SEPTEMBER 2018 # 25

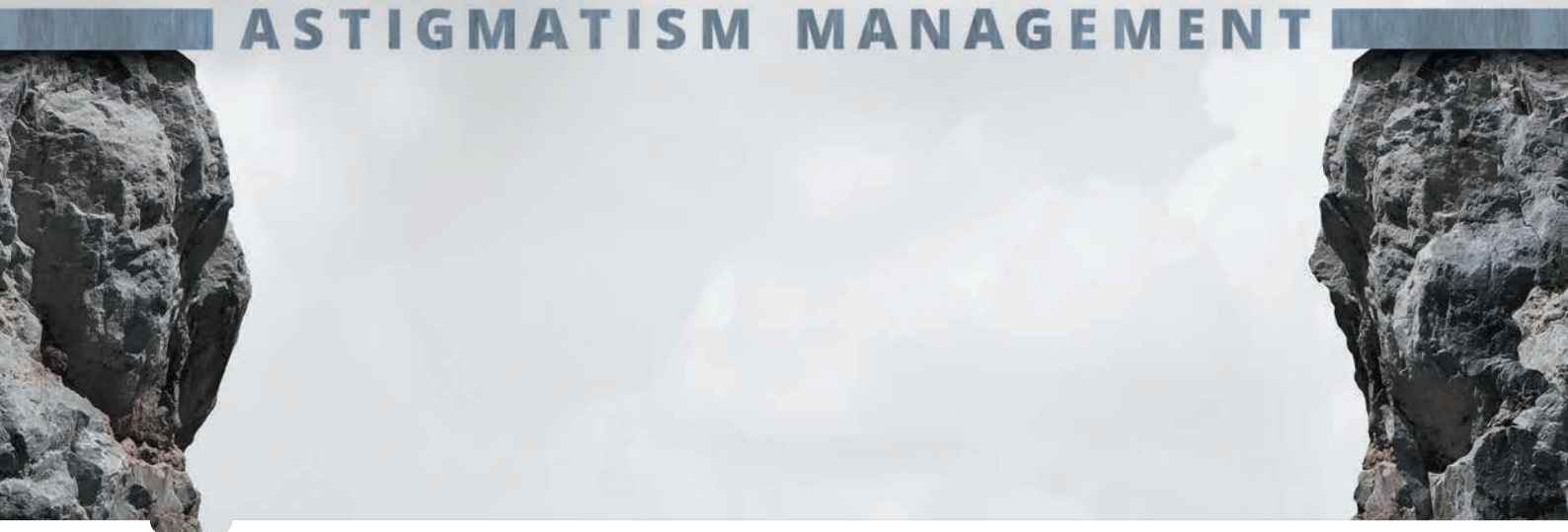
the Ophthalmologist™

A Life-Changing Gift

One patient and one physician on what it really means to restore 20/20 vision.

1,386,254.5 Diopters

of astigmatism went unmanaged in U.S. cataract ORs in 2016.*[,1]



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*Based on data from Dr. Warren Hill. Assumes mid-range distribution of pre-op astigmatism. Excludes irregular and other conditions that impact toric selection.
1. Alcon Data on File.

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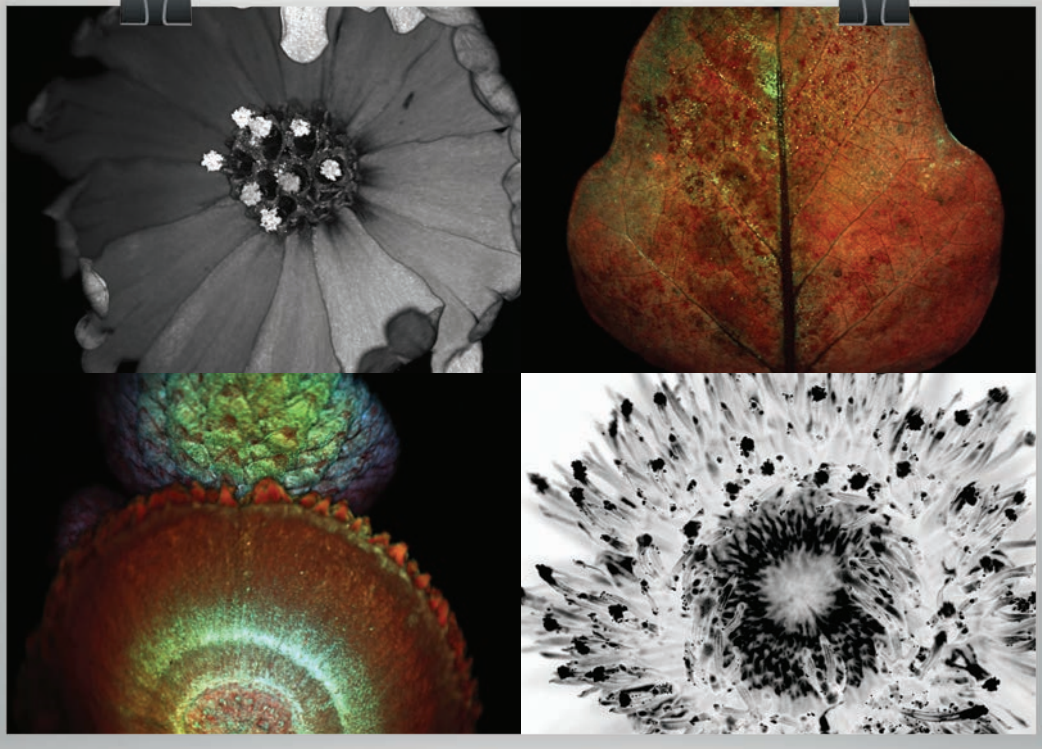
Image of the Month



Fun After Hours

These images were submitted by Trina Toyama, a Clinical Applications Specialist at Heidelberg Engineering. "As a technician, I have had the privilege of using many precision eyecare instruments and cameras. Though the retina is an endless source of fascination, over my career I have used non-ocular images as a way to better understand the functions, strengths, and limitations of a device. Turning the camera to the plants and debris surrounding clinic buildings created these images, which were acquired with a SPECTRALIS diagnostic imaging platform." Using only the tools and features available with the system – such as automated real-time tracking – Toyama says that the device "easily transitions from the most demanding science to playfully act as a fascinating high magnification camera with a lot of latitude for after-hours fun." But can you guess what they are?

Credit: Trina Toyama, Clinical Applications Specialist, Heidelberg Engineering. *Top left, flower; top right, leaf; bottom left, acorn caps; bottom right; flower.*

Do you have an image you'd like to see featured in The Ophthalmologist? Contact edit@theophthalmologist.com

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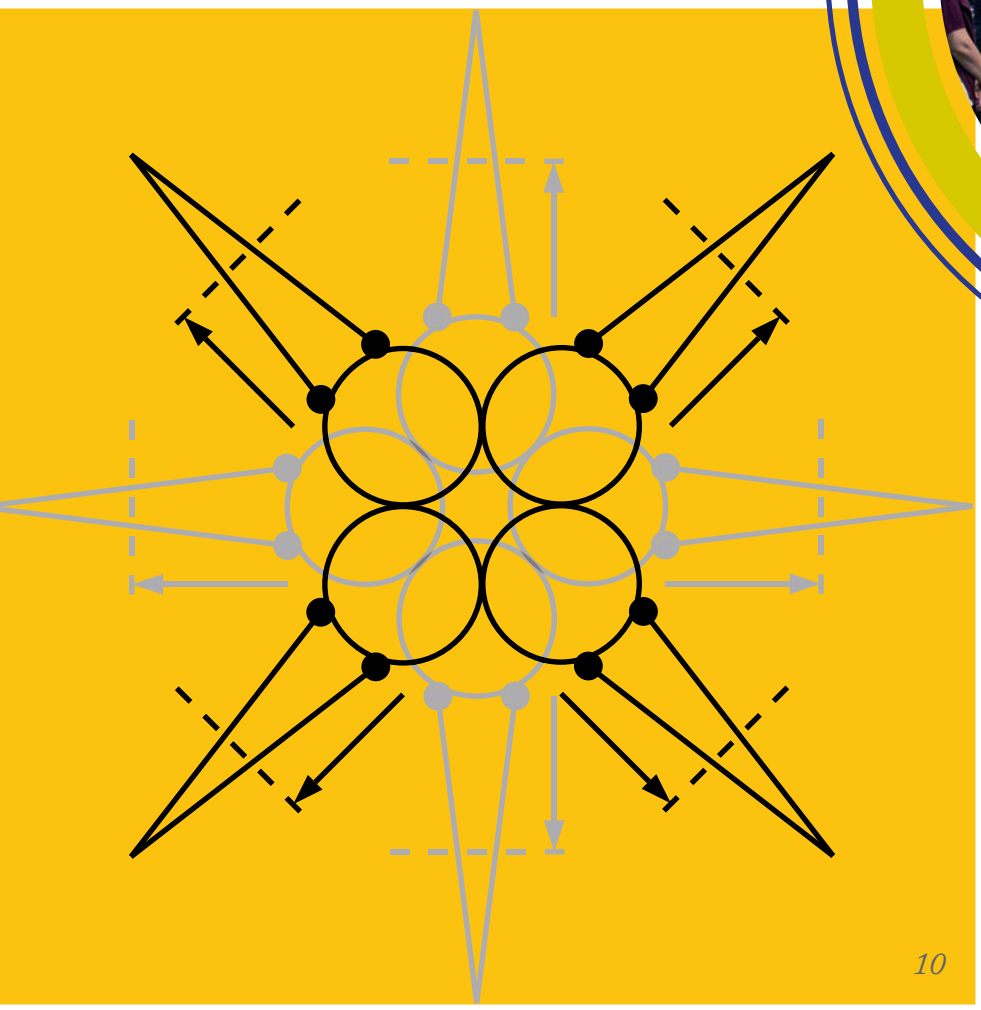

On The Cover

Artwork inspired by the uplifting story of Crystal Ellis, a corneal transplant recipient and Transplant Games of America medal winner.

Upfront

In My View

Feature

Credit: Ace Kvale, Mekelle, Ethiopia.

In Practice

NextGen

Profession

Sitting Down With...

the Ophthalmologist

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The Gift of Sight…

… is one that truly keeps giving. How and where the gift is presented can vary widely, but the impact is always great.

If I were to ask you what you find most rewarding about your occupation (which I do on a regular basis), many of you will answer, "saving and improving sight" – unsurprising, as it is at the very core of what you do on a daily basis. But in a profession that encompasses many different specialties and disciplines – and varies across countries - how each individual ophthalmologist works to present this gift can be very different. And that's why this issue features two inspiring – but quite different – approaches to saving sight.

In our cover feature, a patient and physician tell their stories. Crystal Ellis was in middle school when, for an unknown reason, she lost vision in one eye. She had a corneal transplant – but her vision did not improve. A positive individual, Crystal shares her experiences and perspectives as a patient. She also tells the heart-warming tale of her relationship with the cornea donor's family, which really brings home the humanity integral to tissue and organ donation and how 'precious' that gift can be.

Around the same time, Crystal crossed paths with Christine Sindt – Professor of Ophthalmology at the University of Iowa hospital – whose innovative, custom-printed prosthetic lens technology went on to give Crystal 20/20 vision. Sindt explores her motivation to create a product to restore sight to those with corneal defects. And Crystal offers the perfect example of impact with her relentless motivation to 'go for gold' with her sight restored.

Following on the theme of the gift of sight, in our Profession section Geoff Tabin reveals the backstory to the Himalayan Cataract Project. Many of you will be familiar with the Project and its aims to eradicate global blindness. A truly inspiring individual, Tabin reveals how his interest in humanitarian efforts arose from him witnessing, first-hand, the global inequity in access to care. Almost 30 years after setting up the project, Tabin hasn't wavered in his goal – and has extended the project well beyond the Himalayas to tackle blindness in many other countries.

The long and the short of it is: whether working for profit or for non-profit, the impact of the gift of sight is universal – and it is clear that everyone working in ophthalmology strives to make a real difference to people's lives in their own way.

Ruth Steer
Editor

Upfront

Reporting on the innovations in medicine and surgery, the research policies and personalities that shape the practice of ophthalmology.

We welcome suggestions on anything that's impactful on ophthalmology; please email edit@theophthalmologist.com

Blinded by the Light

How blue light can induce retinal cell death

As a child, you may have been told, "Don't spend so long in front of the TV… your eyes will go square!" – but what if the truth was more serious? A team at the University of Toledo, OH, USA, has found that blue light emitted by digital devices – and the sun – could permanently affect eyesight.

The research, led by Ajith Karunarathne, found that, when exposed to photoexcitation by blue light, the photoreceptor chromophore 11-cis retinal (11CR) and its photoproduct, all-trans-retinal (ATR), could irreversibly distort PIP2 (a plasma membrane-bound phospholipid), disrupting downstream signaling and inducing oxidative damage, ultimately leading to cell death (Figure 1; 1)

"When retinal absorbs blue light, it becomes excited with photon energy. It releases that energy to oxygen, which generates highly oxidative chemical molecules, oxidizing important signaling lipids and proteins in cells, leading to cytotoxicity," explains Karunarathne. And the results were the same when the team introduced retinal molecules to other non-receptor cell types. "Many reports have indicated the likelihood of blue light being cytotoxic," says Karunarathne. "Our work clearly shows cell death occurs when retinal

molecules are present, even without photoreceptors."

Given that photodegradation of this kind is linked with diseases such as AMD, can anything be done to avoid blue-light induced vision loss? "Avoiding prolonged exposure can help," says Karunarathne, who also recommends sunglasses that not only block out UV light but also blue light, as well as advising against looking at cell phones or tablets in the dark.

Karunarathne has a worthy end goal in mind: "By learning more about the mechanisms of blindness, and searching for a method to intercept the toxic reactions caused by the combination of retinal and blue light, we hope to find a way to protect the vision of children growing up in a high-tech world (2)."

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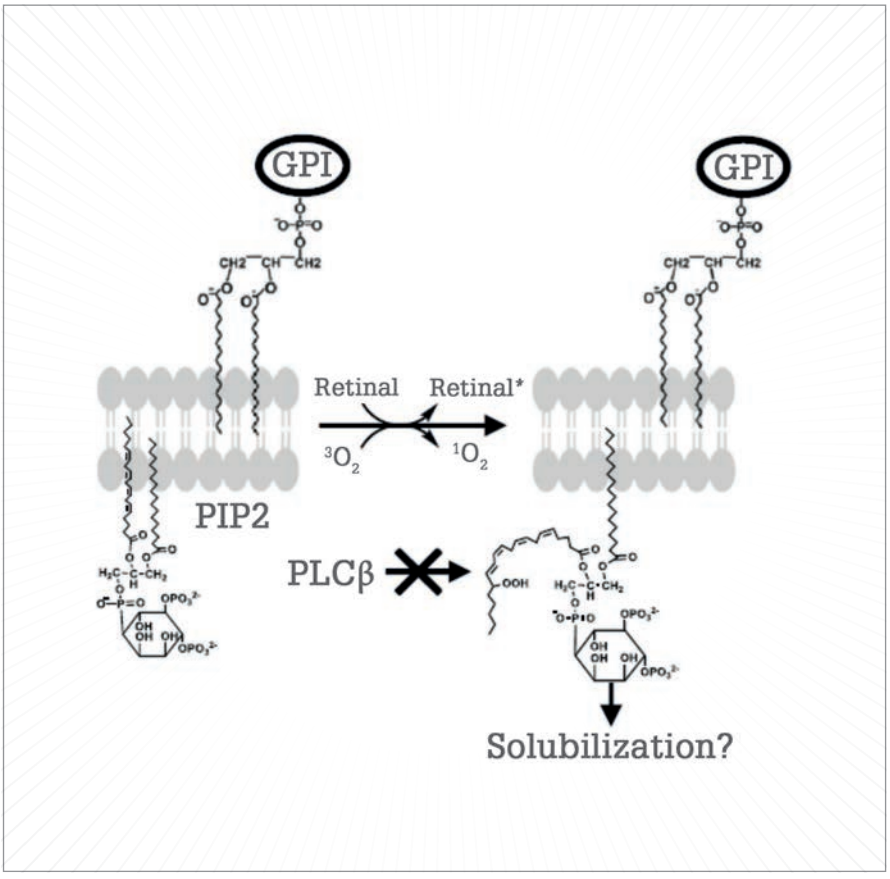
2. *The University of Toledo, "UR chemists discover how blue light speeds blindness", (2018). Available at: https://tinyurl.com/y735e8cq. Accessed August 16, 2018.*



Credit: K Ratnayake et al., (1).

