FEBRUARY 2019 # 30

the Ophthalmologist™

Off the Beaten Track

We talk to the ophthalmologists crossing continents to help vulnerable communities

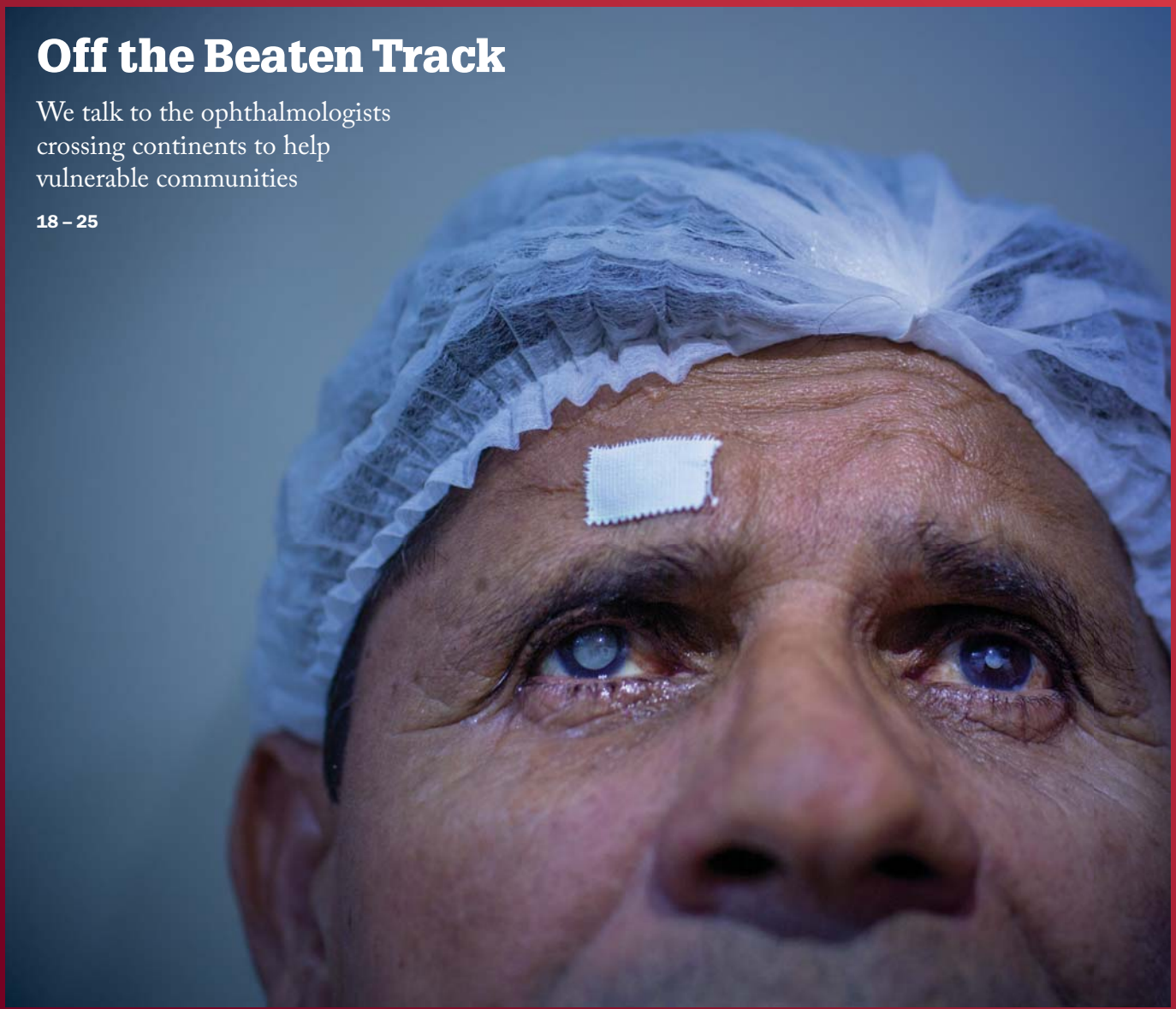

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Image of the Month

Changing Lives

This month's image shows successful processing of a cornea. The corneal transplant will be kept fixed and well-fed in an antibiotic nutrient solution for up to 34 days until transplantation. The picture is part of a photo documentary by photographer Alexandra Bidian, capturing the process of tissue donation, processing and transplantation.

