Groundbreaking discoveries are leading to new therapies and a holistic approach to patient care.
Rethinking the “Silent Thief of Sight”

Glaucoma is one of ophthalmology’s greatest puzzles. We can often slow its progress, but compliance with drops is low, we lack effective drug therapies, and surgery is a still-evolving field. Outcomes suffer further as half of all glaucoma patients don’t even know they have the disease until significant vision is lost.

Recently, our understanding of glaucoma has evolved. Rather than focusing solely on reducing intraocular pressure, Moran Eye Center researchers are looking at systemic issues that relate to glaucoma, and they have made groundbreaking discoveries regarding the mechanisms that cause pressure to damage the eye. These discoveries are leading to exciting new drug therapies. At the same time, our physicians are customizing treatment plans and are figuring out more effective ways to treat patients in countries where access to regular care is limited. In this edition of Clinical Focus, you’ll learn how broadening our thinking about glaucoma is moving us closer to solving the puzzle of this complicated disease.

Moran researchers have discovered new noninvasive drugs to treat the effects of excessive swelling in glaucoma. These drugs also have promising implications for treating traumatic ocular/brain injury, stroke, and epilepsy.

Glaucoma Research Results in New Targets to Protect Neural Cells from Dying

David Krizaj, PhD

No new glaucoma drugs have been launched over the past decade, in part because the mechanism that causes pressure to damage the eye was unknown. We thought that if we could find the mechanism, we could block those pressure sensors with pressure-reducing drugs. We found it—and we were able to successfully protect cells from dying.
**Challenge** Physiologically, glaucoma correlates with increased intraocular pressure (IOP). Over time, elevated IOP triggers a pressure-induced inflammatory response by retinal glial cells, which then cause retinal ganglion cells (RGCs) to degenerate, resulting in irreversible vision loss. Ideally, glaucoma treatment should combine IOP-lowering medications with treatments that protect RGCs from elevated IOP. Unfortunately, this is not the case. No current medications target the primary fluid outflow of the trabecular pathway; instead, they target outflow through the less efficient uveoscleral pathway. And there have been no neuroprotective treatments because the pressure-sensing mechanism in RGCs had not been identified until now.

**Method** We researched how cells communicate with each other and have now identified and characterized a mechanism that is confined to the trabecular meshwork, ciliary epithelium, RGC, and retinal glial cells—the exact cells that are the most impacted by elevated IOP in glaucoma. This mechanism is activated by pressure-sensitive TRPV4 channels, which are permeable to calcium and a major modulator of cell function. When the channels are activated by pressure, they drive a panoply of signaling pathways that are a hallmark of glaucoma. We characterized the functional expression of TRPV4 in trabecular meshwork cells, RGCs, and glia using a combination of electrophysiological, optical imaging, genetic, and molecular approaches to show that they mediate cell swelling, stretch, and the effects of elevated IOP on reactive gliosis and RGC death (Ryskamp et al., 2011; Krizaj et al., 2014; Ryskamp et al., 2014; Jo et al., 2015, *Journal of Neuroscience*).

**Results** In collaboration with medicinal chemists and pharmacology/toxicology experts at the University of Utah, we developed systemic and prodrug formulations of TRPV4 antagonists. These novel drugs dramatically lowered IOP in mouse and non-human primate glaucoma models and are 100 percent effective in protecting RGCs from the effects of elevated pressure and cell death.

**Implications** By developing new, noninvasive treatments that lower IOP and protect its RGC target, we are turning a new page that allows us to protect retinal cells from mechanical stress, elevated IOP in glaucoma, and neural death. The new drugs have been patented, licensed, and are currently being tested in preclinical trials for treatment of glaucoma, traumatic eye injury, and epilepsy.

David Krizaj, PhD, is a professor of ophthalmology and visual sciences and deputy director of research at the Moran Eye Center. He specializes in retinal neurobiology, calcium regulation, and glaucoma. Krizaj received the Neuroscience Initiative Collaborative Pilot Project grant, University of Utah, “Development of TRPV4 Channel Antagonists to Treat Glaucoma,” June 30 2015.
Barbara Wirostko, MD, is a clinical adjunct associate professor, Ophthalmology and Visual Sciences, Moran Eye Center, and an adjunct associate professor in Bioengineering, University of Utah. She has been invited to present findings from this study at the World Ophthalmology Conference in Guadalajara, Mexico, February 2016. Dr. Wirostko has specialized fellowship training in glaucoma, treats glaucoma and comprehensive ophthalmology patients, and specializes in clinical research and drug development for ocular pharmaceutical therapies. Her research interest is in sustained delivery of therapeutics for ophthalmic pathologies and in approaching glaucoma through non-intraocular pressure targets.