Figure 1. Proposed mechanism of how blue light-excited retinal incudes PIP2 distortion.

Inject or Reject

Are vasoactive intestinal peptides the secret to corneal transplant survival?

Globally, there are millions of people with corneal blindness. But as countries struggle generally with donor cornea shortages, there is another factor that can affect the availability – and success – of corneal transplants: corneal endothelial cell integrity. If corneal endothelial cell density or function becomes inadequate after the transplant, graft opacity and/or rejection can occur, prompting research into how to boost success rates.

Previous studies have revealed that vasoactive intestinal peptide (VIP) could enhance corneal cell survival during donor cornea storage, so a team from Massachusetts' Eye and Ear Institute, Boston, USA, theorized that it could also help after corneal transplantation. "Our experiment revealed that our hypothesis was correct; the postoperative use of VIP improved the survival of corneal grafts in mice," says Ahmad Kheirkhan, co-author of the paper (1).

The team is currently conducting further studies to unravel the exact mechanisms by which VIP enhances corneal graft survival, but Kheirkhan points to one likely possibility: "VIP increases the migration of corneal endothelial cells, and decreases cell apoptosis by modulating resistance to pro-inflammatory cytokines."

If the findings successfully translate to the clinic, the implications are significant, says Kheirkhan. "The use of VIP could help a large number of patients with corneal endothelial abnormalities, and enhance the outcome of corneal transplantation."

Reference

1. *V Satitpitakul et al., "Vasoactive intestinal peptide promotes corneal allograft survival", Am J Pathol, [Epub ahead of print] (2018). PMID: 30097165.*

Not Immune to Damage

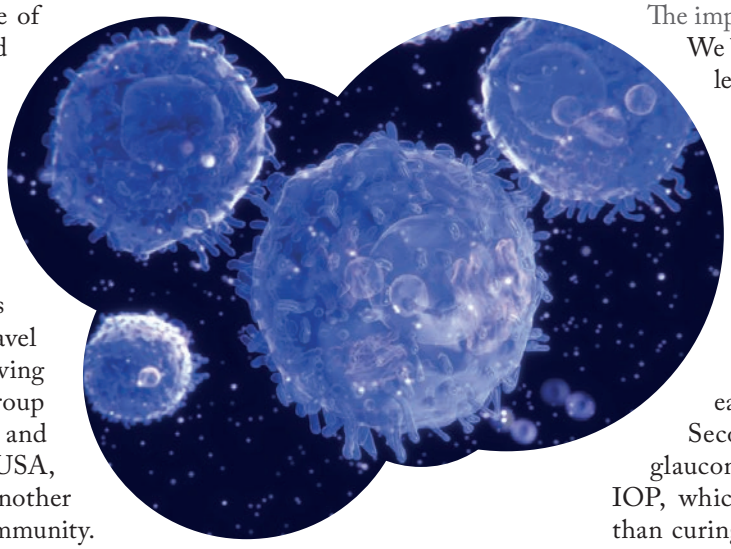
Could activated T cells play a major role in driving neurodegeneration in glaucoma?

Glaucoma may be one of the leading causes of irreversible blindness worldwide but it is also one of the most mysterious. Elevated IOP might explain some of the pathology, but fails to explain glaucomatous damage occurring in patients with normal IOP – or in those whose IOP is maintained with therapy. As research teams the world over look to unravel the complex mechanisms driving the disease, a research group from Massachusetts's Eye and Ear Hospital, Boston, MA, USA, have evidence suggesting another factor might be at play: autoimmunity.

In brief, the team found that increased IOP could induce stress on retinal neurons, leading to an elevated expression of heat shock proteins (HSPs), which, in turn, activates HSP-specific CD4+ T cells. Primed by commensal microbial flora, these T cells appear to induce progressive neurodegeneration. Dong Feng Chen, senior author on the paper (1), talks about their work.

The inspiration…

The work was started several years ago, when we first developed an inducible model of glaucoma in mice. We noted that a transient 2–3 week elevation of IOP resulted in progressive neuron loss even after the eye pressure returned to a normal range. This finding agreed with clinical observations that many glaucoma patients whose IOP was perfectly controlled would still undergo progressive vision loss. We began to speculate that elevated eye pressure triggered a long-lasting event, such as immune reactions, that contribute to vision loss. We thus looked for T and B cells in the glaucomatous retina and found T cells, which should not be present because eye is thought to be an immune privileged site.



Unexpected findings…

We were surprised that mere elevation of eye pressure for a short time can induce T cell infiltration into the eye and cause T cell-mediated attack to neurons. Second, we were surprised that mice never exposed to bacteria are completely free from getting the disease, which truly indicates that elevation of eye pressure is not the direct cause of glaucoma, but rather the immune responses that lead to neuron and vision loss.

In humans…

By examining human blood samples, we showed that patients with primary open angle glaucoma (POAG) exhibited five-fold higher levels of HSP-specific T cells compared with control subjects, suggesting that a similar mechanism underlies the disease process in humans. Though only a 2–3 week elevation of IOP is sufficient to induce HSP-specific T cell responses in mice, we do not yet know what duration in humans is required to induce a response. However, we speculate that at least some patients with normal tension glaucoma have had a transient elevation of IOP.

The impact…

We believe that our findings may lead to a future paradigm shift in both the diagnosis and management/treatment of glaucoma. First, though glaucoma causes permanent loss of vision, its early diagnosis has long been a challenge. Our finding may provide a potential biomarker for early diagnosis of the disease. Second, current therapies for glaucoma solely target reducing IOP, which slows vision loss rather than curing the disease. Our findings suggest new therapeutic targets, which may eventually lead to the cure of the disease.

Next steps...

Our goals are to develop and evaluate new interventions that target T cell or immune pathways for preventing vision loss in glaucoma. In collaboration with clinicians, we'd like to examine the possibility and potential of predicting disease development or progression by detecting abnormal or heightened T cell responses to HSPs.

Reference

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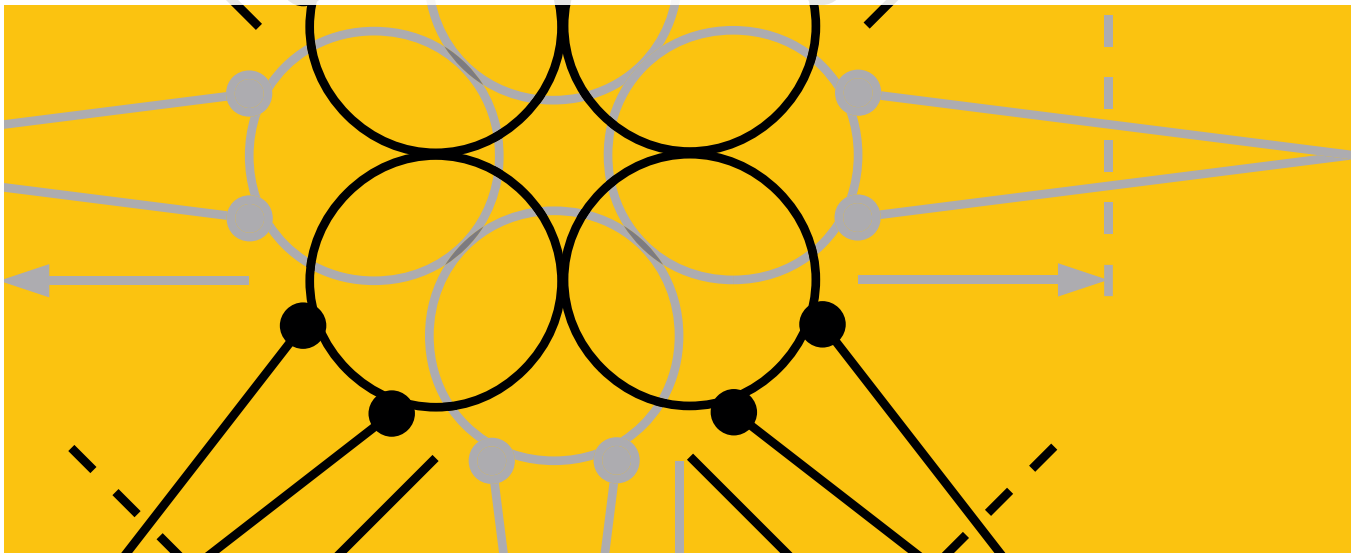

An Abnormal Connection

Uncovering mechanisms that may underpin the development of strabismus

Strabismus is just one of the conditions caused by abnormalities in the cranial neuromuscular system. Despite affecting four percent of the US population (1), tissue inaccessibility has left it, and other brain-muscle conditions, relatively unexplored. It's why a team at the National Institute of Genetics in Japan has turned to zebrafish to help understand genetic mutations that might be driving the condition.

"Strabismus is one of the conditions where brain and muscle connections can be abnormal. The connection between abducens motor neurons and their target muscle – the lateral rectus – is an excellent model to study the basic principle of brain-muscle connections," explains Kazuhide Asawaka, who led the associated study (2). "As neurons in the abducens nucleus connect only with lateral rectus, and the sole behavioral role is to generate outward eye movements, this allows us to evaluate the effects of a genetic mutation at the molecular, cellular and behavioral level." Their target? Protocadherin – a protein expressed in abducens motor neurons that the team hypothesized might play a key role in axon growth.

Using CRISPR-Cas9, the team induced mutations in *pcdh17* – the gene encoding for protocadherin. "The changes that occurred were striking," says Asakawa. "When mutant Pcdh17 was expressed, the abducens motor neurons formed cellular aggregates, and failed to position properly in the brain and extend axons toward the eye globe. This led us to believe that abducens motor neurons actually repel each other." He adds: "This was somewhat counterintuitive to us because neurons with similar functions usually cluster together, making it difficult for us to imagine repulsive force operating in between."

According to Asawaka, their findings have uncovered the importance of protocadherins in connecting the abducens nucleus to the lateral rectus muscle – the brain and eye muscle, respectively. "The involvement of protocadherins in strabismus has not been established yet in humans, but we hope our work in zebrafish contributes to help estimate the risk of developing strabismus, and increase the chances of initiating early treatment to prevent impaired eye movement." Outside the realm of ophthalmology, Asakawa and his team hope to explore how protocadherins contribute towards connecting other neurons and muscle fibers. "Some connections in the brain and eye are selectively resistant to degeneration. We hope our work can go some way in contributing towards the protection of motor neurons in fatal diseases such as ALS."

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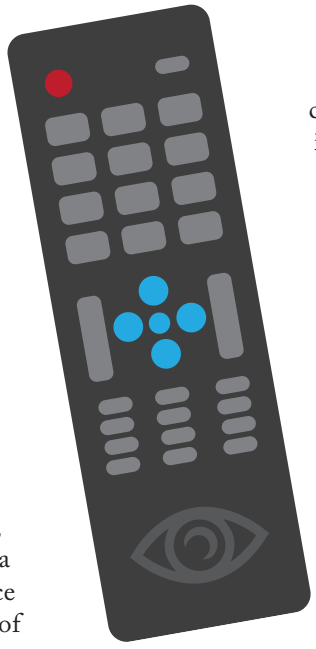
Changing the Program

Reprogramming murine Müller glia to drive photoreceptor genesis and restoration of vision

Müller glia cells, abundant in the retina, are known to support retinal cell function. But they also have another support function: retinal regeneration. In cold-blooded vertebrates, such as zebrafish, it is well known that Müller glia can act as a source of stem cells to induce retinal repair and regeneration. But this regenerative capacity is absent in mammals; although cell proliferation might occur in response to injury, these cells do not repair or regenerate the retina. Now, a team from Icahn School of Medicine at Mount Sinai, New York, USA, have shown that they were able to reprogram Müller glia to generate rod photoreceptors, and restore light perception in a mouse model of congenital blindness (1).



Lead investigator, Bo Chen, explained: "This study opens a new pathway for potentially treating blinding diseases by manipulating our own regenerative capability to self-repair" (2). In their study, they reprogrammed Müller glia to generate rod photoreceptors through a two-step process. First, they induced Müller glia proliferation in adult mice through gene transfer of β-catenin. Second, they reprogrammed the proliferating Müller glia cells into rod photoreceptors through gene transfer of the transcription factors *Otx2*, *Crx* and *Nrl*. After confirming that they could generate rod photoreceptors, the team tested whether reprogramming Müller glia in a mouse model of congenital blindness (*Gnat1*^{rd17}*Gnat*^{cpfl3}) could restore visual function. Four weeks after Müller glial cells were reprogrammed in *Gnat*^{1rd17}*Gnat*^{cpfl3} mice, the team were able to show that the mice could respond to light.

Although there is a long way to go between the laboratory bench and the clinic, Chen said that their work could "lead to extraordinary opportunities in the future where we can potentially use the same strategy to reactivate these stem cells in the diseased human eye" (2).

References

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Bitesize Breakthroughs

Analyzing the tear film layer, screening for neural disease, and a curious contact lens case: a brief selection of the latest ophthalmology news

Eye Spy

- A team at Seoul National University, South Korea, has linked thinning of the retina with Parkinson's disease (1). In patients with early stage Parkinson's disease, the team identified retinal thinning, and found that it correlated with disease severity and may be linked with an increased loss of dopamine-producing brain cells. Looking to the future, the authors hope this study may help neurologists detect Parkinson's in its earliest stages with a simple eye scan.

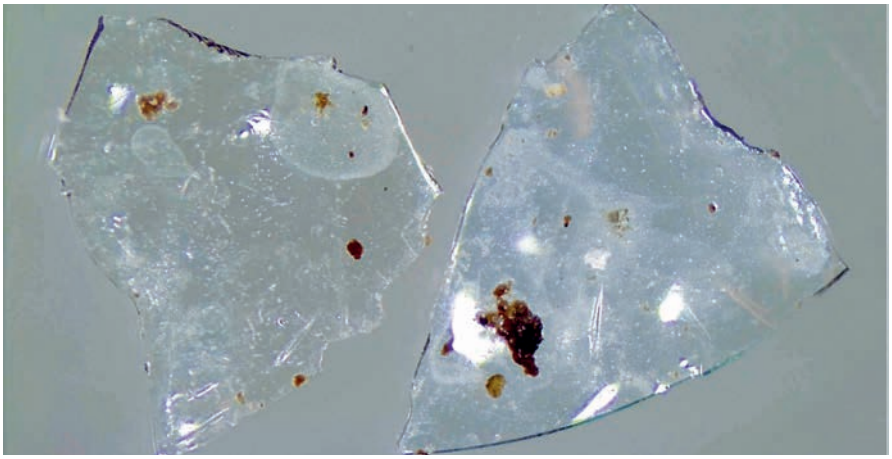
Dry Eye Developments

- Using advanced mass spectrometry techniques, a team of Australian researchers have characterized ultra-long-chain fatty acids from human meibum. The team from Queensland University of Technology in Brisbane are now working with Allergan, who co-founded the research, to incorporate a synthetic long-chain lipid chain into future dry eye treatments (2).

D for Diagnosis

- Researchers at the University of Washington, Seattle, USA, have uncovered potentially promising screening criteria for Alzheimer's disease. By analyzing a population of 3,855 patients, they identified a significant association between the disease and three common eye conditions – AMD, diabetic retinopathy and glaucoma (3).

Contact lenses recovered from treated sewage sludge which, according to new research findings, could harm the environment (6).



Credit: Charles Rolsky

RP Revelations

- Birch et al. (4) have published findings showing that oral valproic acid was no better than placebo for the treatment of autosomal dominant retinitis pigmentosa (ADRP). In the randomized Phase II multicenter placebo-controlled trial, 37 patients with ADRP were treated for 12 months with 1,000 mg or 500 mg valproic acid; 42 patients were administered placebo. Valproic acid failed to meet its primary endpoint – change in visual field area between baseline and 12 months. The authors noted that one scientific premise for the study was the "concern that patients with RP were taking off-label valproic acid without adequate monitoring."

Contact Lens Concerns

- In a curious case, a 42-year-old patient presenting with eyelid swelling and ptosis has had a contact lens removed from her eyelid – 28 years after it became embedded there (5). According to the authors, the patient believed that the lens had been lost at the age of 14 when she was hit in the eye with a shuttlecock during a game of badminton. The authors report it isn't clear why the lens resided in the eyelid asymptomatically for 28 years.
- According to findings presented at the American Chemical Society annual meeting, disposable contact lenses are an emerging environmental contaminant (6). As 15–20 percent of contact lens wearers reported flushing their lenses down the toilet or sink, it might be time to check how patients are disposing of their disposables...