Credit: Alexandra Bidian for Deutsche Gesellschaft für Gewebetransplantation (DGFG), Clean Room at Tissue Bank Hannover, Germany (2018)

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

From the Amazon to central Africa – this month's cover features an image from one of the global ophthalmic outreach projects. Photo by Marizilda Cruppe

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the Ophthalmologist

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Thinking of the Children

The prevalence of childhood blindness is much higher in developing countries – and it is largely avoidable.

Over the last couple of days, my inbox has been full of article proposals and submissions with a common theme: pediatric ophthalmology. Genetic testing in pediatric eye diseases, the myopia epidemic among children in developed countries, a novel way of dealing with vernal keratoconjunctivitis, gene therapies for Leber congenital amaurosis… These are just a few of the topics that you can look out for in The Ophthalmologist.

As with many other aspects of life, the risk of childhood blindness and vision impairment is directly related to a person's place of birth. Socioeconomics and the availability of adequate care are the main drivers; around three quarters of the world's blind children live in the most deprived regions.

And, as Kevin Waltz points out in this issue's cover feature (page 16), in locations with sporadic access to care, vision-impaired children are much more vulnerable than adults. Impaired vision hinders children's social and emotional development, as well as their education, which not only affect the future prospects of those children, but also their family members, who must give extra care and support. And so, even though blind children represent a relatively small percentage of the world's blind population (around 5 percent), the cost of childhood blindness is estimated to constitute nearly one third of the global economic blindness cost (1).

Ophthalmologists continue to do great work for children in resource-poor nations and remote regions, freely offering their time, expertise – and the gift of sight. But are they being sufficiently supported by the wider community? Consider that corneal scarring caused by vitamin A deficiency and complications from measles and other infections are leading causes of childhood sight loss in developing countries. Interventions that focus on the causes of sight loss – immunization programs, supplementation of vitamin A, promotion of breastfeeding, comprehensive screenings – are also much needed.

In short, any efforts aimed at improving quality of life and care in the world's most underserved regions can have a huge impact on children's visual outcomes – and the happiness and productivity of millions of people.

Aleksandra Jones
Editor

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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

Roll Call

Fighting global blindness, one employee at a time

Well respected in the ophthalmic community, Halma is a global technology group made up of over 40 companies – five dedicated to eye health. Halma prides itself on "growing a safer, cleaner, healthier future for everyone, every day" – a statement that it is apparently taking literally. The group has announced that it will offer free eye screening to all 6,000 of its employees as part of its Gift of Sight campaign. That's certainly great for the employees, but what has it got to do with global blindness? Halma will contribute $25 to the Himalayan Cataract Project (HCP) for each employee who takes part in the eye screening – up to a total of $100,000 – and also match HCP donations from its employees up to another $100,000.

"Blindness creates social dependency, reduces the workforce, shortens lives, and robs children of education," said Andrew Williams, Group Chief Executive, in a statement. "As companies within Halma produce the world's leading eye health technology, we want to raise awareness of the importance of good eye health through regular screening, and at the same time, raise up to $200,000 for the Himalayan Cataract Project (HCP) – an international NGO focused on curing blindness in underserved communities."

With preventable blindness set to treble by 2050 – affecting more than 115 million people – every dollar counts.

H(eye) – or Low?

