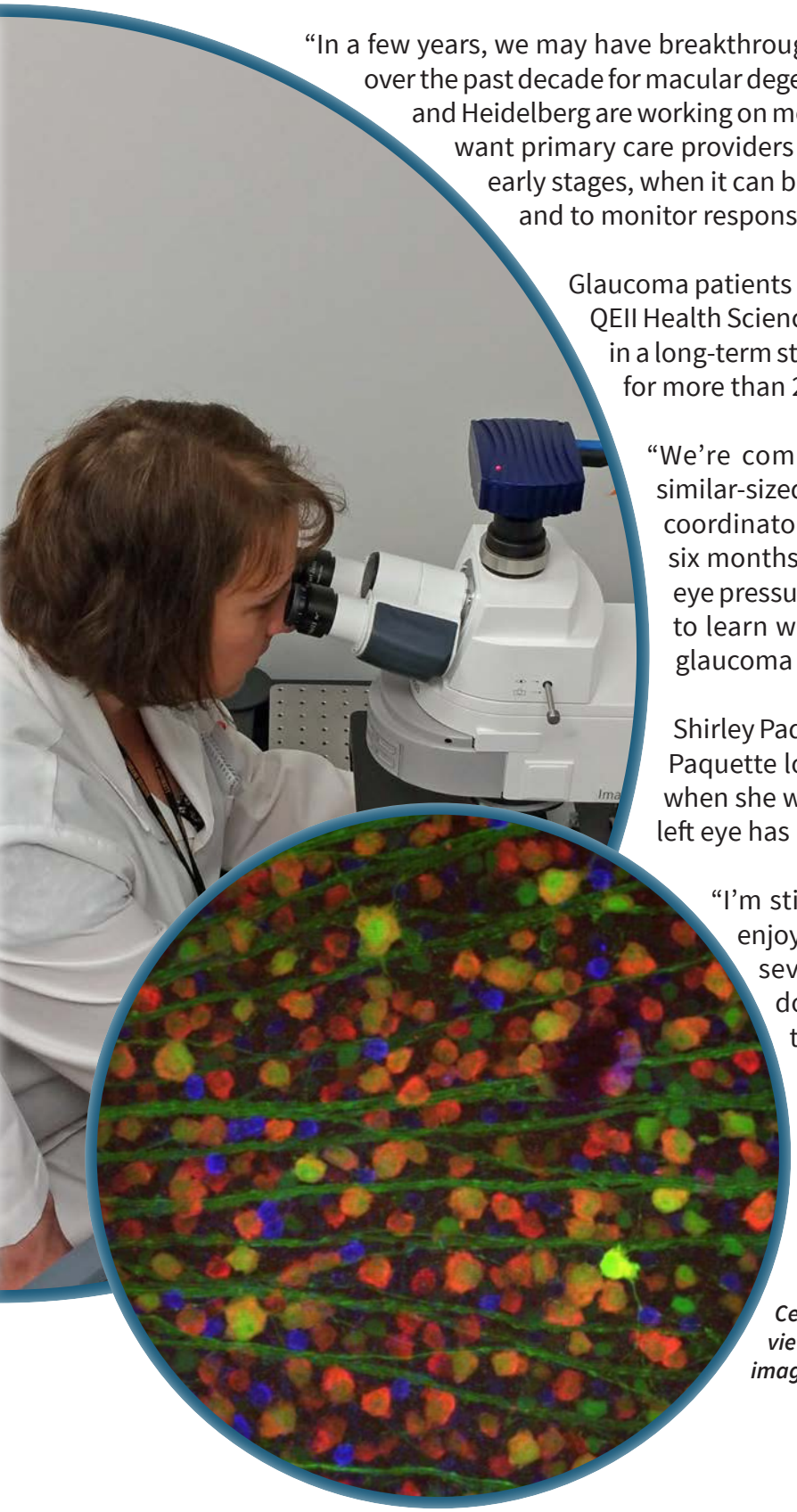
"The resolution and precision of our technology is high enough that we are finally able to trace glaucoma development at the cellular level."