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In My View

In this opinion section, experts from across the world share a single strongly-held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of ophthalmology. They can be up to 600 words in length and written in the first person.

Contact the Editor at edit@theophthalmologist.com

Awakening Sleeping Giants

How and why the laser refractive market is set to grow

By Rod Solar, Director of Practice Development, LiveseySolar, London, UK

What if I said that the size of the laser refractive surgery market could be multiplied fourfold in less than a decade? And that only those with foresight and adaptability will have a chance to grasp this opportunity?

Since the early 2000s, companies have introduced improvements to traditional LASIK, such as wavefront-guided procedures, femtosecond flaps and small incision lenticule extraction (SMILE). Results improved, complication rates declined, and today, LASIK is as safe and effective as ever. Consumers have, however, responded tepidly. Since the financial crisis of the late 2000s, volumes have not grown significantly. The primary target for laser refractive surgeons today is millennials (born 1980–2000). But despite the hopes placed on them to fuel a laser vision correction renaissance, procedure volumes have remained relatively flat since 2009 (1). Why is that? I think a key problem is that equipment manufacturers are optimizing procedures for only one market segment: people with refractive errors who dislike their glasses and contact lenses enough to opt for laser eye surgery. So far, EyeWorld estimates surgeons have performed 40 million LASIK procedures since 1991 (2). That might sound like a significant number, but considering just how many people worldwide have refractive errors it's an exceedingly small penetration rate.

I think that a significant opportunity is appearing on the refractive horizon: presbyopic LASIK. And I believe that 'Generation X-ers' (born 1965–1979) and 'baby boomers' (born 1946–1964) are the sleeping giants of the refractive surgery market. Here's why:

1. The market size for presbyopic LASIK is much larger than that of regular LASIK. According to Statista (3), the population of millennials in the USA is estimated to be 72 million, with the population of Generation X-ers estimated at 66 million, and baby boomers at 74 million. But there are together 140 million Generation X and baby boomers – almost double the size. And when you consider that only half of millennials are likely to even need refractive surgery (around 36 million), and compare that with the numbers of people over 50 that have presbyopia (roughly 120 million), it is clear that the presbyopic opportunity is almost four times the size. Of course, as some of these elder Boomers will present with early signs of cataract they will be ideal candidates for refractive lens replacement. With that said, a significant percentage of them will require an enhancement to achieve '20-perfect' vision.
2. People aged over 40, especially emmetropes, are highly motivated to have vision correction treatment for presbyopia. It's not difficult to understand why so many people who could benefit from laser eye

"I believe that 'Generation X-ers' and 'baby boomers' are the sleeping giants of the refractive surgery market."

surgery haven't elected to do it. They've adapted to their glasses and contact lenses. But evidence exists in mice that age can limit neural adaptability (4), which may partly explain why some people over 40 experience difficulty adapting to reading glasses. Though I have yet to find specific evidence supporting this claim, it follows that people tend to exhibit more motivation to address a problem they have trouble adapting to versus a problem they adapted to when they may have been cut 'were' more neurologically flexible and plastic (0 to 25 years of age).

3. The presbyopic market has the spending power. Business Insider reports: "Millennials, are spending less on consumer goods because of expensive healthcare and education costs. But baby boomers, are the 'biggest spenders' because they have extra cash from decades of saving and investing" (5).

The take home message? Generation X-ers and baby boomers have the size, the motivation and the spending power to potentially quadruple the laser eye surgery market. In my view, presbyopic LASIK is likely to be the most significant opportunity on the refractive horizon for the next 30 plus years. Growth-minded refractive surgeons should look to new technologies and adapt their marketing strategies for when the sleeping giants awaken.

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Financial disclosure: Solar reports that he is a Consultant for Carl Zeiss Meditec.

Pioneer or Buccaneer?

Great minds across the ages have struggled to make their work understood. In the digital age, are we doing enough to push truly pioneering efforts to the forefront?

By Karl Stonecipher, Medical Director of TLC Greensboro, NC, USA

I was lost in a great read the other day: "The Butchering Art" by Lindsey Fitzharris. I asked my staff if anyone had read it – they hadn't and couldn't believe a book like that even existed. I explained

that it was all about medicine in the early 1800s – before people thought microbes caused disease. Believe it or not, the conversation around infection is still relevant today. Postoperative infection prevention is, and always will be, a number one priority with any type of surgery. Patients don't want to be hurt as a result of a procedure – not

"People like Harold Ridley and Charles Kelman changed the surgical world as we know it, but were hammered by mainstream ophthalmologists of the day."

least one you performed.

Which brings me nicely to the point of this article. In 2018, what is the difference between a pioneer and a buccaneer? Technically, a pioneer is defined by Webster as, "a person or group that originates or helps open up a new line of thought or activity" (3). A buccaneer is, "any freebooter preying on Spanish and English ships and settlements, especially in the 17th and 18th century" (4). These guys and girls got out of prison and moved to the Islands. When... they got bored of sipping piña coladas, they decided to take a bold move forward – commandeer a boat and rob the Spanish and English oppressing them. That's what the pirates of the 17th and 18th century are known for, and why the modern definition of a buccaneer is "an unscrupulous adventurer especially in politics or business."

With that in mind, let's go back to the 19th century. It was here that one of the most famous doctors of the decade performed an amputation in under three minutes without anesthesia. That's pretty amazing in itself – until you remember that the technician helping, the medical student watching, and the patient all died. With 300 percent mortality in one procedure, fast isn't always better. It may be more cost efficient, but does it help the patient?

Fast forward to the early 20th century when a guy called Eddington wanted to prove that another guy called Einstein was a genius. The problem? Everyone was at war. Instead of working on the theory of relativity, scientists were figuring out how to kill soldiers with mustard gas. Eddington decided to go to Africa and prove that Einstein was right, which he did. Immediately, Einstein was hailed a hero back home. In doing so, Eddington proved that the buccaneer was really a pioneer.

In terms of ophthalmology, people like Harold Ridley and Charles Kelman changed the surgical world as we know it, but were hammered by mainstream ophthalmologists of the day. Now, let's think of the modern ophthalmologist. She has a great idea, but how that idea develops is dependent on where she lives in the world. If it involves embryologic tissue, religion may jump in. If the cost-to-goods are high, private equity jumps in. If she needs to run an investigative review-board sponsored device exemption trial as a surgeon, cost and liability come in to play. Those are just some of the inhibitors to really great ideas today. The old guard hate transition and the new guard embrace it. As the world becomes flatter, we see across the planet in a femtosecond (5). We can think of the 'new' world as a big web with thoughts being shared instantly by Googling this or that, but the exchange of ideas is occurring at a phenomenal rate.

In 2018, we are looking at an explosion of technology to treat dysfunctional lens syndrome – or "I can't see what I want to without glasses or contact lenses" syndrome. Who is the buccaneer and the pioneer of today? How would Webster define it if he were still alive? The definition could be legal, technical or geographical. We have companies that finally get Food and Drug Administration approval but have ended up bankrupt, while other companies fall out of the running because of a lack of venture capital. Where's the middle ground between protecting patients from adversity – the buccaneer – and providing patients with sight they want – the pioneer? And how can we make it affordable? That is the million or 100-million-dollar question – because that's roughly what it costs for a company to participate in an investigator device exemption for an indication for surgery in the US today.

For the most part, Einstein, Ridley, Kelman, and the surgeon today want people to have a better existence. Doctors do what they do to make people better – the money is just a necessary evil. Remember, in the early 19th century, many surgeons weren't even paid. So what are the hurdles to enlightenment today? How do we create a better world? How do we define the pioneer and the buccaneer? Only time can tell.

"Where's the middle ground between protecting patients from adversity – the buccaneer – and providing patients with sight they want – the pioneer?"

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Fancy Your Chances?

Intracameral antibiotics reduce the risk of cataract complications – so why aren't we using them?

By John Berdahl, Partner at Vance Thompson Vision, Sioux Falls, SD, USA

Cataract surgery is the most common ophthalmological procedure in the world. And like all procedures, it has some risks – the worst being endophthalmitis. Endophthalmitis affects between 0.13 percent and 0.7 percent of patients (1) and can have devastating consequences, with some losing light perception all together. So what can we do about it?

The answer is intracameral antibiotics. In my mind, they're one of the most important innovations in modern ophthalmology. Several studies have shown that intracameral antibiotics unequivocally decrease the incidence of endophthalmitis. But we're not using them in the US.

Why? Firstly, there are no commercially available antibiotics for intracameral use in the US, so surgeons who want to use intracameral antibiotics have to be creative. Some take Vigamox straight from the bottle and inject it into the eye, others dilute it themselves – while others have their local hospital or pharmacy compound it for them. As you can imagine, this homemade approach has its flaws. There have been some isolated but well-publicized incidents where improperly mixed intracameral antibiotics have led to concentration errors. In some cases, toxic vehicles within the antibiotics have caused significant vision loss due to inflammation inside the eye. Vancomycin, one of the drugs associated with the procedure, has also been implicated in a condition called HORV – hemorrhagic occlusive retinal vasculitis. Although patients appear well after their first eye surgery, a very small subset begin to exhibit hypersensitivity after their second, experiencing bilateral retinal vasculitis and some even bilateral blindness.

These stories have made US ophthalmologists wary of intracameral antibiotics, even though the majority of us know that they are ideal for the prevention of endophthalmitis.

Right now, I use a non-FDA approved combination of FDA approved drugs, including dymethazine, moxifloxacin and ketorolac. They are all prepared under 503B manufacturing conditions, which means that the manufacturer, Imprimis, is FDA-inspected to the same high standards a traditional drug manufacturer, resulting in an exceptionally high quality product. To my knowledge, there have been no reports of improperly formulated medication.

The second reason US ophthalmologists are wary of intraocular antibiotics is cost. Compounded intraocular injections cost around $25 – and come directly from the surgery center or doctor's pocket. In my mind, $25 is a small price to pay to guarantee a good outcome for my patients, but not every surgeon feels the same way. Part of the problem is that intraocular injections are considered part of the bundle of cataract surgeries, which means we can't bill patients or insurance companies for individual treatments. Understandably, there are few people willing to invest dollars in the development of a technology that cannot return those dollars later down the line.

"In my mind, $25 is a small price to pay to guarantee a good outcome for my patients."

Europe has already proved the value of intraocular antibiotics in the clinical sphere – but in the US we need to put an economic engine behind it. The first step? Establishing a satisfactory reimbursement program. Fortunately, there are a number of groups encouraging the FDA and Medicare to collaborate on a solution. If they succeed and we find a way of returning investment, we can start the large-scale clinical studies needed to demonstrate the safety and efficacy of intraocular antibiotics.

I am hopeful that we will get an FDA approved antibiotic in the next few years. As with all new products, they will go through the natural innovation process before prices eventually settle. It is only then we'll be able to provide real value to investors – and, crucially, to our patients too.

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1
2
DONOR FAMILY

A LIFE-CHANGING GIFT

We share the story of one patient, one donor family and one physician to show what it really takes to restore 20/20 vision.

Phoebe Harkin with Crystal Ellis and Christine Sindt

Ophthalmic surgeons perform around 40,000 corneal transplants in the US every year. Here is the story of just one of them. Crystal Ellis was in middle school when she lost sight in her right eye. It took 19 years and the ingenuity of Christine Sindt for her to see properly again.

"Just a regular kid" – the Patient's Perspective

With Crystal Ellis

It all started in 1999. I was just a regular kid – going through middle school, trying to pass driver's ed. I woke up one morning with blurry vision in my right eye. I went to the doctor thinking it was pink eye and they treated it like that for two weeks. When it didn't go away, they referred me to an ophthalmologist; but they were stumped too. Scarring, which looked like pockets of crystals, suggested a viral infection, but there was no evidence to prove it – and there is still none to this day. Without a diagnosis, there was nothing they could do. And that's how I lived for the next few years.

A gift that's impossible to repay

Fast forward to 2005, and my eye was in really bad shape. Everything seemed dark and murky; it was like trying to see through layers of wax paper – there were blobs of color but no definition. Not only that, but the scarring had thinned the corneal tissue. A doctor took one look during a check-up and said, "If you bump your head, your eye could rupture. You need surgery – now."

It takes a lot to psych yourself up for surgery. I didn't realize just how much until I woke up and was told that the transplant hadn't happened. The donated cornea had been cut incorrectly and would have been rejected by my eye. I was crushed. Luckily for me, it only took two weeks before another became available. So, on June 5, 2005, I got my new cornea.

Part of me thought I would wake up from the transplant and my eye would be like it was before. But it wasn't at all. My vision had barely improved. Instead of looking through multiple sheets of wax paper, it now felt I was looking through one. I could make out a letter or a number if the writing was big enough, but that was it. I told myself this is how it's going to be forever. I better get used to it.

About six weeks after the operation, the Iowa Lions Eye Bank asked if I wanted to receive a letter from the donor family. What they sent was beautiful. It was from a mother who had just lost her five-year-old son – my donor. She told me how he had been an outdoorsy, adventurous little boy who loved animals and fire trucks. That's when it hit me that someone had to die for me to see. This little boy had saved my sight – my life.

I didn't write back straight away. I just didn't know what to say… "Thanks, and I'm so sorry your son died," wasn't going to cut it. It felt like I could never say enough, so I said nothing. I had already taken an entire semester off college and was just about finding my feet when I discovered I had thyroid cancer. It took another four years before I had a full bill of health.

I was 24 when I finally finished college. I was moving into my first house a year later when I rediscovered and re-read the letter. Why had I never replied? After I stopped crying over what a terrible person I was, I wrote to tell them about everything I had been going through – while admitting it was no excuse for not getting in touch. I told her how I thought about her and her family every day. We wrote each other back and forth and I really got to know her; Misty was a kind, generous woman and mother to a beautiful family.

Fulfilling a dream, reliving a nightmare

I had wanted to go skydiving for a long time, but scarring from the transplant had left me with a thin cornea, and the doctors didn't know if it could take the pressure of the jump. I got the all-clear just in time for my birthday. I invited Misty and her family to come down as a way of saying thank you for the gift they gave me. They said they couldn't make it but appreciated the offer.

The big day came and I did the jump. As I landed, I walked past a bunch of people – including my donor family. Apparently, my stepmom had been coordinating with Misty the whole time. It took me a minute but as soon as I realized who they were, I burst into tears. It took seeing Misty in person for me to truly realize that I'd been given a gift I could never repay. Even now, it gives me goosebumps just thinking about it.

That day was a turning point for me. Misty and her children became my extended family, and now we volunteer together as donor and recipient speakers at the Iowa Lions Eye Bank. It is so rewarding to hear people say, "I was going to write to the people who received my loved one's organ or tissue, but I didn't know what to say. Now that I've seen how much it means to you, I'm going to reach out to them." And I know people say the same thing to Misty too. Misty and her family live two hours away, but we get together when we can to share our stories.

Despite accomplishing my dream to skydive and gaining a new extended family, I was still having trouble with my eye. The stitches had started to pop through the surface of the transplant. To remove them, the doctor had to break the knot under the surface, which was uncomfortable. Not only that, my eye didn't heal correctly: instead of being round, it protruded at the top, and I still couldn't see much.

"That's when it hit me that someone had to die for me to see. This little boy had saved my sight – my life."

A twist of fate

Around the same time, Steven Jacobs – my ophthalmologist since 1999 – was retiring; I didn't know what I was going to do. Steven, and everyone who worked in his department, were like family to me (I still send them Christmas cards now!). As luck would have it, his replacement was Elizabeth Geiger, who had just done an internship at the University of Iowa, where she'd met a doctor called Christine Sindt. Christine was apparently doing "amazing things" – inventing an entirely custom-made lens that had the potential to correct my vision. Elizabeth got me an appointment right away – and Christine told me I was a great candidate for the lens. The catch? It costs $4,000 and my insurance wouldn't cover it.