Two chemical components; opposite effects. How medical marijuana impacts glaucoma for better – and for worse

Scientists have known that cannabis reduces ocular pressure since the '60s, but the reason why has remained a mystery – until now. A team at the University of Indiana has delved into the endogenous cannabinoid signaling system and made an unexpected discovery – the drug's two major chemical components, THC and CBD, counteract. While THC, the primary psychoactive ingredient, was found to effectively lower eye pressure, CBD appeared to block its affect. Moreover, CBD appeared to worsen the primary underpinning of glaucoma by causing a rise in intraocular pressure (an average of 18 percent for at least four hours after use). So what does this mean for patients being treated with medical marijuana? "Given the popular embrace of CBD and its recent approval for childhood epilepsy, this potential rise in IOP is a side effect that we should be aware of," says lead author Alex Straiker, an associate scientist from the university's Department of Psychological and Brain Sciences.

Straiker and his team used knockout mice to separate neuroreceptors in a bid to understand more about the conflicting effects of THC and CBD. They found that three different cannabinoid-related receptors – CB1, GPR18 and GPR119 – all regulate ocular pressure independently. Moreover, they identified CB1 and GPR18 as those susceptible to pressure lowering.

Interestingly, the study also found that the THC's effect was sex-dependent; male mice experienced an average drop in eye pressure of nearly 30 percent four hours after exposure to THC alone, along with a lower pressure drop of 22 percent after eight hours. On the other hand, female mice experienced an average pressure drop of just 17 percent after four hours, with no difference in eye pressure after eight hours.

"The difference seems to be due to a variation in the number of receptors but it's hard to say why there should be a sex difference. Strangely, we find that GPR119 lowers pressure, but only in female mice. Maybe the CB1/GPR18 system is up-regulated to compensate, but we don't know for sure," says Straiker. Offering some explanation, Straiker notes that THC and CBD are somewhat non-specific in their action. "CBD acts as an (allosteric) antagonist at CB1, so it is opposing the pressure-lowering effects of those receptors," he says. "The fact that the pressure rises is probably an indication that CB1 receptors are always partially activated to lower pressure. But it looks as though CBD also lowers pressure via GPR18. The truth is, we just don't know."

Regardless, the study challenges long-held beliefs on cannabis as a glaucoma treatment. "The position of the medical community is that THC is ineffective in humans when applied topically. This is based on four studies from the early 1980s, three of them fairly small and with mixed-sex subject pools. Since there is a sex-dependence, they may have missed an effect," says Straiker. "Despite all the usual caveats, such as our study being done in mice, our work suggests that the question is still open. Certainly, our study argues that lower-CBD strains would work better that existing formulas, as CBD antagonizes the salutary THC effects."

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Three (Hundred) Blind Mice

Californian researchers discover 261 new genes for hereditary eye disease

Who would have guessed the key to understanding the human genome could fit into the palm of your hand? That key, of course, is the humble mouse – and it has just helped a team at the University of California, Davis, identify 347 new genes linked to visual function. The results are the latest to come from the International Mouse Phenotyping Consortium (IMPC), a global cooperative dedicated to identifying the function of every gene in the mammalian genome. So far, the IMPC has characterized more than 4,364 genes across 11 organ systems – a figure that is growing day by day.

Mice are often the heroes of genetic research, due to the similarity of their genome to our own – humans and mice share around 20,000 genes.

"We identified dozens of ocular conditions that strongly resemble blinding eye diseases in people," says Ala Moshiri, an assistant professor in ophthalmology and vision science at UC Davis, who helped run the study. "These include numerous mouse models of retinal degeneration diseases, like retinitis pigmentosa, as well as some unusual ocular conditions, including those that also affect other organ systems, such as the skin, kidneys, or musculoskeletal system." Only 86 of the recently discovered genes were already known to be associated with vision, while three-quarters – 261 – were not previously implicated in eye health in any species (1).

Kent Lloyd, director of the UC Davis Mouse Biology Program and principal investigator of the Knockout Mouse Production and Phenotyping (KOMP2) project, explains how they did it: "Male and female knockout mice were created for each gene and analyzed using the standardized protocols shared by all IMPC member laboratories. Ophthalmological studies took place at 15 to 16 weeks of age, with ocular and adnexal structures examined by highly-trained and experienced technical support staff, including both human and animal ophthalmologists."