Dr. Chauhan is leading a multi-pronged research effort to understand how glaucoma progresses.

He and his team in the Optic Nerve & Retina Lab are making a quantum leap in diagnostic imaging. In partnership with Germany's Heidelberg Engineering and with funding from ACOA's Atlantic Innovation Fund, they are developing sophisticated new technologies with the potential to image individual retinal ganglion cells.

"The resolution and precision of our technology is high enough that we are finally able to trace glaucoma development at the cellular level," Dr. Chauhan explains. "Learning this and other aspects of glaucoma progression is providing us with new targets for therapeutic agents."

Currently glaucoma is treated by reducing eye pressure. With these new imaging developments, however, Dr. Chauhan and his team are poised to test candidate molecules in pre-clinical models of the disease. They want to see if these agents can protect retinal ganglion cells and their axons from glaucoma damage, when combined with reducing eye pressure.



"In a few years, we may have breakthrough treatments for glaucoma, such as we've seen over the past decade for macular degeneration," says Dr. Chauhan. Meanwhile, his team and Heidelberg are working on more compact and affordable imaging devices. "We want primary care providers to have the means to diagnose glaucoma in the early stages, when it can be better managed to prevent or delay vision loss, and to monitor response to treatment over time."

Glaucoma patients are followed closely in the Eye Care Centre at the QEII Health Science Centre. About 70 of these patients are involved in a long-term study of glaucoma progression that's been running for more than 25 years.

"We're comparing a group of glaucoma patients with a similar-sized group of healthy volunteers," explains research coordinator Donna Hutchison. "Participants come in every six months and we test their visual acuity, visual field, and eye pressure, and image the retina, macula and optic nerve, to learn what's changing with age and how this differs in glaucoma compared to healthy vision."

Shirley Paquette joined the study 20 years ago. Now 90, Mrs. Paquette lost the vision in her right eye literally overnight, when she was in her 70s. The loss of peripheral vision in her left eye has been more gradual.

"I'm still able to see clearly into the distance, so I can enjoy my harbour view," says Mrs. Paquette. "I've had several surgeries to control the eye pressure so I don't need drops anymore. I'm very confident in the care I'm receiving, especially with the regular and thorough follow-up through the study. If I can help the doctors learn more about how glaucoma progresses, that's something I feel very good about."

Centre: Team members Corey Smith and Michele Hooper view the image of a mouse retina. Inset: This high-resolution image of a mouse retina shows individual ganglion cells .

Optic Nerve & Retina Lab

The Circuitry of Sight

Scientists in the Optic Nerve & Retina Laboratory at Dalhousie Medical School are shedding light on the circuitry of the retina and mechanisms of blinding diseases.

- **Drs. Bill Baldridge**, **Steven Barnes** and **François Tremblay** want to know how nerve cells work together in the eye to capture and send visual signals to the brain, enabling sight.
- **Dr. Baldridge** and **Dr. Melanie Kelly** are studying chemicals that neurons in the eye use to communicate, as potential targets for treatment of eye diseases in which these connections are lost.
- **Dr. Balwantray Chauhan** is developing world-leading imaging technologies to examine the mechanisms of glaucoma progression and effects of potential new treatments.
- **Dr. Johane Robitaille** is identifying genes behind inherited ocular diseases and investigating potential treatments.
- **Dr. Barnes** and **Dr. Tremblay** are collaborating with ophthalmology resident, **Dr. Tom Zhao**, on a technology to restore vision in diseases caused by irreversible loss of light-sensitive neurons (photoreceptors). They're using molecular tools called chemical photoswitches to transform retinal ganglion cells into new photoreceptors.