So here it was, the thing I'd been waiting for – a way to see again – and I couldn't afford it. I almost didn't want to tell my friends and family about the appointment, because I couldn't bear to see the

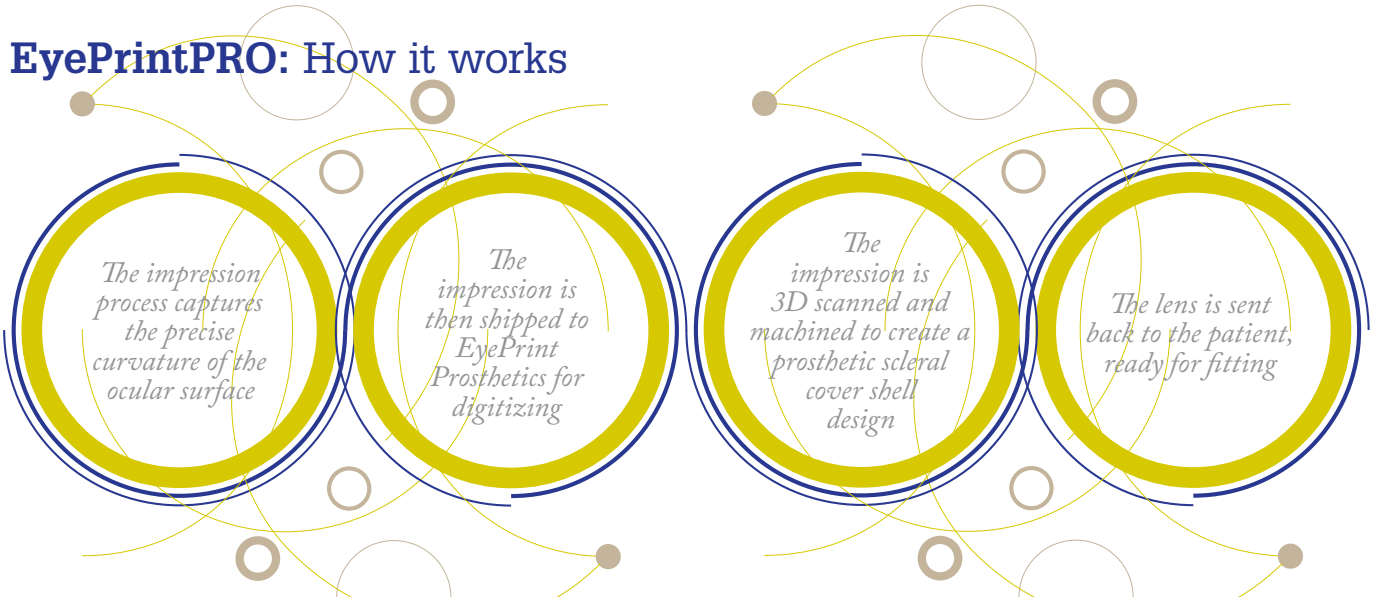
"It feels strange reflecting on my journey because, for a long time, I didn't think I'd see properly again and I'd come to terms with that."

Crystal wears a ribbon bearing the face of her donor, five year old Jarren Moser

disappointment on their faces. But telling them was the best decision I have ever made; they suggested I set up a "YouCaring" page to ask for donations. It was actually easier than I thought. I had been sharing my transplant story on Facebook for years, and people had got to know me and my 'bionic eye.' I posted a link to the page and within two weeks, I had $5,000.

I called the clinic that day and told them I had the money. I'm not sure who was more surprised – them or me! From there, the money was split three ways – $1,000 for the imprint, $2,500 for the contact, and $1,500 between office visits, co-pay for a specialty doctor, and tools, solutions and saline sticks to get the contact in and out of my eye. Christine was wonderful through it all – but particularly when it came to the impressions. They were done with an epoxy mold like the kind you

EyePrintPRO: How it works



get at the dentist. I remember sitting in the chair watching Christine flick blue goo into a funnel. "What are you going to do with that?"

"We're going to take a mold of your eye," she said.

"You're going to do what?"

She must have seen my face because I was told that it would be totally painless: "I'm going to do it so quick you won't even know it happened." And she was right, it didn't hurt at all.

A second gift

I vividly remember the day I received my lens. It was winter and I was wearing a purple jacket. Up until that day, colors were dull – even with my good eye. Being able to see properly with my new lens made everything so bright. I remember walking out of Christine's office and seeing a picture of a sunset on the wall. I started bawling. "Look at that picture!" I said. "It's so orange! Was it always that way?" I couldn't get over how pretty it was. Even my jacket looked beautiful – how could it be… so purple?

It feels strange reflecting on my journey because for a long time, I didn't think I'd see properly again and I'd come to terms with that. My eye had healed – no more 'virus', no more scar. Getting told there's a chance I could see was almost worse, because I couldn't stand the disappointment if it didn't work. But it did work and now, for the first time in years, I have 20/20 vision. Of course, there have been some teething issues. Trying to tell my brain to use that eye again is hard. After all, I couldn't see properly for 19 years! You want to simply turn on a switch, but it doesn't work that way.

I recently had the honor of representing Team Iowa in the Transplant Games of America. The Games is a multi-sport event for people who have undergone life-changing transplant surgeries. It celebrates the lives of donors and recipients, and raises awareness of the need for organ, eye, bone, and tissue transplants in every state. When the Iowa Donor Network asked me to take part, I was uncertain at first because I don't have a competitive bone in my body! But it was Deb Schuett, my contact at the Iowa Lions Bank, who encouraged me to say yes. Deb was the person who put me in touch with my donor family, and we were still very close. With her support, I joined Team Iowa, and we even ended up rooming together at the games! Despite not playing a day in my life, I decided on cornhole and darts. When I told Christine, she couldn't believe my choice: "Don't you know darts is a leading cause of eye injuries?!"

The games turned out to be a huge success – not only because I didn't get hit in the eye, but also because I won gold in darts and two golds in cornhole – one for playing as part of a team, and another as an individual. It must have been beginner's luck! But the medals were just a small part of what made the games so amazing. I met some phenomenal people, and made new friends that will be part of my life forever. I also got the chance to hear the most beautiful and heartbreaking stories. It was incredibly humbling to consider that many of these people would not be around without organ and tissue donation. But here they were – cheering each other on, celebrating each other's victories. It was the best experience ever. Life is good.

Seeing Eye to Eye – the Physician's Perspective

With Christine Sindt

About 20 years ago, I was treating a little girl who fell on a glass. It shattered and a shard went in her eye. She lost the lens and had a large corneal scar that caused a millimeter height difference in her ocular surface. I administered corneal gas permeable lenses for as long as I could, but she became intolerant. I thought there had to be a better way. In eyes that have suffered trauma, like hers, the ocular surface stops being round. If I could just get a lens to lock in to the eye like a Lego piece, I could get this child to 20/20. And that's really where my journey into "eye printing" all began.

I thought about my patients and decided that I had to develop something that met the unique complexity of their eyes. I wanted the design to work, not just in terms of the eye-to-lens relationship, but also on a human level. Whatever it was, it had to be fast. As physicians, we can make our patients crazy when we don't have answers. I wanted to be able to say: "This is what's going to happen next."

A human(e) approach

This drive to do better for my patients formed the foundation for the EyePrintPRO, an optically clear prosthetic scleral device designed to match the exact contours of each individual eye. We take an impression of the eye, and then use high-resolution instrumentation to develop a 3D model that can be used to create a custom lens – in as little as two days.

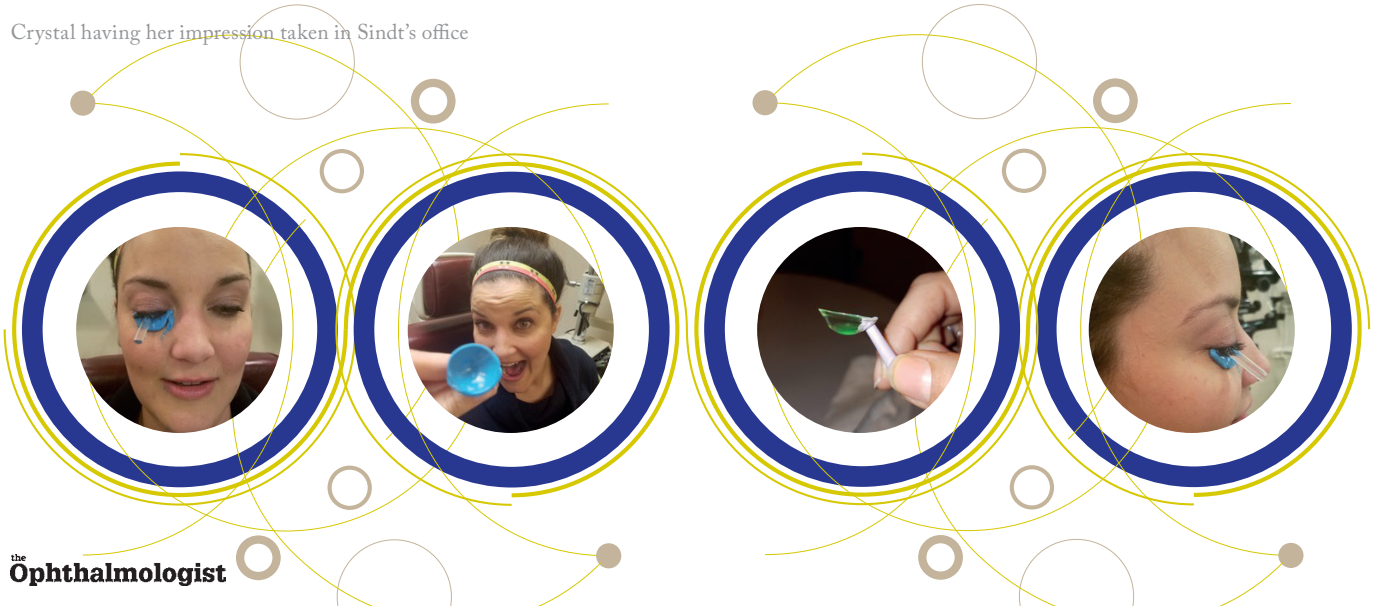
Like all good ideas, it took significant time and effort to get where we are today. And I am very fortunate that I have always had patients with patience! One patient in particular had keratoconus and wasn't eligible for a transplant, so we kept trying new things. He was with me through more eye impressions than I like to remember until I finally got "the one." When we discovered he'd got 20/20 vision using his eye print, he cried – and I sat next to him and cried too.

Making a good impression

The impression process was particularly important to me. Previously, molds were made using alginate, which was uncomfortable and painful for the patient. By using polyvinyl siloxanes, we found we could still capture the eye's precise curvature, without any discomfort. Patients actually call it "cool blue goo." It doesn't hurt, it doesn't need anesthetic, and it doesn't disrupt anything on the surface of the eye. Not only that, the impressions can be done anywhere. I've gone to the bedside of quadriplegic patients, I've gone into operating rooms, I've gone into the field – and I've even done impressions at parties. We can go where people don't have high-tech devices and high-tech scanners, and offer world-class healthcare in a very affordable way.

Once the impression is taken, it is sent for digitizing. We use the latest 3D scanning technology and numerically controlled

Crystal having her impression taken in Sindt's office



"Because each lens is custom, it allows us to use really unique optics on the device – and not just in the center as with other lenses."

machining systems to get an exact match of the individual cornea and sclera. Because each lens is custom, it allows us to use really unique optics on the device – and not just in the center as with other lenses. I can put higher order aberrations on the lens, I can put prism in any direction, I can put a multifocal on the lens, I can do torics – I can even do them all at the same time. And the best part? It all happens so quickly. We use a virtual eyeball to do a theoretical fit to get the best alignment, the best optics, the best comfort – 95 percent of lenses are completed within two attempts. Compare that process with current pre-manufactured designs that use trial and error to find the best fit.

Changing lives

My patients aren't eyeballs in a chair, they are people – and it's always important to remember that. Because what they want to do – their goals in life – will determine what choices we make together. Oftentimes, there are several different routes we could take, but I can't advise somebody unless I know what's really important them. And that makes it a very personal journey.

Take Crystal. Her story is unique. By getting to know it, and her, we were able to find a solution. And I'm happy to say her vision is now as fabulous as she is! She has such a positive attitude, despite everything that has happened to her. When I see her, I also see the five-year-old boy who gave his cornea so that Crystal could see. I choke up when I think about it. What I do, I do for people like him and his mom. I do it for all eye donors.

When it comes to my patients, I know I've done a good job when they stop talking to me about their eyes and start showing me pictures: "Do you want to see my kids?" – "Do you want to see where I went on vacation?" It means their eyes aren't their number one concern anymore. I've worked myself out of a job – and that, to me, is a huge success.

Crystal Ellis is a volunteer for the Iowa Lions Eye Bank and the Iowa Donor Network.

Christine Sindt is a Director at Contact Lens Service, and a Clinical Professor of Ophthalmology and Visual Sciences at the University of Iowa. Sindt reports that she is Founder of EyePrintProsthetics and co-creator of the EyePrintPRO. Dr Sindt is the inventor and owner of EyePrint Prosthetics.

OIS X | OPHTHALMOLOGY INNOVATOR AWARDS DINNER GALA

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In Practice

Surgical Procedures
Diagnosis
New Drugs

DME, Steroids and Glaucoma

Addressing concerns about steroid-induced intraocular pressure increases and the risk of glaucoma when managing diabetic macular edema

By Charles C. Wykoff

In my practice, I consider using intravitreal corticosteroids for managing diabetic macular edema (DME) in two categories of patients. First, among patients who respond adequately to anti-VEGF therapy, but the durability of current generation anti-VEGF monotherapies is insufficient for their lifestyle or preference. In this context, utilization of a steroid implant can often achieve a decreased treatment burden. Second, among patients who demonstrate an incomplete response to adequate anti-VEGF dosing.

At a Glance

- *Intravitreal corticosteroids are associated with risks, including IOP elevation which occurs in approximately 30–40 percent of treated patients*
- *Elevated IOP alone does not constitute glaucoma, and when secondary to an intravitreal steroid injection, is usually readily manageable with observation or topical ophthalmic drops in the large majority of cases*
- *For appropriate DME patients, intravitreal corticosteroids can represent a valuable alternative treatment option, with the possibility of a decreased treatment burden.*

There are legitimate reasons to pause before initiating corticosteroid therapy for DME. First, they are well recognized to increase the risk of cataract acceleration. In my view, even a single intravitreal steroid injection permanently changes the trajectory of cataract progression in that eye. Second, they have the potential to increase intraocular pressure (IOP); but there can be misconceptions about the correlation between IOP and glaucoma.

Elevated IOP alone does not constitute glaucoma. This simple distinction is often confused on the podium and in the published literature. While more data is needed related to the scenario of elevated IOP following pharmaceutical interventional, multiple studies have considered the complex relationship of absolute IOP and glaucoma. For example, the Baltimore Eye Survey involving 5,308 individuals (ages 40 years and older who underwent detailed ocular exams including perimetry), reported that even with an IOP of 30 mmHg, the majority of patients (95 percent) did not have glaucoma (1). Additionally, the Ocular Hypertension Treatment Study (OHTS) reported that with an untreated IOP of 24 to 32 mmHg, 9.5 percent of participants developed primary open-angle glaucoma (POAG) after 5 years of follow-up; this rate was reduced in OHTS to 4.4 percent among participants randomized to use of a topical ocular hypotensive medication regimen (2) (Figure 1).

Recognition that elevated IOP is not a surrogate for a diagnosis of glaucoma was highlighted by the removal of IOP as part of the definition of POAG in the American Academy of Ophthalmology (AAO) 2015 Preferred Practice Pattern® Guidelines for POAG (3). The current definition reads in part:

"POAG is defined as a chronic, progressive optic neuropathy in adults in which there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons."

Elevating the discussion of steroid-induced IOP

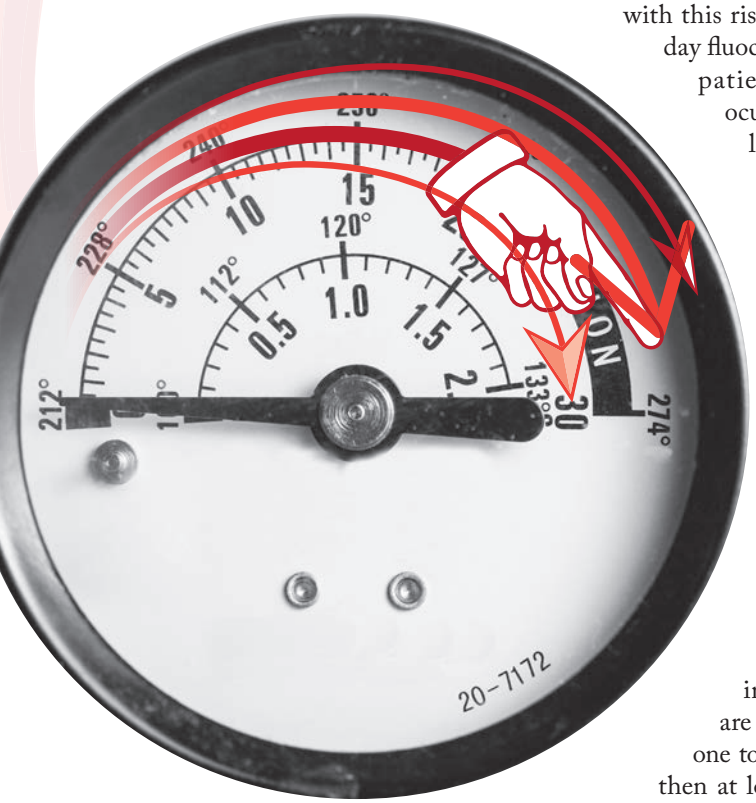
While elevated IOP is not synonymous with glaucoma, that does not negate the real clinical concern that steroid treatments can and often do increase IOP in treated patients. Specifically, approximately 30-40 percent of patients treated with intravitreal steroids will experience a clinically relevant elevation of IOP. In consideration of how to manage such an elevated IOP clinically, it may help to consider what we know about its cause and its course in reported prospective clinical trials.