The next step in the project – validating the genes in humans – is already underway, and the researchers hope that the process could eventually help provide answers to the families of the 25 to 50 percent of patients with presumed inherited blindness whose mutations cannot be identified after genome sequencing.

These findings could potentially guide doctors to new locations in the genome that may be responsible for eye disease. "When each mouse gene is validated in a human family, the knockout mouse model for that exact condition will be immediately available to researchers. These mice are publicly available and are suited to test gene therapies, stem cells, or potential medications to help slow down or reverse the disease process," says Moshiri. "So the mice are not only leading us to diagnosing new disease genes, they are also serving as an ideal testing ground for new therapies in this era of precision medicine."

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Back to the Future

Researchers pinpoint the moment our brains combine separate visual signals into a singular view

In 1981, Hubel and Wiesel received the Nobel Prize for their groundbreaking work in the primary visual cortex. They proposed that signals from our eyes merge at a point beyond the cortical input stage, but – because of technical limitations – they were unable to tell whether these monocular neurons might alter their activity if both eyes were stimulated at the same time. Well, it has taken 38 years, but the mystery has now been solved. A team at Vanderbilt University has discovered that monocular neurons do alter their activity if both eyes are stimulated, moving the point of binocular convergence further along than previously thought, to where visual signals enter cortical processing. "Combining signals is a challenging task because each eye has a slightly different perspective," explains Alex Maier, assistant professor at the Department of Ophthalmology and Visual Sciences and lead author of the study. "So it was surprising to find out that this process starts just one synapse away from the retina – at the input stage of visual cortex."

Unlike Hubel and Wiesel, Maier and his team had the ability to measure when neurons were active and where they were located within each of the six layers of the visual cortex. This information was combined with a stereoscope consisting of two pairs of mirrors, positioned in such a fashion that each eye could only see one half of a computer monitor, to act as visual stimulation. This allowed the team to show images to the left eye or right eye in isolation, or both eyes simultaneously. "Using this technique we confirmed that many neurons in the (middle) input layers of visual cortex respond to only one eye, which is why they are called monocular neurons," explains Maier. "We then found that these monocular neurons change their activity when both eyes see a stimulus at the same time. Thus, those so-called monocular neurons are actually sensitive to what both eyes view."

The process, whereby the brain combines visual signals into a single coherent view, is known as binocular combination or integration, and is commonly disturbed in amblyopia. "By improving our understanding of how binocular integration works in individuals with normal binocular vision, we will better understand how it can go awry, as in amblyopia," says Maier. "Knowing the neural sites and mechanisms of binocular integration may provide cortical targets for future therapies for amblyopia, and we hope that our work can help pave the way."