Custom Cannabinoids to Treat Eye Problems Safely

Dr. Melanie Kelly, chief scientific officer of Panag Pharma Inc., in the Optic Nerve & Retina Lab in Halifax

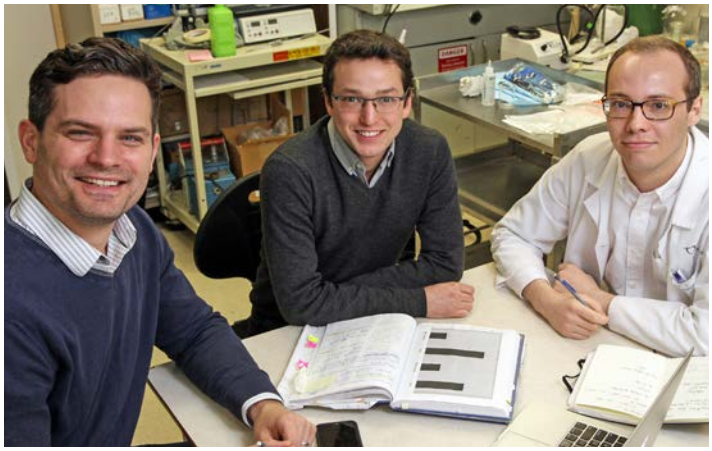
Vision scientist and pharmacology professor, Dr. Melanie Kelly, has been studying cannabinoids for nearly 20 years in the Optic Nerve & Retina Lab, sifting through hundreds of potential targets and cannabinoids to identify their effects in the eye and other parts of the body.

Now Dr. Kelly is chief scientific officer of Panag Pharma Inc., a Nova Scotia startup company that's commercializing cannabinoids, custom-made and naturally sourced, to ensure they are both effective and safe. NSHA/Dalhousie anesthesiology/pain management specialists Dr. Mary Lynch, Dr. Christian Lehmann and Dr. Orlando Hung are also key members of the Panag team.

"Over the years, I've worked with cannabinoids that occur naturally in marijuana and other plants, as well as synthetic derivatives designed to provide a targeted therapeutic effect without creating a 'high,'" she says. "We have two patented and trade-secret formulas through Panag—the first will begin clinical trials in spring 2017, the other will follow soon after. One is a topical cream to treat pain in muscles and joints, the other is a medication to treat pain and inflammation in the eye."

Dr. Kelly and others have found that marijuana's effectiveness in lowering eye pressure in glaucoma is transient. She and U.S. collaborators are developing and testing more targeted cannabinoid formulations they hope will provide sustained eye-pressure-lowering effects, as well as protect neurons in the eye.

Resident Research: A New Approach to Treating Post-Op Eye Infections



Dr. Mark Seamone collaborates with Pharmacology resident Dr. J. Thomas Toguri and Dalhousie student J. Daniel Lafrenière

Fourth-year ophthalmology resident Dr. Mark Seamone is pioneering a new approach to treating post-operative eye infections.

"In my second year of residency, I started to wonder how the ocular immune system responds to infection," says Dr. Seamone, who also holds a master's degree in immunology. While assisting with vitrectomies—a procedure that removes vitreous gel from the eyeball, often to treat post-operative eye infections—he noticed that samples of the vitreous gel were routinely taken for laboratory analysis. "I analyzed some of these samples and discovered that VEGF and other cytokines were elevated."

VEGF-A—or vascular endothelial growth factor A—is a cytokine best known for its role in promoting blood-vessel proliferation. It also promotes inflammation, contributing to vascular leakage and the recruitment of immune cells.

"Leaky blood vessels are very dangerous in the eye," says Dr. Seamone. "The eye is normally shielded from systemic immune activation by the blood-ocular barrier. Breakdown of this barrier can expose delicate ocular structures to systemic immune responses that lead to tissue injury."

With funding from the Department of Ophthalmology & Visual Sciences, Dr. Seamone embarked on a study to see if the VEGF blocker, Avastin, could reduce inflammation in a pre-clinical model of ocular inflammation. Avastin is routinely used to treat diabetic retinopathy, macular degeneration and retinal vein occlusion.

"We found that blocking VEGF-A significantly reduced ocular inflammation compared to controls in our pre-clinical model," he says. "Our preliminary results indicate Avastin would be an effective adjuvant in combination with antibiotics and vitrectomy to protect ocular tissues from the effects of intraocular infection."