The pathophysiology of IOP elevation following intravitreal steroid treatment is incompletely understood. It is hypothesized that such elevation may be related to increased outflow resistance (4). Specifically, increased IOP may be facilitated by modulation of glucocorticoid receptors within trabecular meshwork cells, theoretically altering the rate of protein synthesis and inhibiting degradation of the extracellular matrix (ECM) (5). However, other studies have reported the opposite (6).

Some of the clinical factors to consider when determining if steroid treatment may be appropriate include historical points such as a personal or immediate family history of POAG, or a history of steroid-induced IOP elevation. Examination findings to consider include higher baseline IOP, high myopia, evidence of glaucomatous nerve damage even in the absence of a definitive diagnosis of glaucoma, and evidence of angle recession. In any of these situations, I am typically more hesitant to consider administering intravitreal steroids.

When treating patients with intravitreal steroids, data from the

prospective MEAD and FAME trials are good sources of information to gauge risk and guide management of IOP elevation. In the MEAD trial, the pooled results from two randomized, sham-controlled, 3-year studies of 347 0.7 mg dexamethasone- and 350 sham-treated patients found that 27.7 percent of patients given dexamethasone had an IOP increase >10 mmHg from baseline; 41.5 percent were prescribed



IOP-lowering drops compared to 9.1 percent of control patients. The study also found that two patients (0.6 percent) in the 0.7 mg group underwent surgical intervention for elevated IOP, one attributed to steroid-induced IOP elevation and one to neovascularization of the anterior segment (7, 8). Additionally, the collective results of the 36-month FAME trials, which consisted of two randomized, sham-controlled, phase III studies reported that 38.4 percent of 0.2 µg/day fluocinolone acetonide treated patients were prescribed IOP-lowering drops compared to 14.1 percent of control patients. The study also found that while 4.8 percent of 0.2 µg/day fluocinolone acetonide treated patients underwent incisional surgery for elevated IOP, prior ocular steroid treatment correlated strongly with this risk; specifically, no 0.2 µg/day fluocinolone acetonide-treated patients who received prior ocular steroids required IOP-lowering surgery (9). This finding contributed to the FDA-approved package insert for fluocinolone for DME which requires that patients be "previously treated with a course of corticosteroids" and not have "a clinically significant rise in IOP" (10).

"There are legitimate reasons to pause before initiating corticosteroid therapy for DME."

Focusing on management

In my own practice, patients treated with intravitreal corticosteroids are typically monitored every one to two months initially and then at longer intervals, generally not exceeding 3 months, after achieving disease stability. When a patient presents with elevated IOP following intravitreal steroid delivery, how I manage them depends on the degree of IOP elevation and their individual baseline risk profile (11). When possible, since an individual's IOP can vary, correctly assessing levels and potential treatments are ideally based on several IOP measurements rather than a single assessment. In most cases, I will obtain a retinal nerve fiber layer (RNFL) OCT scan if not already obtained; this allows me to follow their RNFL longitudinally for evidence of thinning.

In the setting of mild IOP elevation, I will often simply observe the patient without intervention and in many cases the IOP will return to baseline as the effect of the steroid diminishes. If IOP rises to above 30 mmHg, regardless of baseline risk status, I often treat with a topical IOP-lowering medication. If IOP has risen more than 10 mmHg but is not above 30 mmHg, I will follow these eyes closely often without treatment. When initiating topical therapy, I typically will use an aqueous suppressant. If intravitreal steroid therapy is continued, I will continue the topical IOP-lowering medication; if intravitreal steroid therapy is discontinued, I will often discontinue the topical IOP-lowering medication once the IOP has normalized. In most cases, steroid-induced elevated IOP can be treated with topical IOP-lowering medications. In cases where alternative or additional treatment is required, laser trabeculoplasty and surgery that could involve either a trabeculectomy or tube shunt are options to consider; I often co-manage these patients with either referring ophthalmologists or referring optometrists comfortable with managing IOP.

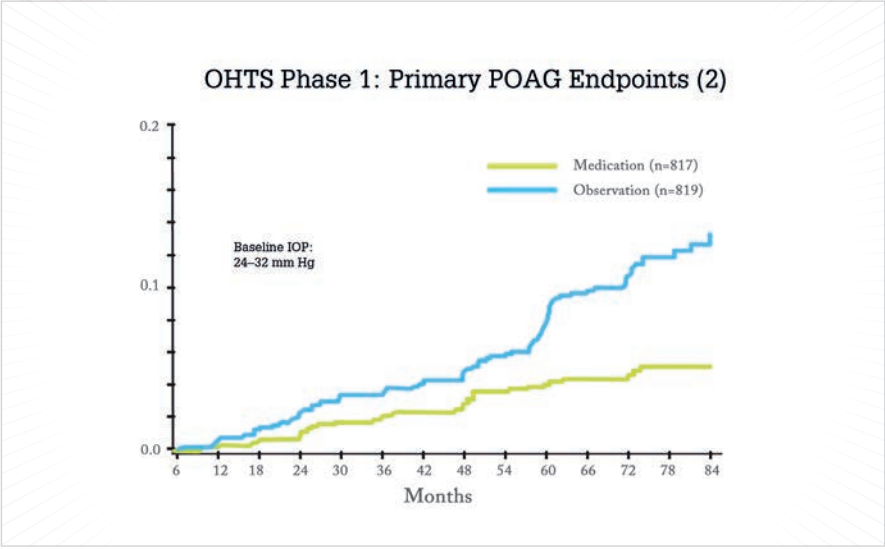


Figure 1. OHTS was a randomized trial conducted at 22 clinical centers. A total of 1,636 participants 40 to 80 years of age, with no evidence of glaucomatous damage and an IOP between 24–32 mm Hg in one eye and 21–32 mm Hg in the other eye were randomized to either observation (n=819) or treatment with commercially available topical ocular hypotensive medication (n=817). The goal in the medication group was to reduce the IOP by 20 percent or more and to reach an IOP of 24 mm Hg or less. The primary outcome was the development of primary open-angle glaucoma (POAG) in one or both eyes (2). Log rank P value < .0001, hazard ratio 0.40, 95% confidence interval (0.27, 0.59). Cumulative proportion POAG at 60 months, 9.5 percent in observation group and 4.4 percent in medication group. Adapted from (1, 2, 11).

Summary

With an appreciation of the multiple pathophysiologic pathways involved in DME, corticosteroids can play a role in its management in certain patient populations. Based on current evidence and my experience with patient responses to intravitreal corticosteroids, while IOP elevation is a common clinical reality in treated patients, these elevations are typically readily managed with either observation or topical IOP-lowering medications. Isolated IOP elevation is not equivalent to a diagnosis of glaucoma. The potential benefits of corticosteroids need to be weighed against the risks of cataract acceleration and IOP elevation for each individual patient.

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The Matchmaker

Introducing the easy-to-use system that offers patients lower risks of complications – regardless of surgeon experience

By Paul Ursell

Cataract surgery is very safe – but it could be even safer. A third of all cataract procedures in the UK are performed by trainees; junior trainees have posterior capsule rupture (PCR) rates of 3.2–5.1 percent (1–3), which compares poorly with the overall PCR rate of 1.9 percent. Intuitively, we all know we could improve this situation by protecting less experienced trainees from more difficult cases. But how can we do this in practice? In my clinic, we have been matching surgeons to cases on a rational basis for nine years – and our retrospective data analysis (4) shows a significant reduction in complications.

At a Glance

- *In the UK, cataract surgery is often performed by trainees – with complication rates two- to three-fold higher than consultants*
- *We have devised a cataract surgery scoring system to stratify patients according to risk, categorize surgeons by experience, and match patients to surgeons accordingly*
- *Data from over 8,000 cases shows that our system removed the association between case complexity and posterior capsule rupture, and almost completely eliminated outcome differences between trainees and consultants*
- *Our system reduces cataract surgery complications, assists practice management and ensures compliance with recent NICE guidelines. We believe the concept is also applicable to other surgical procedures.*

Mix and match

Like much good research, our work has been low tech – but high concept and high impact. In brief, our study builds on a 2009 report (5), which used data from around 56,000 cataract operations to calculate the odds ratio of a surgical complication arising in a given case. Though useful work, it wasn't very user-friendly – it required a complicated program to calculate the complication probability. I wanted to make it easier for

"We haven't eliminated the learning curve in cataract surgery, but we have controlled its impact on patients."

Examples of cataract surgery and complexity scores (4)

Factors associated with PCR

- Male, assigned score: 1
- Age 80–90 years, assigned score: 2
- Dilated pupil ≤4.0 mm, assigned score: 5
- White cataract/ no fundal view, assigned score: 8
- Patient specific score
- Significant hearing impairment, assigned score: 2
- Pachymetry ≥600 μm^2, assigned score: 5
- Permanent VA (other eye) 6/36 or worse, assigned score: 8

Complexity score and trainee recommendations

- Group 1 complexity: total assigned score of 0–1, for trainees with a minimum of 0–50 cases
- Group 5 complexity: total assigned score of ≥10, for trainees with a minimum of 351 cases

clinics to assess the risk of a given case: what we needed, I thought, was a system of classifying both patients and surgeons, and matching them accordingly (see Sidebar).

The first step was to sit down with a group of surgeons, discuss the various case presentations and risk factors, and assign each factor a risk value. We based our approach on the 11 PCR risk factors identified by the cataract national database (CND); we also incorporated important patient-specific factors (absent in the CND dataset) that suggested an experienced surgeon would be more appropriate than a trainee – for example, patients with corneal edema or only one eye. It took some thought, but eventually we identified 16 risk factors, and assigned them values that fairly represented our own surgical experience.

Next, we needed a sensible way of grouping surgeons according to experience. Bearing in mind that, in the UK, surgeons who have performed 350 or more cataract procedures are deemed competent, we created five skill categories based on procedures performed: 0–50, 50–100, 100–250, 250–350, and 350 or more.

Then, we had to develop a rational way of matching patient scores to surgeon skill and experience. Obviously, a Category 1 surgeon needs to be given the easiest cases, while the most complex cases should be passed to Category 5 individuals – surgeons who've done 350 or more cataract procedures. But where should the risk cut-off points be for each intermediate category? My feeling was that surgeons should reach the stage of 'unconscious competence' – where they can perform effectively without having to think about it – before they move on to the next level. Therefore, we arranged cut-offs with the intent that surgeons don't move up to the trickier levels until they are really competent at the previous level.

Finally, as a test, we checked the scoring system against historical cases where a trainee-operated patient had developed complications. It was so exciting to see that in about 20 percent of cases that had a PCR or other complication during surgery, the trainee had been attempting cases that, according to our scoring system, were beyond their competence. It looked certain that we were onto a winner.

Real-world advantages

The theory was sound – but what about in practice? As you can imagine, it took a bit of time to introduce it into a multi-disciplinary National Health Service (NHS) department and get everybody on board. But to everyone's credit it was adopted successfully. One reason for that success is the simplicity of the system; the doctor marks a few things on the patient's score card, the nurse adds additional information, such as biometry, and double-checks the information. The result is a total patient score.

We found that our system generated many unforeseen – but welcome – knock-on effects. First, the trainees were much more comfortable knowing their cases were more appropriate to their level. Second, it helped with scheduling: the

trainees and the secretary would organize the list so that there were always cases of an appropriate level for the trainee, and the consultants picked up the rest. Third, the system helps us avoid situations where a case list is over-burdened with difficult cases and leads to surgeries over-running (and when that is unavoidable, the complexity scores justify the time taken, defusing discussions with clinic managers). Fourth, when patients are reluctant for a junior doctor to operate on them, we can reassure them that under our scoring system, trainees only operate within their level of competence. And fifth, it alerts clinicians to complex cases where the patient should, as part of the informed consent obligation, be informed of particular procedure risks.

The impact has been very positive in our department. And now that people have understood its advantages, it is part of the process.

In fact, we've come to rely on it very heavily; it's considered bad practice when a patient score is missing.

More compatibility, less complication

We've been running this scoring and allocation system in our department for almost a decade now. But analyzing and quantifying its effect was challenging because the scoring system and outcomes data were stored in different databases. I was very fortunate to be joined by a trainee called Paul Nderitu, who worked on merging the two databases; from six years of operation (January 1, 2011, to December 31, 2016) and 11,468 cases, he extracted complexity data on 8,200 cases. The results of the analysis were better than I'd hoped for: our system had practically eliminated the variation between trainees and consultants in terms of complications and patient outcomes! By rationally allocating cases to appropriate surgeons, we ensured that our patients were subjected to similar chances of complications, and equivalent outcomes, regardless of the surgeon's experience. In other words, the risk of complications is almost the same regardless of whether a trainee or a consultant is operating – simply because we match case difficulty to surgeon competence. It puts me in the happy position of being able to assure patients that they will be allocated a surgeon of a level suitable for their specific needs, and that the outcome won't change – regardless of the individual surgeon.

Good matching

I don't know if others are using our system, but plenty of people have asked me about it over the years. I'd expect increased interest – the NICE guideline on cataract surgery in the UK, which came out earlier this year, recommends that all cataract surgery units use some form of scoring system, and ours is by far the largest and most validated of the available cataract scoring systems. Remember, it was not only derived from validated national cataract data, but also validated with 8,000 of our own cases, which provided strong evidence that our system is effective. If you want to improve outcomes (and comply with NICE guidelines if you are in the UK), you could do far worse than to adopt our system!

I believe we've produced something incredibly powerful. Our aim was to minimize complications, optimize outcomes, and maximize patient safety, and I think we have done all of those things. Our system rationally matches patients with surgeons in a way that is good for both. It is ideal for cataract surgery, because the procedure doesn't vary much – but I'm sure the concept could be applied in other types of ophthalmic surgery – or other medical fields, such as orthopedics. To that end, I'd like to explore ways of publicising our work in other surgical disciplines. I'm very proud of what we've done; we haven't eliminated the learning curve in cataract surgery, but we have controlled its impact on patients. And that is a wonderful thing!

Paul Ursell is a consultant ophthalmologist at Epsom & St Helier University NHS Trust, Surrey, UK.

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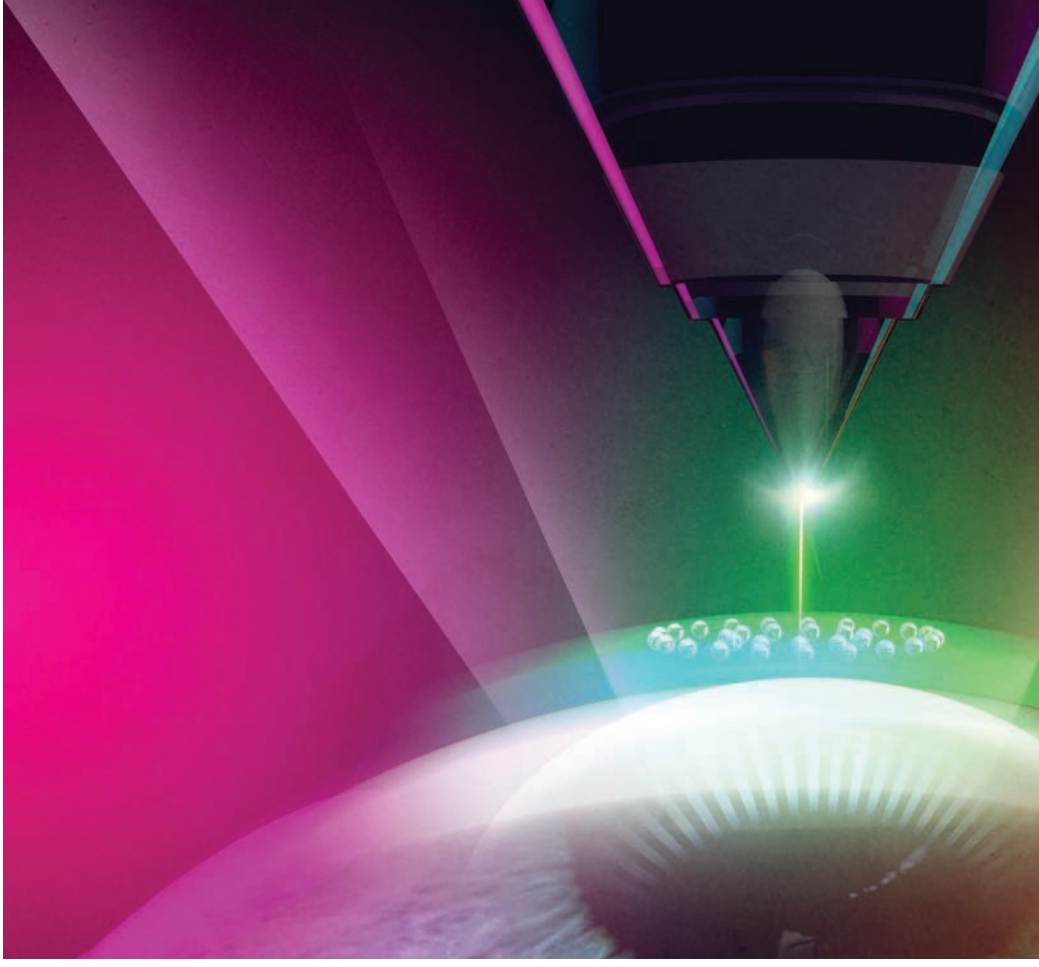

Engineering Non-Invasive Refractive Correction

Could femtosecond laser-induced corneal crosslinking transform standard refractive surgery – and provide a vision correction procedure that is suitable for all?