We know that glaucoma is more than just an IOP-related disease. It is a progressive optic neuropathy, and we don’t fully understand the cause in many cases. From a drug development perspective, we are still in need of new therapies for treating various versions of this enigmatic disease. We need to shift our focus from just lowering IOP to assessing underlying systemic risk factors—to think more about the whole patient and to delve into personal histories and habits.
Glaucoma in general can have associated comorbidities, and primary open angle glaucoma (POAG) tends to be very heterogeneous. Sometimes we are not sure a patient has it; sometimes we call them a suspect; sometimes the pressure is not high, yet they have glaucoma optic nerve damage—so the clinical phenotype is not well defined. However, one type of secondary open angle glaucoma caused by pseudoexfoliative syndrome (XFS) with eventual glaucoma (XFG) is well-characterized and clinically identifiable, marked by elastin and fibrillin on structures of the eye within the anterior segment, especially on the lens capsule and in the trabecular meshwork. This type of glaucoma is associated with a genetic abnormality in the LOXL1 gene; it causes more advanced cataracts and blood vessel occlusions at the back of the eye. And, we know from tissue samples that XFS material collects in skin, lungs, heart, abdominal wall, and brain.

As researchers, we asked the question: If this is a genetic disorder that presents in the eye, what is this material doing to the rest of the body?

A preliminary search of the Utah Population Data Base (UPDB) revealed over 2,000 patients with XFS and related comorbidities that alerted us to some of the systemic possibilities. Since we believe that XFS is an abnormality in the reparative/elastin/collagen process, any tissue that undergoes the reparative process or involves elastin and collagen may be abnormal in these patients. And there is some indication that patients with XFS run a higher risk of aortic aneurysms, hernias, pelvic floor disorders, and cardiovascular disease.

Since our UPDB search, we have received IRB approval to launch a pilot study to examine the epidemiologic, genetic, and clinical risk factors associated with XFS/XFG conditions which can better characterize the phenotype and genotype of this disease. We will evaluate patients in the Moran system, UPDB, University of Utah Health Care System, and throughout the state of Utah. This access, along with collaborations with the University’s epidemiologists, OB/GYN, and cardiology departments, allows us to interview patients, learn about their family and medical histories, perform standard eye exams, and collect blood and other discarded tissue samples for genetic studies. It will provide the foundation for future studies aimed at greater understanding of the genetics, related comorbidities, and pathophysiology of XFS/XFG as well as other related disorders in affected individuals and family members. This goal is critical: if we can look at the underlying genetic causes—not just manifestations in the eye—perhaps we can actually find new therapies to cure this glaucoma.

Through our collaboration on a national global genetics project, Dr. Tin Aung and colleagues at the Genome Institute of Singapore will provide the genetic analysis on DNA samples. This data will be shared under an established collaboration with Duke University's Dr. Rand Allingham, professor of ophthalmology and director of Glaucoma Services. Moran faculty participating in the study includes Drs. Norm A. Zabriskie, Alan S. Crandall, Craig Chaya, Susan Chortkoff, and Kristin Chapman.
What I Tell My Glaucoma Fellows: “Consider the Whole Patient, Not Just the Eyes”

Alan S. Crandall, MD

From a clinical perspective, glaucoma is a chronic, incurable, and lifelong disease. Once you have it, the goal is to not lose any more vision. Nothing has changed in that regard, but the way we now approach clinical care for our glaucoma patients has evolved.

While we used to define glaucoma solely by intraocular pressure (IOP), we now define it by damage to the optic nerve and are taking a holistic approach in treating patients. This includes understanding each patient as an individual, realizing that each has significantly different issues and concerns. That’s why I emphasize a partnership with my patients, and it is a lifelong process.

In assessing patients for glaucoma, I create a checklist in my mind:

- IOP is 40—this is going to lead to vision loss.

- IOP is not that high. Do they have a vascular phenomenon that could lead to optic nerve damage not related specifically to IOP?

- Do they have high blood pressure, low blood pressure? When do they take their medication? I want to know, because they shouldn’t take it at night—there is the potential for vision loss when they sleep because their blood pressure is too low.

- Do they snore? They need to have a sleep apnea test.

- Do you have a thin female patient who is shocked to find out she has sleep apnea? It’s important for her to know this affects eyes the same way that it produces strokes and heart attacks.

- Diabetic? Are their hemoglobin and A1C levels low? They need to be under exceptional control.

- Is your patient of African descent? He/she may be more responsive to early surgical intervention because in this population pressure is harder to control.

- Is there pseudoexfoliation? This may cause more advanced cataracts and blood vessel occlusions at the back of the eye.

- Do you have a patient with high pressure and immediately prescribe drops? What if that patient has severe arthritis and can’t use the drops unless there is someone at home to administer them?

Openly discuss all these things with your patients. You are the captain of the ship, so you have to make judgements. And it is not just based on pressure alone.

Alan S. Crandall, MD, is the senior vice chair of the Department of Ophthalmology and Visual Sciences, director of Moran’s Glaucoma and Cataract Division, co-director of Moran’s Global Outreach Division, and the Val A. and Edith D. Green Presidential Endowed Chair in Ophthalmology.
Intraocular Lens (IOL) Considerations in Glaucoma Patients

Norm A. Zabriskie, MD

Optimizing visual outcomes after cataract surgery in patients with glaucoma presents several challenges—among them, choosing the best IOL. Lens and refractive options vary with the severity of the disease.