Dr. Seamone hopes to initiate clinical trials to assess the efficacy of Avastin as adjuvant therapy in post-operative endophthalmitis, an infectious complication of cataract and other ocular surgeries.

A Broad Spectrum of Resident Projects

- **Dr. William Best**, assessing needs in undergraduate ophthalmology education
- **Dr. Wesley Chan**, transverse venous sinous stenosis on magnetic resonance imaging in patients with idiopathic intracranial hypertension
- **Dr. Harald Gerde**, assessing the utility of an FZD4 knockdown zebrafish model for use as an efficacious drug screen
- **Dr. Claire Hamilton**, comparing outcomes of trabeculectomy with subconjunctival injection of Mitomycin C, versus topical application with cellulose sponge
- **Dr. Darrell Lewis**, UV-A cross-linking of cryopreserved donor corneas
- **Dr. Aaron Winter**, traumatic brain injury and retinal vascular pathology
- **Dr. Amr Zaki,** assessing anxiety and pain associated with intravitreal injections
- **Dr. Tom Zhao**, DENAQ photo-switch as a chemical visual prosthesis in a model of acquired retinal degeneration

Research Support

Ophthalmology Builds Funding for the Future on a Solid Base

The Department of Ophthalmology & Visual Sciences has been able to build productive, high-impact research programs—not only through the ability of its members to attract peer-reviewed grant funding, but also through its own base of endowed funds. "Thanks to generous donors and support from Dalhousie University and the QEII Foundation, we have an endowment that allows us to help trainees and faculty members establish and sustain their research careers," says department head, Dr. Marcelo Nicolela.

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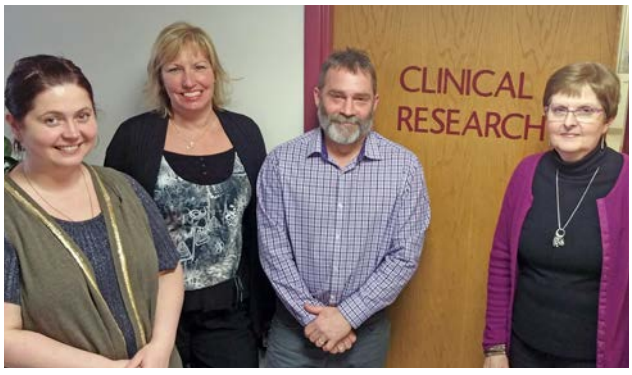
In 2012, the late Peggy St. George made the last of three donations totalling $9 million, in honour of her stepparents, Dr. R. Evatt and Rita Mathers. According to family members and historical archives, Dr. Mathers was "the leading ophthalmologist in the city" in his time. The Mathers fund supports the research chair currently held by Dr. Balwantray Chauhan, as well as scholarships for graduate students, fellows, trainees in clinical vision science, and residents pursuing a master's degree in conjunction with their residency training in ophthalmology.

Ophthalmology & Visual Sciences recently established a new endowment, with help from the QEII Foundation, to fund a clinical scholar award in glaucoma research. The next goal is to raise enough funds to support a clinical scholar award in retina research. "Clinical scholar awards provide faculty members with protected time for pursuing research," notes Dr. Nicolela. "This is crucial to their long-term success as clinician scientists."

Funding from within the department allows researchers to kick start their research projects and gather preliminary data, so that they have a solid base from which to apply for funding from outside sources.

Strong Staff Support Enables Successful Research

Long-term cohort studies and clinical trials in the Department of Ophthalmology & Visual Sciences would not be possible without the dedicated efforts of skilled and knowledgeable research staff. These include four research coordinators, pictured right: Oksana Dyachok, Christine Morrison, Glen Sharpe and Donna Hutchison.



To further boost its research success, the department hired Leah Wood as research manager in 2015. Ms. Wood provides guidance and support regarding grant applications, research ethics board submissions, budget proposals, study protocols and many other aspects of research.

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