By Sinisa Vukelic

My laboratory in the Department of Mechanical Engineering at Columbia University (New York, USA) approaches ophthalmology in a very different way from most: in particular, our expertise in biomechanics and laser materials processing provides a fresh perspective on the eye. Of course, we've had to learn a lot about collagen and tissue biomechanics – very different from the single crystal and bicrystal mechanics that we've previously worked on – but good things happen when you embrace new concepts and think outside the box. In fact, our open-minded approach helped us make a key discovery: a loosely-focused laser beam can non-invasively modulate corneal geometry and stably alter the eye's refractive power.

At a Glance

- *Normal femtosecond laser surgery employs a highly-focused beam, resulting in a high-density plasma that creates pressure waves, which can disrupt corneal biomechanics and cause post-surgical complications*
- *By contrast, a loosely-focused femtosecond beam creates a low density plasma (LDP) that does not generate damaging pressure waves*
- *We have discovered that LDP, by ionizing water and creating oxygen free radicals, creates crosslinks in corneal proteins and thereby alters corneal geometry in a modulatable, predictable way*
- *Results from animal models suggest that our LDP approach could be the basis of safer, non-invasive, permanent vision correction procedures suitable for virtually all patients.*

Clouds not avalanches

I am a mechanical engineer by training, and have always been fascinated by the plasma physics of ultrafast lasers. In retrospect, this turned out to be the perfect background to kick-start our investigations into the adjustment of corneal biomechanics. Nevertheless, making progress in this field required a great deal of time and effort; for example, once we'd found that a loosely-focused laser beam strengthened the cornea, we had to go back to first principles and do some very basic science to figure out what was happening. It took years! The end result is a procedure that is rather different from the standard ophthalmological application of lasers – we are using femtosecond lasers not to cut tissue, but to strengthen it by inducing crosslinks.

How does this work? Normally, surgical use of femtosecond lasers relies on 'avalanche ionization,' where multiple photons ionize a substrate molecule; the freed electrons hit electrons associated with other molecules, thereby ionizing other molecules and liberating more electrons, and so on. The cascade effect requires the electron cloud to reach a critical density such that all the incoming photons from the laser pulse are absorbed by electrons, thus creating a dense plasma. Being under pressure, however, the plasma expands and creates damaging shock waves and cavitation bubbles. Hence, normal femtosecond laser operation allows the surgeon to cut a flap in the cornea but also causes unwanted damage, and may lead to post-surgical complications, such ectasia and corneal weakening.

By contrast, our approach involves

modulating the power and focus of the laser beam such that there are enough photons to create an ionization cloud, but not enough for avalanche ionization and dense plasma formation. The resulting low density plasma (LDP) does not generate shockwaves, and therefore does not damage biological tissue in the same way as a high density plasma. Importantly, however, the LDP ionizes water molecules, thereby generating oxygen free radicals which react with corneal proteins, creating crosslinks that strengthen the cornea in the precise area covered by the laser. The ability to target crosslink induction to very small volumes of corneal tissue allows us to precisely and predictably modulate corneal geometry.

Correction without cutting

Once we had shown that we were creating crosslinks that strengthened the cornea, I knew we'd found something important: a new therapeutic approach that could be tailored to different patients' needs. Our next step was to conduct proof-of-principle studies in enucleated porcine eyes and in rabbit eyes in vivo (see 'Plasma physics for configuring corneas'). For the in vitro porcine eye studies, we removed the epithelial layer, not because our approach requires it, but because abattoir-sourced eyes often have superficial damage that can interfere with imaging. We didn't need to remove the epithelial layer in the rabbit animal models. Indeed, a big advantage of our method is that it is truly non-invasive.

The results from these animal studies are highly promising. In enucleated porcine eyes, LDP-mediated corneal flattening (as would be used for the treatment of myopia) changed refractive power by about 12 percent (~ 5.11 diopters) during the initial 8 hours. After 24 hours of recovery, refractive power stabilized at ~92 percent (~3.45 diopters) of the initial level. In LDP-mediated corneal steepening (as would be used for the treatment of hyperopia), the refractive power of enucleated porcine eyes increased gradually for 12 hours before stabilizing. In no case was there evidence of laser-induced thermal denaturation or other tissue damage. Additionally, we have very new and exciting – albeit preliminary – observations regarding LDP treatment and keratinocyte populations.

In rabbit eyes in vivo, we observed a relative change in effective refractive power of ~1.94 diopters for treated eyes (the difference between porcine and rabbit eyes in the refractive change achieved is expected, as the two species have very different corneal geometries). Treatment of live rabbits was not associated with the wounds or wound-healing responses seen in refractive surgery. Equally, there was no evidence of thermal damage, such as edema or endothelial cell detachment; microscopy after sacrifice suggested that treated eyes were no different from controls. Some of our treated rabbits have now been followed up for seven months; data suggest that the refractory power change is stable, and confocal imaging indicates that the eyes show no significant structural changes over this period. And that's exactly what we expected; remember that we are creating covalent bonds, which are difficult to break. Therefore, as long as there is no significant collagen turnover, the refractive power changes we achieve should persist.

We are very pleased with our data so far, but we'd also be delighted to work with anyone who wants to try replicating our results; we all have a duty to make sure that our data are valid. After all, we want to develop a treatment that works every time – 85 or 90 percent success rates are not good enough. Excellent outcomes, every time: that's our goal.

Future focus

Currently, we are moving ahead in two major directions: basic research and clinical development. The former will include extensive parametric studies to ensure that we know exactly what is going on during LDP treatment of the cornea. And however many samples the power analysis tells me I should do, I will always multiply that by five! It upsets the statisticians, but my view is that you only need to mess up once to lose credibility. In addition, we are developing a model that treats crosslinks as external load, and developing equations relevant to this; the aim is to fully understand the cornea's viscoelastic response to the LDP procedure. This knowledge should enable us to precisely tailor LDP treatment to each patient. Treating crosslinks as a load has not been done before, at least not to my knowledge – so there's enough work for two PhD theses! We are also looking at longitudinal studies on the nature of the crosslinks generated by LDP.

With regard to clinical trials, we are working hard on developing suitable device prototypes and procedures. I'd hope to be in human trials by the end of the year, certainly some time in 2019. We are already talking with potential partners about clinical trials in Europe – people have been very enthusiastic whenever we present this work. In particular, we are optimizing

Plasma physics for configuring corneas

Porcine eyes:

- Fresh eyes (~2 hours old; n=60) were mounted in a chamber that permits control of IOP
- Epithelia were removed because of abattoir-associated damage that would interfere with imaging
- A coverslip was applied to press the cornea into a single plane and thereby allow consistent delivery of laser energy over the treated area
- The laser was applied in a boustrophedon pattern; successively deeper 'treatment layers' were achieved by consecutive applications at increasing depth (50 µm increments)
- Treatment of square 5 mm by 5 mm, over the center of the eye, induced corneal flattening (n=15; matched with 10 controls)
- Treatment of ring-shaped area induced corneal steepening (n=13; matched with 10 controls)
- A separate control study was undertaken to evaluate any effects of experimental set-up itself (n=12)
- After treatment, refractive power was measured hourly over 24 hours
- After 24 hours, corneas were cultured for one week to assess stability of crosslinking

Rabbit eyes:

- Mainly as above, but modified to accommodate live animal (for example, the coverslip arrangement permitted addition of drops to keep eyes moist)
- Epithelium left in place
- Treated area of 5 mm diameter
- Followed up at 24 hours, 7 days, then weekly up to 3 months

the procedure so that it is at least on a par with LASIK with regard to treatment time; everyone would prefer a 5 minute procedure to a 40 minute procedure. We also intend to modify the LDP procedure so that it is applicable to other conditions, including keratoconus, which is the condition we were originally targeting before our ophthalmological colleagues steered us towards refractive surgery. In fact, keratoconus is a great opportunity, given that the current standard of care requires 'epithelium-off' crosslinking. Our 'epi-on' approach would remove many risks, and could represent a significant advance.

We are also looking at applications beyond ophthalmology; for example, applying LDP to articular cartilage in osteoarthritis has given us some fantastic results, and we have now received NIH grants to further pursue this.

Clear benefits

The theoretical advantages are profound. Firstly, being non-invasive, our technique is preferable to standard surgical approaches to vision correction. Furthermore, our approach is gentler than other crosslinking methods: we do not need to peel off the keratocytes, and we don't need to risk damage to keratocytes and epithelial cells by applying UV light, as required in standard crosslinking. Secondly, unlike standard surgical procedures, our method will be applicable to 'difficult' patients; for example, older individuals, patients with thin corneas, people with dry eye syndrome, and those with abnormal corneas. Thus, we hope that many people who are currently ineligible for refractive surgery could be treatable by our method.

I firmly believe that LDP could be the start of a new standard of care in permanent vision correction.

Sinisa Vukelic is a Lecturer in Discipline at Columbia University, New York, NY, USA. His laser research interests lie in laser induced mechanical deformation, single crystal and bicrystal micromechanics and strain gradient plasticity, structural modification of transparent dielectrics and laser imaging and diagnostics.

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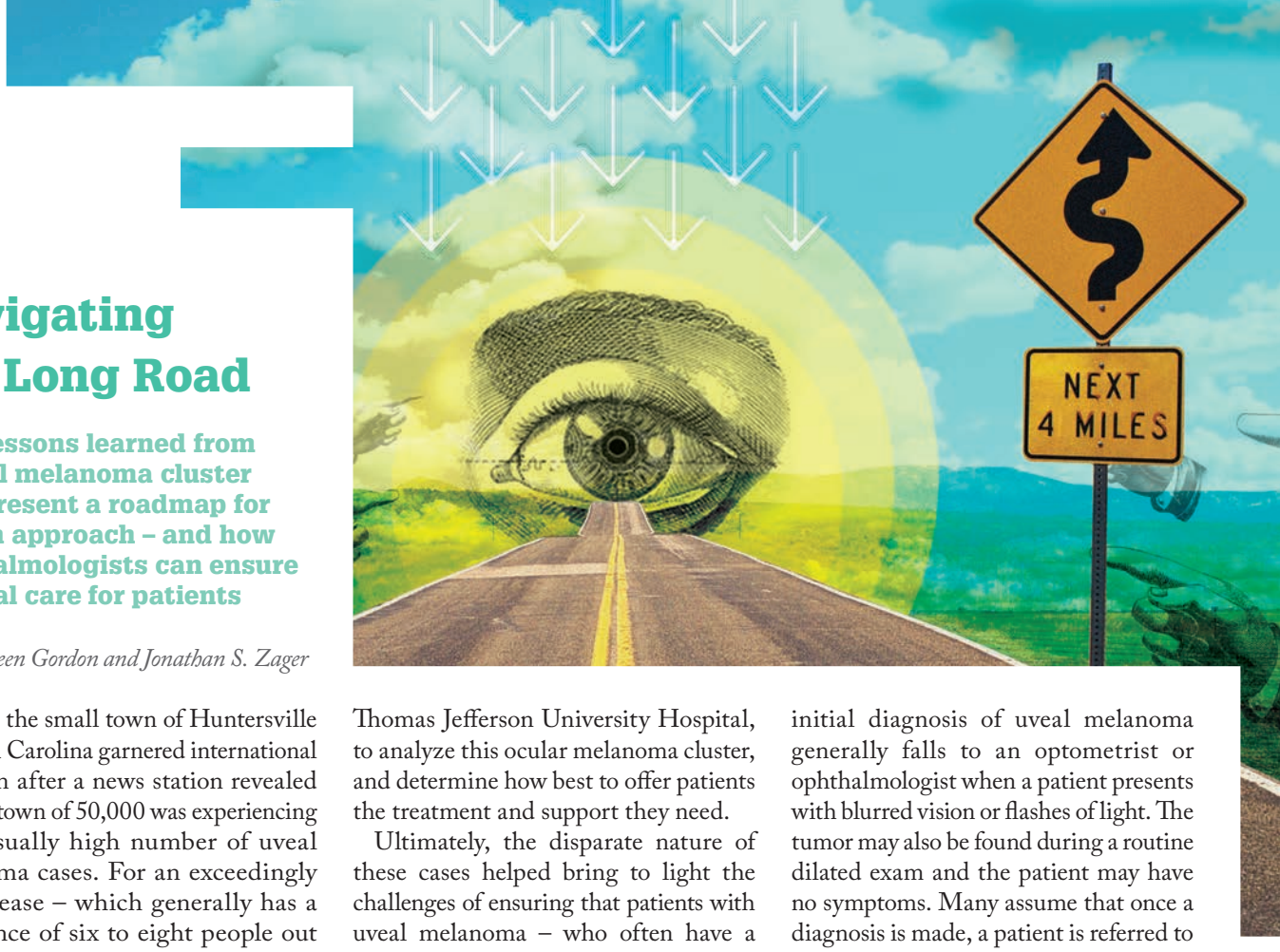
Illustrations by Andy Potts for Vukelic Group and Clarity Vision Technologies



Navigating the Long Road

How lessons learned from a uveal melanoma cluster may present a roadmap for a team approach – and how ophthalmologists can ensure optimal care for patients

By Kathleen Gordon and Jonathan S. Zager

In 2014, the small town of Huntersville in North Carolina garnered international attention after a news station revealed that the town of 50,000 was experiencing an unusually high number of uveal melanoma cases. For an exceedingly rare disease – which generally has a prevalence of six to eight people out of every million per year (1) – the 12 cases found in the town over a 10-year period certainly raised concern. After securing $100,000 in state grants, local legislators were able to assemble a panel of experts – including ophthalmologists and oncologists – at the University of North Carolina, Duke University and Thomas Jefferson University Hospital, to analyze this ocular melanoma cluster, and determine how best to offer patients the treatment and support they need.

Ultimately, the disparate nature of these cases helped bring to light the challenges of ensuring that patients with uveal melanoma – who often have a lengthy disease progression – have access to appropriate immediate and long-term medical care. Most significantly these events have reinforced the pivotal role ophthalmologists play in their patients' short- and long-term care – and the importance that all ophthalmologists remain abreast of the latest and upcoming treatment options for patients with uveal melanoma and metastatic uveal melanoma.

At a Glance

- *Uveal melanoma is a systemic illness that requires long-term monitoring and care*
- *Ophthalmologists play a pivotal role in multidisplinary teams for the short- and long-term care of patients with the disease*
- *Ophthalmologists can further aid patients by understanding the advancements that are currently being made in uveal melanoma and metastatic uveal melanoma*
- *Lessons learned in the Huntersville North Carolina uveal melanoma cluster may present a roadmap for a care-team approach to the disease.*

Understanding uveal melanoma

Uveal melanoma is the most commonly diagnosed intraocular malignancy in adults. In most cases, it develops from the pigmented cells of the choroid, but it can also develop from the pigmented cells of the iris and ciliary body. In general, uveal melanoma presents most commonly in older patients, with a higher incidence in men (2). The Huntersville cluster bucks this trend. Among the initial 12 identified individuals, nine were female and six were younger than 30 when they were diagnosed.