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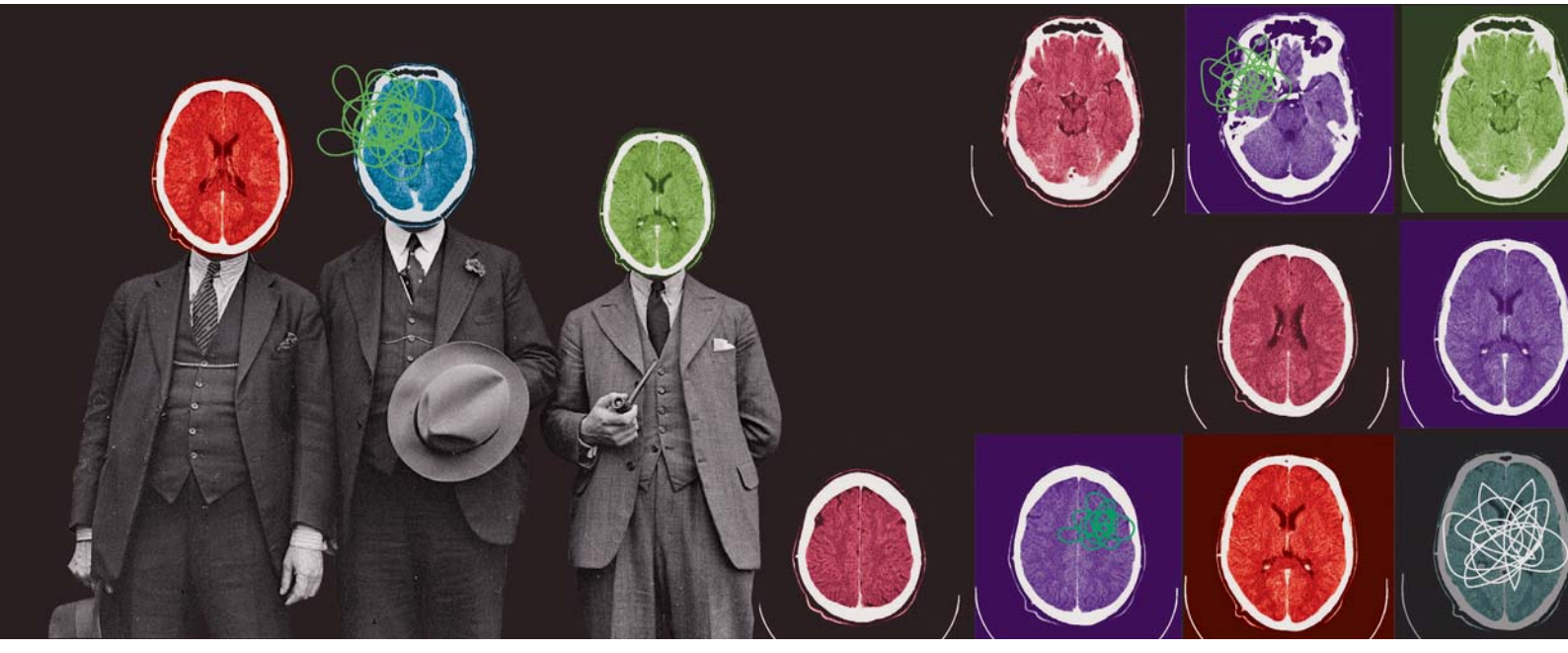

In My View

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 team at edit@theophthalmologist.com

A Glimpse Over the Horizon

What research is tackling the pressing and substantial need for new gene medications targeting conventional aqueous outflow?

By Jeffrey O'Callaghan, Institute of Genetics, Trinity College, University of Dublin

When it comes to open-angle glaucoma, up to 10 percent of patients are not optimally responsive to current topical pressure-reducing medications; moreover, patient compliance is not an insignificant issue. In other words, there is room to improve.

Interestingly, the majority of medications in use today do not primarily target the major (conventional) aqueous outflow pathway – where aqueous humor drains through the trabecular meshwork (TM) into Schlemm's canal (SC), and thus into the episcleral veins. Rather, they inhibit aqueous production by the ciliary body, or enhance its removal through the minor (uveoscleral) route. Much commercial interest therefore lies in the development of formulations that are more active on conventional outflow, and, indeed, such formulations have now emerged (Rhopressa) (1).

Glaucoma can be legitimately classified as a progressive retinopathy, elevated intraocular pressure-inducing degeneration at the optic nerve head with concomitant demise of the retinal ganglion cells. However, it is essentially unique among retinopathies in that the primary cause of the disease lies within the anterior portion of the eye, where aqueous drainage through the TM and SC is compromised, resulting in IOP elevation.

So far, no genetically-based therapeutics have been approved that target the primary outflow tissues (or indeed any aimed at protecting the viability of the ganglion cells), but there are signs on the horizon.

"Glaucoma can be legitimately classified as a progressive retinopathy, elevated intraocular pressure-inducing degeneration at the optic nerve head with concomitant demise of the retinal ganglion cells."