Early, Stable Glaucoma
Patients with ocular hypertension (OHT) and those with very early, stable glaucoma can benefit from any of the available IOL and refractive options. Monovision or a multifocal IOL may prove to be somewhat less helpful depending on how the disease progresses over time, but I do not discourage these patients from selecting any IOL or refractive alternative.

Moderate to Severe Glaucoma
In patients with moderate to severe glaucoma, their decreased visual function can reduce the intended outcome of some lenses. Because aspheric IOLs reportedly produce better contrast sensitivity than conventional lenses, I favor them for patients with glaucoma, and have often used these lenses successfully. I also find aspheric lenses to be highly biocompatible and to have excellent centration. In my experience, modern aspheric toric IOLs can be used successfully in glaucoma patients, even with severe disease. Aspheric toric IOLs can be particularly effective at reducing astigmatism induced by previous filtering surgery.

I do not use toric IOLs if I am combining the cataract procedure with traditional filtering surgery because the postoperative corneal astigmatism is too difficult to predict. These lenses can be used successfully, however, when cataract surgery is combined with a more minimally invasive angle-based glaucoma surgery. In patients with exfoliation disease, it is debatable whether these IOLs should be used because of the potential for a decentered lens.

Advanced Glaucoma
In patients with advanced glaucoma, I tend to discourage some refractive options, particularly monovision and presbyopia-correcting IOLs. In advanced glaucoma, a permanent visual defect sometimes does not allow one or both eyes to function independently at an adequate level to support monovision. This can be true even if the patient successfully used monovision contact lenses years earlier.

Multifocal IOLs can provide spectacle-free postoperative vision to many patients, but the technology has limitations. The ideal candidate for a multifocal IOL is motivated and has a cataract but otherwise normal eyes. Unfortunately, there is little published data to guide the use of multifocal IOLs in this patient population, so surgeons are left mostly with anecdotal experience. Current multifocal IOLs can reduce contrast sensitivity compared with monofocal lenses. So someone with advanced glaucoma, decreased contrast sensitivity, and visual field compromise—often very near fixation—may not benefit from the potential advantages of a multifocal IOL.
Glaucoma Challenges in Developing Countries

Craig J. Chaya, MD

Glaucoma remains the second leading cause of blindness around the world. Treatment in developed countries includes myriad options, such as medications, laser, and surgery. This is in stark contrast to many developing countries, such as Haiti, where economic forces and limited access to specialists and medications present ongoing challenges.

Since 2013, the Moran Eye Center has joined with the Vision Plus Clinique in Cap-Haitien, Haiti to develop a glaucoma blindness prevention program. The task has been daunting because of the sheer scope of the problem. My impression is that 20 percent or more of the patients there either have glaucoma or are at risk of developing glaucoma. We have procured new surgical microscopes and supplies. Industry has contributed innumerable medications that help bridge patients along until they undergo surgery.

Ultimately, surgery is the best approach to treat most Haitian patients as they have a difficult time obtaining medications and adhering to complex regimens. We have success with MIGS drainage devices like the Hydrus™ microstent and the iStent® Trabecular Micro-Bypass Stent. These have proven to be easier and safer than traditional surgery and well-suited to difficult cases—those that have failed other conservative options and in conjunction with cataract surgery, which is an ideal time to intervene. These devices have the potential to transform glaucoma care in Haiti. Cataract surgery is easy for patients to understand as they experience an immediate benefit. Glaucoma surgery is hard for patients to accept because there is no tangible benefit, like having your cataract removed.

Moran is committed to protecting future generations in Haiti from unnecessary blindness, but this work would not be possible without the close collaboration we have fostered with industry leaders. Alcon, Allergan, Glaukos, Ivantis, MST, Katena, New World Medical, and many others have proven to be generous and invaluable partners. However, what really distinguishes Moran is our sustainable approach—our commitment to educating, training, and empowering local ophthalmic leaders.

A wonderful side benefit to our outreach work is the discovery of unique clinical findings in the populations we work with. Dr. Alan Crandall has discovered a large community in Guatemala with pseudoexfoliation, and we’ve found similar patients in Haiti. Conversely, we have screened close to 750 patients in Micronesia and found no cases of either typical open angle glaucoma or the angle closure glaucoma that is commonly found in many parts of Asia. Could they have some sort of genetic protection against these diseases? We anticipate that our observations may lead to new breakthroughs in understanding how certain diseases develop and how to better treat them.

This is the synergy that is created in our outreach work—it constantly stirs our curiosity. The toughest cases I have ever participated in have been during outreach trips. They teach you to be resourceful, flexible, and creative—things I bring home with me to Moran when I’m treating patients here and teaching the next generation of ophthalmologists.