Uveal melanoma has an overall mortality rate of about 50 percent. The initial diagnosis of uveal melanoma generally falls to an optometrist or ophthalmologist when a patient presents with blurred vision or flashes of light. The tumor may also be found during a routine dilated exam and the patient may have no symptoms. Many assume that once a diagnosis is made, a patient is referred to an oncologist, who undertakes any future care. The reality is that because uveal melanoma is so rare, a patient who has been diagnosed with the cancer may have to travel 100 miles or more to work with an ocular oncologist who is familiar with the illness. Once treatment of the primary tumor is complete, surveillance for metastatic disease may be variable. Many patients prefer to be monitored close to home. Some will educate themselves about their risks for metastatic disease through advocacy organizations, such as the Ocular Melanoma Foundation (OMF). Unfortunately, many patients will mistakenly believe that once the tumor – which was localized to the eye – is treated that they are cancer-free and no longer need to see an oncologist. But nearly half of all patients who develop uveal melanoma will go on to suffer from metastatic disease (1). In some cases, patients may not experience progression of the disease for as many as 15 years after the initial diagnosis (3). Anecdotally, care teams who provided initial treatment to uveal melanoma patients report that

they often don't hear that a patient had developed metastatic disease and passed away until years after. Not only does this leave care teams wondering whether the patient received regular monitoring, but it also keeps clinicians from gathering vital data that can help improve care for other patients – an essential step for a cancer as rare as uveal melanoma.

As uveal melanoma is a systemic disease rather than just an ocular one, it is crucial to surround patients with a multidisciplinary team (MDT) of clinicians – including an ophthalmologist and a medical oncologist – to monitor and treat the patient over the long-term. In urban areas, these teams may be conveniently working at the same hospital – as they are at the University of North Caroline and Moffitt Cancer Center – and so may meet patients and discuss treatment strategies together. But patients in more rural areas may rely on their local hometown ophthalmologists who they see on a regular basis to help them understand their treatment options and assess next steps. For these patients, MDTs may need to come together from unaffiliated institutions and meet electronically. In either case, it is critical for all team members to understand the diagnostic and treatment options available to a patient, and ophthalmologists – regardless of specialty – play a pivotal role in the care of patients.

Approaches to treatment

Patients who present with primary tumors can often be successfully treated with local radiation therapy and ablative treatments. Depending on the size and location of the melanoma, it might be possible to retain some vision using these treatment approaches. For large melanomas, enucleation is the preferred approach, but some physicians have achieved fairly good results and comparable survival rates treating them with proton beam radiation therapy (4).

But given that approximately one out of every two patients will go on to develop metastatic disease – the leading cause of death among patients with uveal melanoma (5) – treating the primary tumor is only the first step, and patients require routine surveillance to monitor for tumor spread. Metastatic uveal melanoma often involves hepatic metastases, which can occur in as many as 93 percent of patients with metastatic disease (6). Median survival after liver involvement is poor, often ranging from 4 to 6 months, with a one-year survival of only 10-15 percent (5). Surgical resection, however, offers limited success because of the classic miliary spread of the metastases in the liver. In fact, only a small number of patients have enough healthy liver tissue uninvolved by tumor remaining for this to be an option, which is why effective therapies are crucial. Although several treatment options have come to market in recent years and improved overall survival of patients with metastatic cutaneous melanoma (such as ablation, embolization, targeted therapy and immunotherapies) (7), the treatment landscape for metastatic uveal melanoma has remained relatively unchanged. The lack of effective therapies has resulted in a poor prognosis for patients.

Fortunately, recent advancements have been made in the treatment of primary uveal melanoma, as well as the detection and treatment of metastatic uveal melanoma, which could potentially offer new options for both patients and the extended medical team managing care. Here, we overview just some of the options that are currently under investigation.

AU-011 for primary uveal melanoma

AU-011 is an investigational therapy for the primary treatment of uveal melanoma. The therapy – in development by Aura Biosciences – requires an intravitreal injection of a novel recombinant papillomavirus-like particle (VLP) that selectively binds to heparan sulfate proteoglycans on the surface of the tumor cells, and is conjugated to a phthalocyanine photosensitizer, IRDye 700DX (8). When activated by a near-infrared light, IRDye 700DX produces reactive oxygen species that disrupt the membranes of bound cells, inducing tumor necrosis.

In a preclinical study, treatment with AU-011 yielded extensive tumor necrosis in a rabbit xenograft model of uveal melanoma; three out of 10 animals experienced complete tumor response after treatment with activated AU-011 (9). AU-011 shows high affinity for tumor cells while not binding to healthy epithelium, and so should selectively destroy uveal melanoma cells while sparing the adjacent retina; in a rabbit orthotopic model, tumor treatment was found to spare the retina and adjacent ocular structures (10). Phase Ib trials commenced in 2017 and are expected to enroll a total of 12 patients. Although clinical development of AU-011 is early and the treatment is currently experimental, should it prove effective in targeting primary uveal melanoma, it could become a valuable primary

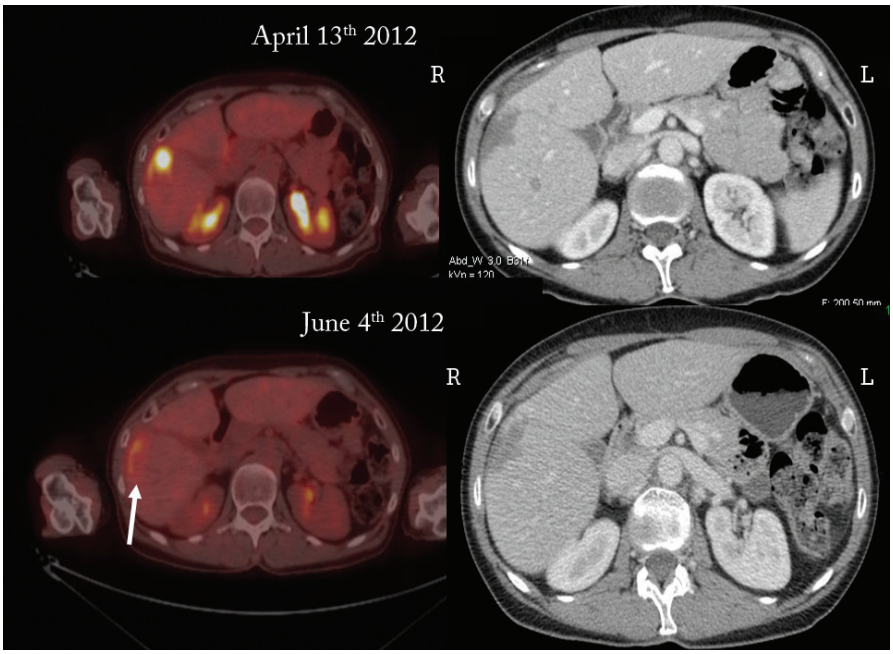
treatment option for patients whose disease is identified early.

Detecting metastatic potential

Though it has not been clinically proven, it is believed that if metastatic disease could be diagnosed early – and thus tumors treated when they are smaller – it could improve long-term survival of patients with metastatic uveal melanoma (10). DecisionDX-UM (Castle Bioscience), a gene expression profile test available since 2009, and the follow-on DecisionDX-PRAME test, which was launched in 2016, were designed with early diagnosis in mind.

The DecisionDX-UM test evaluates the expression patterns of 12 select genes in tumor samples, as well as three control genes shown to be unchanged in uveal melanomas (11). Based on the results, tumors are classified as Class 1A (low risk), Class 1B (intermediate risk) or Class 2 (high risk). Clinical studies have shown the test is 97 percent successful in determining whether patients fall into Class 1 or Class 2 (12). But although Class 1 tumors are lower risk, metastatic disease is still a possibility. To address this, DecisionDX-PRAME was developed. PRAME – or preferentially expressed antigen in melanoma – is a cancer antigen gene that can be increased in some types of cancer. A study published by researchers at the Bascom Palmer Eye Institute showed PRAME to be a strong indicator for metastatic disease in patients who had been previously classified as having Class 1 uveal melanoma (13).

Not all patients will want to undergo this type of genetic testing, but such information adds an important element to the management of patients. Current guidelines recommend that low-risk patients receive a systemic work up every 6 to 12 months, whereas high-risk patients should receive a work up every 3 to 6 months.



Patient before (top) and after (bottom) PHP treatment with melphalan hydrochloride. The white arrow shows the hepatic metastasis after treatment. Credit: Jonathan Zager.

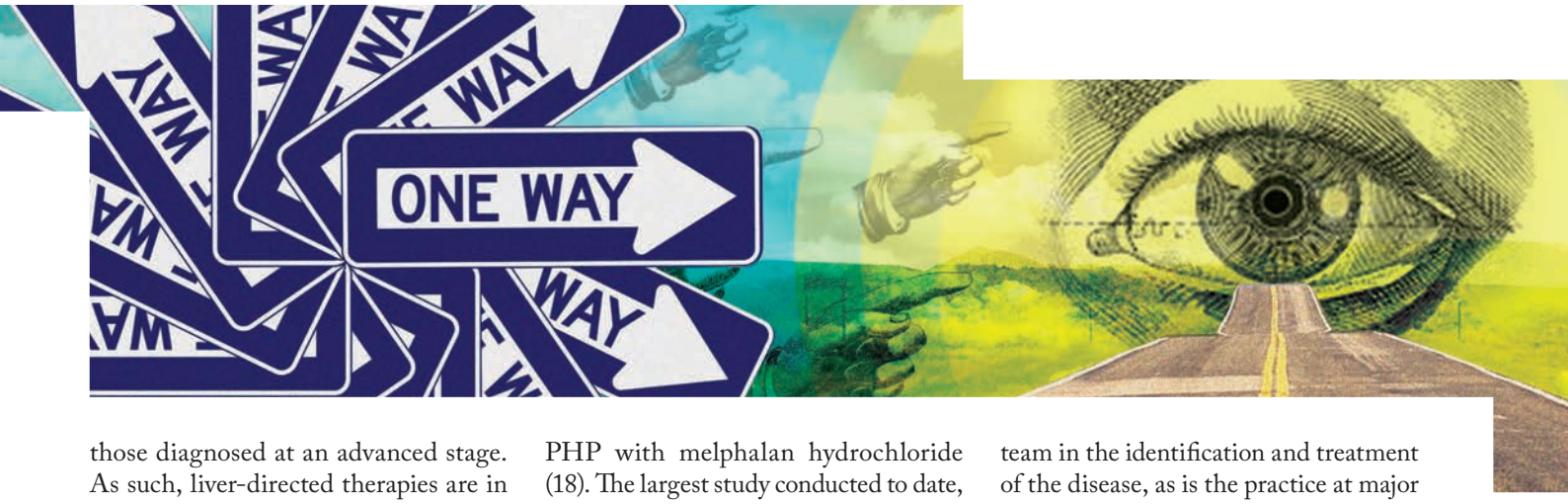
Adjuvant therapy to stave off metastatic disease

In recent years, researchers have started looking at whether cytotoxic and immunotherapy regimens – both alone and in combination – could be applicable as adjuvant therapy in patients shown to be at high risk for metastatic disease.

Currently, several clinical trials are underway in the USA to evaluate adjuvant therapies. One such Phase II trial, occurring at Thomas Jefferson University in Pennsylvania, is evaluating the use of sunitinib malate or valproic acid to prevent metastasis of uveal melanoma (ClinicalTrials.gov, NCT02068586). Sunitinib malate is a tyrosine kinase inhibitor that may prevent metastatic progression through inhibiting c-Kit and receptors, including VEGFR (14). Valproic acid is a histone deacetylase inhibitor that may lower the risk of metastasis by altering the gene expression profile in uveal melanoma cells (15). Another Phase II trial, led by Columbia University, is recruiting patients at five different centers on the East Coast and in the Midwest, and is investigating crizotinib as an adjuvant therapy for uveal melanoma (ClinicalTrials.gov, NCT02223819). Crizotinib, a tyrosine kinase inhibitor that is currently approved for the treatment of non-small cell lung cancer, has been shown to significantly reduce metastasis in a murine model of metastatic uveal melanoma (16). Other strategies being investigated as adjuvant therapies include dacarbazine and interferon-alfa (ClinicalTrials.gov, NCT01100528), ipilimumab and nivolumab (ClinicalTrials.gov, NCT01585194) and a dendritic cell vaccine (ClinicalTrials.gov, NCT00929019). With these trials in early stages, use of adjuvant therapies for uveal melanoma is still several years off.

Liver-directed therapies for metastatic disease

Once uveal melanoma has metastasized to the liver, a limited number of treatment options are available – particularly for



those diagnosed at an advanced stage. As such, liver-directed therapies are in use and under investigation, including embolization and percutaneous hepatic perfusion (PHP). Embolization involves the targeted destruction of tumor cells through radiation or chemotherapy, whereas PHP is a targeted whole organ therapy for the liver. The PHP procedure is a three-step process that i) isolates the liver from the circulatory system, ii) administers a high dose of chemotherapy for 30 minutes before iii) filtering out the chemotherapeutic agent from the blood exiting the liver to reduce systemic exposure and minimize many of the side effects inherent to the drug. PHP is a minimally invasive procedure that is repeatable, with patients being treated as many as eight times in early clinical trials.

A retrospective analysis comparing liver-directed therapies has demonstrated that radioembolization with yttrium-90 (Y90) and chemoembolization had a median progression-free survival (PFS) of 54 days and 52 days, respectively (17). By contrast, PHP with melphalan hydrochloride (Delcath Melphlalan/HDS) demonstrated a significantly higher PFS of 245 days (P=0.03 versus Y90 and chemoembolization). Median overall survival with PHP was also longer at 608 days compared with Y90 (295 days) and chemoembolization (265 days) (P=0.24). An even more recent retrospective analysis of outcomes data of patients with metastatic uveal melanoma has further supported the potential of PHP with melphalan hydrochloride (18). The largest study conducted to date, the analysis included 51 patients who received a total of 134 treatments. Of those, 49 percent achieved a partial (43.1 percent) or complete hepatic response (5.9 percent). The disease stabilized for at least three months in 33.3 percent of patients. Median overall PFS and hepatic PFS was 8.1 and 9.1 months respectively, with median overall survival of 15.3 months. The Moffitt Cancer Center is the lead site in the US for the Phase III clinical trial of Delcath Melphalan/HDS, with select trial sites throughout the US and Europe also involved and actively enrolling patients (ClinicalTrials.gov, NCT02678572). If the treatment receives approval, it could represent a huge step forward in the treatment of metastatic uveal melanoma.

Traveling the long road together

Uveal melanoma can be difficult to treat, especially when it progresses to metastatic disease. Thankfully, new advancements are in development or on the market that might help the fight against the disease. But for these advancements to make a meaningful impact on the long-term survival of patients with uveal melanoma, the care communities (oncologists, ophthalmologists and advocacy partners) must remain educated about the diagnostic and treatment options, and be vigilant about long-term patient monitoring. The key is to involve all members of a patient's care team in the identification and treatment of the disease, as is the practice at major centers such as the University of North Carolina and Moffitt Cancer Center. The Huntersville North Carolina uveal melanoma cluster, while tragic, may become a case study highlighting the potential that exists when medical care teams work in concert. Future uveal melanoma patients in the Huntersville area have the benefit of an educated and coordinated medical community, and their long-term survival may benefit greatly.

In North Carolina, Florida and nationwide, ophthalmologists have been identified as one of the most vital players

"Ophthalmologists have been identified as one of the most vital players on the care team"

on the care team, as they are often the physician with the most sustained patient contact. As the gatekeepers to uveal melanoma patients, they are essential in identifying disease early, treating the primary tumor, educating the patient about potential options available to them and stressing the importance of ongoing surveillance. And because metastatic disease can happen years after the initial diagnosis, ophthalmologists play a critical role in reinforcing the need for monitoring and testing well after many patients may think it's necessary. Uveal melanoma has a long treatment path – and all caregivers should be involved in making sure that patients and clinical teams stay on course.

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Photo by Ace Kvale.

Overcoming the Mountain of Global Blindness

The story behind the Himalayan Cataract Project – the NGO eradicating blindness, one country at a time.