"The polysaccharide hyaluronan can be used to target CD44, and so siRNA encapsulated in nanoparticles coated with hyaluronic acid allow for smaller amounts of siRNA to be efficiently delivered to these tissues."

The retina has been prominent as a target for gene therapy, principally because viral delivery systems (and especially, adeno-associated virus [AAV] vectors) can be introduced into the eye by the sub-retinal route. Proof of the point lies in the first FDA/EMA approval for a gene therapy targeting individuals with the inherited retinopathy, Leber congenital amaurosis (2).

Though tissues of the conventional outflow pathway have proven difficult to transfect with standard AAV vectors (1, 3), success has been seen with self-complementary AAV vectors (4, 5). In addition, AAV-Anc80L65, with its synthetically-designed capsid and a single-stranded genome, has also recently been shown to transfect tissues of the anterior chamber with high efficiency (6).

AAV9 has been similarly shown to transfect corneal endothelium in a highly efficient manner, and we recently reported a strategy for enhancement of outflow facility using this approach (7). Here, AAV9 expressing a matrix metalloproteinase (MMP3) transfects the corneal endothelium of mice (following a single intracameral inoculation), essentially rendering the endothelium a cellular factory for the expression of secretory proteins, which may then enter directly into the anterior chamber.

An entirely different approach recently reported by Tam and colleagues targeted SC itself with small-interfering siRNA (8). Aqueous humor funnels through the TM, converging on the endothelial cells lining SC; fluid then enters the canal either through the formation of vacuoles in endothelial membranes or through the spaces/clefts left between the tight junctions joining the endothelial cells together. By intracamerally inoculating rodents with siRNA targeting transcripts encoding selected tight-junction components, Tam and colleagues saw a subsequent widening of the clefts and an enhancement of canal permeability. Treatment of acute elevations in IOP could be one application of this approach.

It is of interest to note that siRNA delivery systems have recently been enhanced using nanoparticles that increase target specificity (9). In this study, researchers took advantage of the fact that TM and SC cells express the surface marker CD44. The polysaccharide hyaluronan can be used to target CD44, and so siRNA encapsulated in nanoparticles coated with hyaluronic acid allow for smaller amounts of siRNA to be efficiently delivered to these tissues.

Both siRNA and AAV vectors are accepted modes of ocular therapy. I'm personally excited that the advanced approaches shared here – and others like them – could hold significant potential in the future management of elevated IOP.

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Femto for Fuch's

Why FLACS is the way forward for Fuch's dystrophy patients in need of cataract extraction

By Tim Schultz, specialist cataract and cornea surgeon at the University Eye Hospital, Bochum, Germany.

Cataract surgery is a very safe procedure – unless you have a pre-existing ophthalmic condition like Fuch's dystrophy. In this degenerative disease, cells in the corneal endothelium slowly die off, causing the cornea to swell and become cloudy, distorting the patient's vision. Unsurprisingly, Fuch's dystrophy patients are susceptible to further complications during surgery (1) and, as a result, many of these patients may be too frightened to go ahead.

But we have another option. In my experience, femtosecond laser-assisted cataract surgery (FLACS) can help Fuch's dystrophy patients achieve very good visual outcomes, as well as quicker overall recovery times. In some cases, FLACS can even prevent the possibility of corneal transplantation at a later date.

So why FLACS? There are two main reasons. "Firstly, the laser can perform two crucial steps in cataract surgery – capsulorhexis and fragmentation of the nucleus – without the need for intraocular manipulation (2)." Secondly, FLACS reduces exposure to phacoemulsification – the high-level energy of which poses an increased risk of endothelial damage, which is of the greatest concern when it comes to treating Fuch's Dystrophy patients (2, 3).

In our hospital, we use LENSAR with Streamline IV (Orlando, USA), which automatically categorizes cataract density on a scale from 1 to 5 and applies a pre-programmed fragmentation pattern based on my surgical preferences, resulting in precise laser placement and lenticular fragmentation. Most importantly, it causes less damage to the endothelium. We also use an additional OVD during lens aspiration to protect the endothelium, which can, in turn, prevent the need for a corneal transplant.

"In some cases, FLACS can even prevent the possibility of corneal transplantation at a later date."

Of course, there is no guarantee that a patient will not suffer corneal decompensation, regardless of the technique used. I have treated several patients with different methods in each eye, including a case where corneal decompensation occurred after I had performed manual surgery. In this case, I performed a DMEK. Comparatively, where the endothelial damage was milder (in the patient's left eye), I was able to use FLACS to perform cataract surgery on its own. Promisingly, there was no decompensation. One thing I have learned with FLACS for Fuch's dystrophy patients is that, if the cell density is reduced, there may be a need to increase the energy for the capsulotomy (I usually increase it by around one third as the cornea can already be reasonably cloudy and dense).

In conclusion, standard surgical procedures – particularly manual techniques – increase the risk of further complications or progress the symptoms of Fuch's dystrophy. They also carry the major disadvantage of increasing the amount of energy delivered to the eye during lens fragmentation, which results in endothelial cell damage. FLACS provides us with a safe, viable alternative that combats some of these issues – and that's why it is (and will remain) my preferred method of cataract extraction for Fuch's dystrophy patients.

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INDICATION FOR USE. The iStent *inject*® Trabecular Micro-Bypass System Model G2-M-IS is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma. **CONTRAINDICATIONS.** The iStent *inject* is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. **WARNINGS.** Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. **MRI INFORMATION.** The iStent *inject* is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details. **PRECAUTIONS.** The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent *inject* have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SLT performed > 90 days preoperative), glaucoma associated with vascular disorders, pseudoexfoliative, pigmentary or other secondary open-angle glaucomas, pseudophakic eyes, phakic eyes without concomitant cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents. **ADVERSE EVENTS.** Common postoperative adverse events reported in the randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent *inject* vs. 4.2% for cataract surgery only), secondary surgical intervention (5.4% vs. 5.0%) and BCVA loss ≥ 2 lines ≥ 3 months (2.6% vs. 4.2%). **CAUTION:** Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.

REFERENCES: 1. iStent *inject*® Trabecular Micro-Bypass System: Directions for Use, Part #45-0176. **2.** Hengerer FH. Personal experience with second-generation trabecular micro-bypass stents in combination with cataract surgery in patients with glaucoma: 3-year follow-up. ASCRS 2018 Presentation.