By Geoff Tabin

Nepal is the only large, low to moderate income country in the world that has reversed its incidence of blindness, and I'm proud to be part of the reason why. Back in 1995, I co-founded the Himalayan Cataract Project (HCP) with Nepali ophthalmologist Dr. Sanduk Ruit. When we started, there were more than 250,000 people bilaterally blind from cataracts in the Himalayas, with 60,000 more people going blind every year. Nepali surgeons were performing a few thousand cataract surgeries a year, but even fewer were being performed in Tibet, northern India, West Bengal, Sikkim or Bhutan. Today, the number of cataract surgeries performed in Nepal has risen to more than 350,000 a year. Where once, nearly one in 100 people were blind, the figure now stands at less than three per thousand – the same as the West. And all it took was a five-minute procedure.

If the poorest country in south Asia can eradicate preventable blindness, others can too. By establishing a top-to-bottom system based on compassionate capitalism – where paying patients subsidize surgery to keep costs low – it is possible to provide a high standard of care in even the poorest places. That's what HCP is all about. We empower local people to take control of their healthcare. We train doctors, nurses and technicians at every level, from the primary health care workers to a subspecialty trained ophthalmologists. We know surgeons in developing countries are constrained by lack of equipment, so we try to make sure our partners are as well-equipped as possible.

In the beginning…

HCP came about almost by chance. Back in my early 20s, I was lucky enough to receive a Marshall Scholarship to study philosophy at Oxford University in the UK. At that point, I'd already been accepted to medical school in the US. If it weren't for the scholarship, I would probably be an orthopedic surgeon somewhere doing sports medicine. My time at Oxford gave me time to think about what I wanted to do, and I became interested in the moral paradigm behind healthcare delivery, and the disparity in access to healthcare between countries around the world.

Oxford had a number of endowed funds, including the A C Irvine Travel Fund that provided resources for students to enjoy a strenuous mountaineering holiday abroad. I had always been sporty. I played university tennis and skied from an early age, but I became fanatical about climbing. With the help of the fund, I more or less spent half the year on a paid climbing holiday, scaling big walls in Afghanistan, New Guinea and Africa. The opportunity to climb in Asia and Africa allowed me to witness firsthand the consequences of extreme poverty on health, and the disparity in healthcare systems throughout the world.

My focus was already on global health by the time I matriculated at medical school. As it turned out, I wasn't done with climbing just yet. I was asked to join the first American climbing expedition to Tibet. Together, we would attempt the last unclimbed face on Mount Everest. How could I say no?

I was applying for leave of absence from medical school when I got the phone call that would change everything. After making sure I was Geoff Tabin, the man on the other end said, "You're probably the dumbest person ever accepted into Harvard Medical School." His name was Dr. Michael Wiedman, and he was on the committee reviewing request for leaves of absence. "There's no way that you would ever get a leave of absence to go climbing," he said. "Anybody with the intelligence to get into this school should know that if you apply to do research, Harvard will give you credits." It turned out he was interested in the effects of high altitude on retinal physiology, specifically high altitude retinal hemorrhaging as a prognosticator of cerebral edema. He said: "Let's forget about your leave of absence and talk about our research project." So we did.

Climbing high

In 1983, while researching under Wiedman, my team and I made the first successful climb of the east side of Everest. It's still the only route done with only local support. It's very technical – more than any other path up the mountain – and it's never been repeated.

After finishing medical school, I had the opportunity to work as a general doctor at one of the hospitals in Nepal that Sir Edmund Hillary, one of my heroes, had established. Many of the problems I faced were public health issues, problems of poverty. I watched children dying of diarrhea and pneumonia and things that would be so easy to treat in the Western world. Then I saw Dutch ophthalmologist

At a Glance

- *The Himalayan Cataract Project (HCP) was co-founded by Geoff Tabin and Sanduk Ruit in 1995*
- *Aiming to tackle avoidable blindness, the organization began its work in Nepal and has since expanded throughout South Asia and Sub-Saharan Africa*
- *Geoff Tabin tells the story of setting up HCP, and how it all began with a philosophy degree and conquering the world's highest mountain*
- *Tabin also shares his view on how worldwide blindness can be eradicated.*

Geoff Tabin with a patient who had received sight-restoring cataract surgery in Kalimping, India. *Photo by Ace Kvale.*

HCP Co-Founders Sanduk Ruit and Geoff Tabin with patients at a high volume cataract outreach in Dolakha, Nepal. *Photo by Michael Amendolia.*

Geoff Tabin with a cataract patient in South Sudan.
Photo by Jordan Campbell.

Dr. Jan Kok and his team perform cataract surgery. It was mind-boggling. Before they came, blind people just waited to die. They accepted that you get old, your hair turns white, your eyes turn white, and then you die. In an agrarian economy like Nepal, blindness was a burden for the whole family. Often children would leave school to take care of a blind parent or grandparent. But all it took was a small operation to bring these people back to life. I'd never seen anything in medicine ignite such unbelievable joy. It's hard to express the happiness that a totally blind person feels when they are able to see again.

I knew I could make a difference. I wanted to teach people to perform cataract surgery and immediately sought a residency in ophthalmology. What I didn't know then was that the real genius behind anything that I'd be able to accomplish in the future was also in Nepal – my HCP co-founder Sanduk Ruit. Sanduk grew up in a hill village in Nepal four days' walk from the nearest road, with no electricity or running water. At eight years old, his father walked him all the way to Darjeeling, India to attend school. He went on to graduate with top honors and won a full scholarship to one of the best medical schools in India.

Upon seeing the level of blindness in his home country, he re-trained as a micro surgeon in the Netherlands with Jan Kok – the same doctor I saw perform cataract surgery in Nepal – and also completed a fellowship in Australia with Dr. Fred Hollows. It was the late 1980s when he returned to Nepal.

At this time, even the least expensive IOLs were cost-prohibitive for the developing world. Sanduk had the genius to team up with his mentor Fred Hollows and his eponymous foundation to raise the funds to start the first low-cost IOL factory in the world, in Kathmandu, instantly reducing the cost of the lenses from $200 to $4. In doing so, he transformed the economy of global cataract surgery – a procedure that would cost $3,000 in the United States now cost $20 in Nepal.

I heard Fred Hollows lecture in the second year of my residency. I was so impressed by him that I decided to do my corneal fellowship in Australia. Unfortunately, Fred died of cancer before I had chance to start, so I ended up doing my fellowship under Dr. Hugh Taylor, the world authority on river blindness and trachoma. It wasn't until my fellowship that I met Sanduk and everything began to fall into place. He had already set up this amazing system of delivery, taking the best cataract care in India and applying it to Nepal. I was blown away. I finished my fellowship and moved to Nepal to work with Sanduk. That's when HCP was born.

Going above and beyond

During our first cataract outreach together, we restored sight to 224 people in three days. Sanduk did 201 surgeries, while I did 23. The results were incredible. About 80 percent of our patients could see well enough to be able to pass the American driving test one day after surgery. With Sanduk's cataract outreach system, a single doctor in Nepal can provide more than 100 sight-restoring cataract surgeries in a single day.

Unfortunately, people in rural Nepal didn't know they could have their sight restored – they had to be told. And so our mission transformed. Instead of simply teaching doctors, we created an entire

system of care. We established primary eye care centers throughout the hills of Nepal, which referred patients to larger regional cataract centers. We expanded upon our now full-service tertiary eye hospital, the Tilganga Institute of Ophthalmology, in Kathmandu. Sanduk also had the brilliant idea of introducing training programs for nurses, ophthalmic assistants, ophthalmic technicians and residents – making us the first hospital in Nepal to develop a full ophthalmology residency program.

On the move

Today, our work is no longer limited to the Himalayas despite our name. We run training sessions throughout the developing world – from Asia to sub-Saharan Africa. We currently have programs in Ghana, Ethiopia and Rwanda, and initiatives in Tanzania. One of the biggest problems in Africa is access to care. There are no neuro-ophthalmologists or uveitis specialists in East Africa – or West Africa, for that matter. In Ethiopia, there's one ophthalmologist for every 1,000,000 people – and even that figure is deceptive. Of the 130 ophthalmologists in the country of 105,000,000 people, 30 are either working with NGOs or not doing active surgery, while 60 live in the capital, Addis Ababa, which leaves 40 ophthalmologists to serve the rest of the population – several million people each. You don't have to be a mathematician (or ophthalmologist) to know those numbers aren't good.

To that end, our Ethiopian training program is geared towards high-volume cataract surgery, equipping doctors with the necessary skills and equipment to deal with 1,000 cases a week. As in Nepal, we are still having to reach out to patients. And although this works for now, we are working with local partners and the Ministry of Health to establish permanent healthcare sites to make truly lasting change.

HCP doesn't just visit a place, perform a few surgeries, then leave. We want to make a lasting impact, and we do that by finding partners. We give them the resources they need to do things on their own. We build their skills, provide them with equipment and never show them anything they can't replicate themselves. Talented individuals often go abroad to get a better income, but Sanduk has been incredible at identifying young people who are passionate about staying in their own country. In fact, we're currently in the process of providing fellowships in India, Nepal and America for promising ophthalmologists.

"The truth is there are very few public health problems we can't overcome"

And it's a good thing we are, because the need for comprehensive eye care continues to grow. In India, the standard of cataract care has become so great that the upper middle class are now paying for surgery before they lose their sight – leaving the destitute blind behind. To understand why that is such a huge problem, think of it on a global scale. If we were to only operate on blind people, we would need to perform about 16,000,000 cataract surgeries. But if we were to operate at the 20/100 level, it's suddenly 60,000,000. And of those extra 44,000,000 people, many have the means to pay. Imagine if we start operating at the level we do in America, 20/60, or England, 6/18 – that number would be eight times higher. Now think of India again. There are many people who have a little trouble seeing their computer or driving at night, and they're willing to pay to make that go away. Paradoxically, as the quality of surgery has improved, less of the surgery is going to the blind.

When we started out in Nepal, about 80 percent of blindness was due to cataracts. It meant if your dad was blind, you carried him for two days to see a facility and four out of five times he would come back with his sight. Those are pretty good odds. Good enough that people will come back and actively seek care. But if we played out that same scenario in Africa, things would be different. The continent has more glaucoma, more infectious blindness, and more retinal blindness than Nepal. Even people with cataracts often have glaucoma or corneal scarring from trachoma. Suddenly, the odds of a miracle aren't so high. Half of the people who take two days off from work to carry dad to the doctor won't get cured. Walking another two days home to hungry kids and a father who is still just as blind as he was when you left doesn't incentivize you to proactively visit the clinic. So that's what we're working on right now, a way to transpose and develop a sustainable system of care to the poorest of the poor.

Still climbing

The goal may appear to be unreachable, but the truth is that there are very few public health problems we can't overcome. Blindness can be reversed – it happened in Nepal, it happened in Bhutan, and it can happen elsewhere too. All we need is funding. We could eliminate avoidable blindness on the planet for the cost of what America spends every month on war. Just think about that – two and a half billion dollars could restore sight to every single person who is blind from cataracts. It would take $100,000,000 to change the arc of blindness in Africa. Our website, which we got by luck, is cureblindness.org – and that's really what we're trying to do. Help us do it. If you are interested in being part of the Himalayan Cataract Project by donating your time or money, email info@cureblindness.org. Together, we can do great things.

Doing Right by Everyone

Sitting Down With… Elizabeth Yeu, Assistant Professor at Eastern Virginia Medical School and Cornea, Cataract and Refractive Surgeon with Virginia Eye Consultants, VA, USA

What led you to ophthalmology?
As cliché as it sounds, I've wanted to be in medicine since I was four years old. My mother actually discouraged me from going down the more traditional academic route and encouraged me to explore different interests, but I was drawn to the humanism of medicine.

When did you know you'd made the right choice?
I can honestly say that going into residency was that awakening for me. There was no hands-on OR experience during medical school, so I was anxious about my potential as a microsurgeon. Residency was the "a-ha!" moment when I knew I'd found my calling. It was where so much of my life began. I met my husband during residency, and was able to connect with a profession – and a career – that made me feel alive. It was hugely impactful.

Ophthalmology is such a unique blend of medical and surgical care, it really encompasses the joys of being able to positively impact our patients, and maintain relationships with them at the same time. And, unlike other fields of medicine, morbidity is pretty low. I knew I couldn't desensitize myself from taking care of very sick patients.

What are the highlights of your career so far?
There are two that come to mind. The first occurred very early on in my career – my fellowship training and then faculty position at the Cullen Eye Institute at the Baylor College of Medicine. My four colleagues, including Doug Koch and Steve Pflugfelder, truly covered the breadth of the anterior segment sub-specialty, from complex lens-based surgeries through corneal and external disease management. Not only are they experts within our field, but they are also real gentlemen. It was a huge deal for me to train under them, but to be colleagues of theirs? That's a sincere highlight. They also taught me that it's all in the details. Between the exposure, the expertise and all that they have contributed to the field, both Doug and Steve are the quintessential clinician scientists.

Do you have any other "heroes?"
Dick Lindstrom to me is in a different realm. I respect him for his continual commitment to ophthalmology, to driving innovation and to putting his money where his mouth is. I recently learned that he was one of the inventors of Opti-Sol, the storage media that we've used for decades with corneal transplantation, which is tremendous in itself. More than that, he donates all of the royalties to different eye banking associations. To have someone like Dick reinvesting funds just to create better technology in the realm of cornea is invaluable. Can you imagine a time when we're able to inject endothelial cells or potentially 4D print ocular tissue? Cornea as a field has been relatively stagnant in therapeutic advancements. We have been doing it the same way with transplantation for decades more or less! And we may have continued, were it not for someone like Dick.

How are you finding motherhood?
It's a "hat" that I'm still growing accustomed to! My kids are five and seven and that's happened in the blink of the eye. Though I know each stage of motherhood is a challenge in itself, I try to sit back and enjoy each moment, tame my impatience and anxieties, while putting every effort into making sure I do a great job. We must strive to be the best people we can be, but we shouldn't beat ourselves up over the failures.

Do you struggle to balance work and motherhood?
Absolutely! The struggle lies in doing right by everybody. It's really exciting to be involved with extracurricular opportunities, whether that's volunteering or working with industry on innovations, but you get to a point when some of these opportunities collide with family commitments. It goes back to not rushing in too quickly and saying "yes!" to everything. I want to do right by those I say yes to!

I gave myself a goal: by the time my children are 10, I need to be around more, because shaping their adolescence is the biggest responsibility I have, aside from my responsibility to my patients.

Outside of ophthalmology, what makes you happy?
My family is the big one! But I also meditate and do yoga. I make sure I take time to refuel. You can't give to others if you don't center yourself spiritually and mentally – something I didn't recognize the importance of 10 years ago.

What advice would you give to your younger self?
Don't rush the process. If there are tough decisions that need to be made – and there will be many, both personal and professional – don't rush them. Step back, enjoy each success and learn from each failure. Ever since I was little, I've rushed, rushed, rushed. I entered school at the age of four, graduated from high school at 17, and entered medical school at 20. It was great to have those opportunities, but I've come to realize there is so much to enjoy in the present because time goes by so quickly.

We should all aspire for greatness, setting slightly unrealistic goals that push us beyond our comfort zones.Whether we're teaching residents or committing to research, we are all helping patients and bettering our field.

INDICATIONS AND IMPORTANT SAFETY INFORMATION FOR THE CATALYS® PRECISION LASER SYSTEM

Rx Only

INDICATIONS: The OptiMedica® CATALYS® Precision Laser System is indicated for use in patients undergoing cataract surgery for removal of the crystalline lens. Intended uses in cataract surgery include anterior capsulotomy, phacofragmentation, and the creation of single-plane and multi-plane arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure. **CONTRAINDICATIONS:** Should not be used in patients with corneal ring and/or inlay implants, severe corneal opacities, corneal abnormalities, significant corneal edema or diminished aqueous clarity that obscures OCT imaging of the anterior lens capsule, patients younger than 22 years of age, descemetocele with impending corneal rupture, and any contraindications to cataract surgery. **IMPORTANT SAFETY INFORMATION:** Mild petechiae and subconjunctival hemorrhage can occur due to vacuum pressure of the suction ring. Potential complications and adverse events include any of those generally associated with cataract surgery. **CAUTION:** Should be used only by qualified physicians who have extensive knowledge of the use of this device and have been trained and certified by Johnson & Johnson Surgical Vision, Inc. **ATTENTION:** Reference the labeling for a complete listing of Important Indications and Safety Information.

INVISIBLE LASER RADIATION
AVOID EYE OR SKIN EXPOSURE TO DIRECT OR SCATTERED RADIATION
CLASS 4 LASER PRODUCT
Yb Laser: Laser Class 4/IV
Max Output: 1030nm, 10uJ, 1.8W, <900fs Pulse
SLD Laser: Laser Class 3R
Max Output: 820-930nm, <3.48mW, CW
Per IEC 60825-1:2007

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