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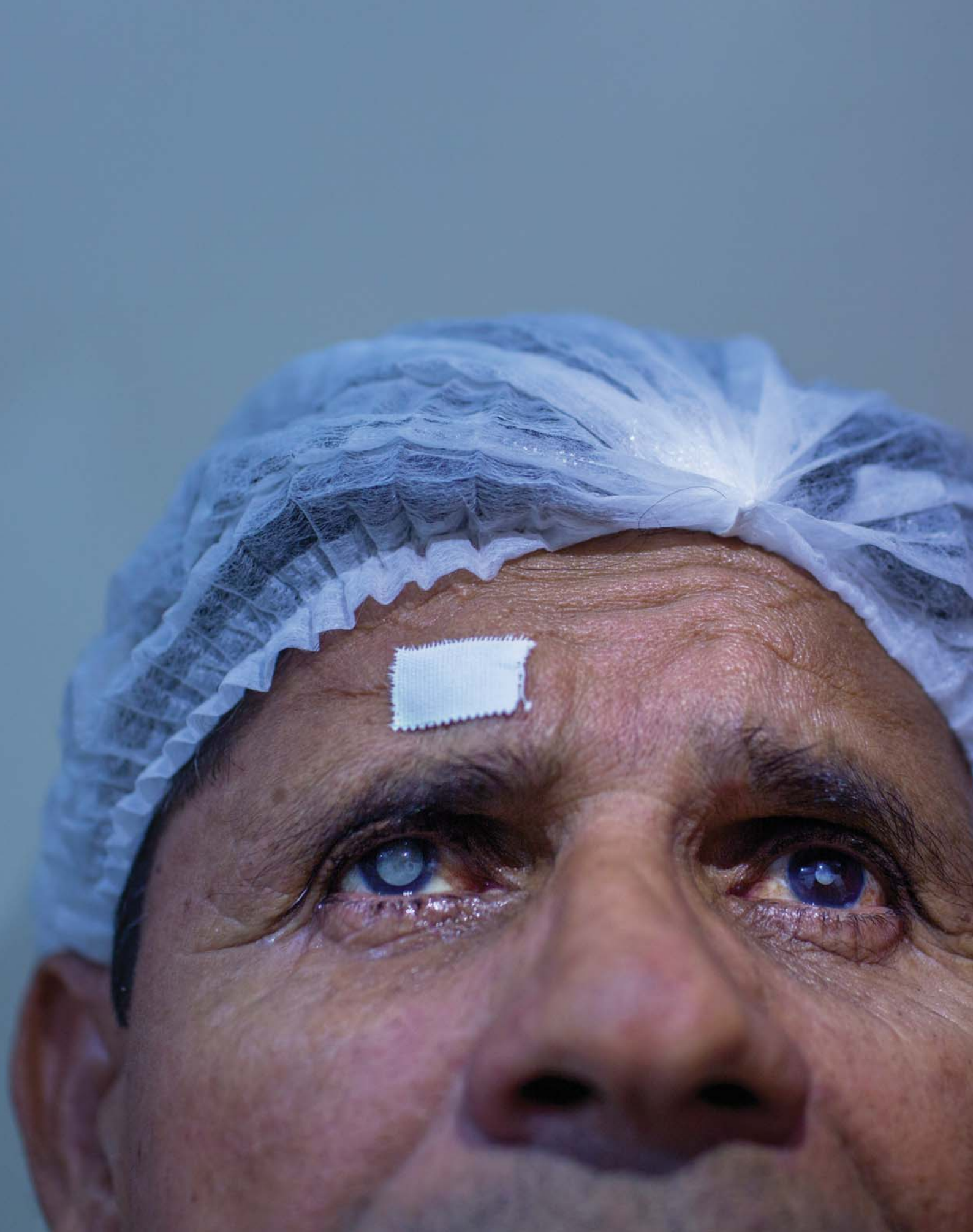
Off the Beaten Track

What does a former Silk Road-trading post like Kashgar have in common with Nuevo Progreso – a tropical municipality of Guatemala? How about a bustling western Honduras town and a colorful coastal city in Mombasa? These places – and their populations – all suffer from limited access to medical treatment and, in particular, eye care. Residents of such remote communities rarely, if ever, see an ophthalmologist. And, as a result, even treatable conditions can leave a patient with total vision loss. It is predicted that preventable blindness will treble by 2050, affecting more than 115 million people; developing countries will bear the brunt of the burden. In light of this – and in anticipation of our upcoming Power List celebrating 'Champions for Change' – this feature celebrates ordinary ophthalmologists doing extraordinary things at home and overseas. We hope you are as inspired by their endeavors as we are.

Images courtesy of Marizilda Cruppe, Barbara Erny and Lisa Park.



The Bigger Picture

In 2010, the ICO attempted to capture the dynamics of the global ophthalmic population. They sent a questionnaire to members in 193 different countries, covering everything from their number of active ophthalmologists to the output of their training programs. 192 countries responded. The answers were then analysed by Serge Resnikoff and his team, and the results published in 2012. They found that the average number of ophthalmologists per million in population varied according to economic development, from fewer than nine per million in low-income countries to 79 per million in high-income countries – an eight-fold difference. The lowest average number of ophthalmologists per million population was observed in Sub Saharan Africa (2.7), while the highest average was observed in countries with former socialist economies (83.8) – a 30-fold difference (1).

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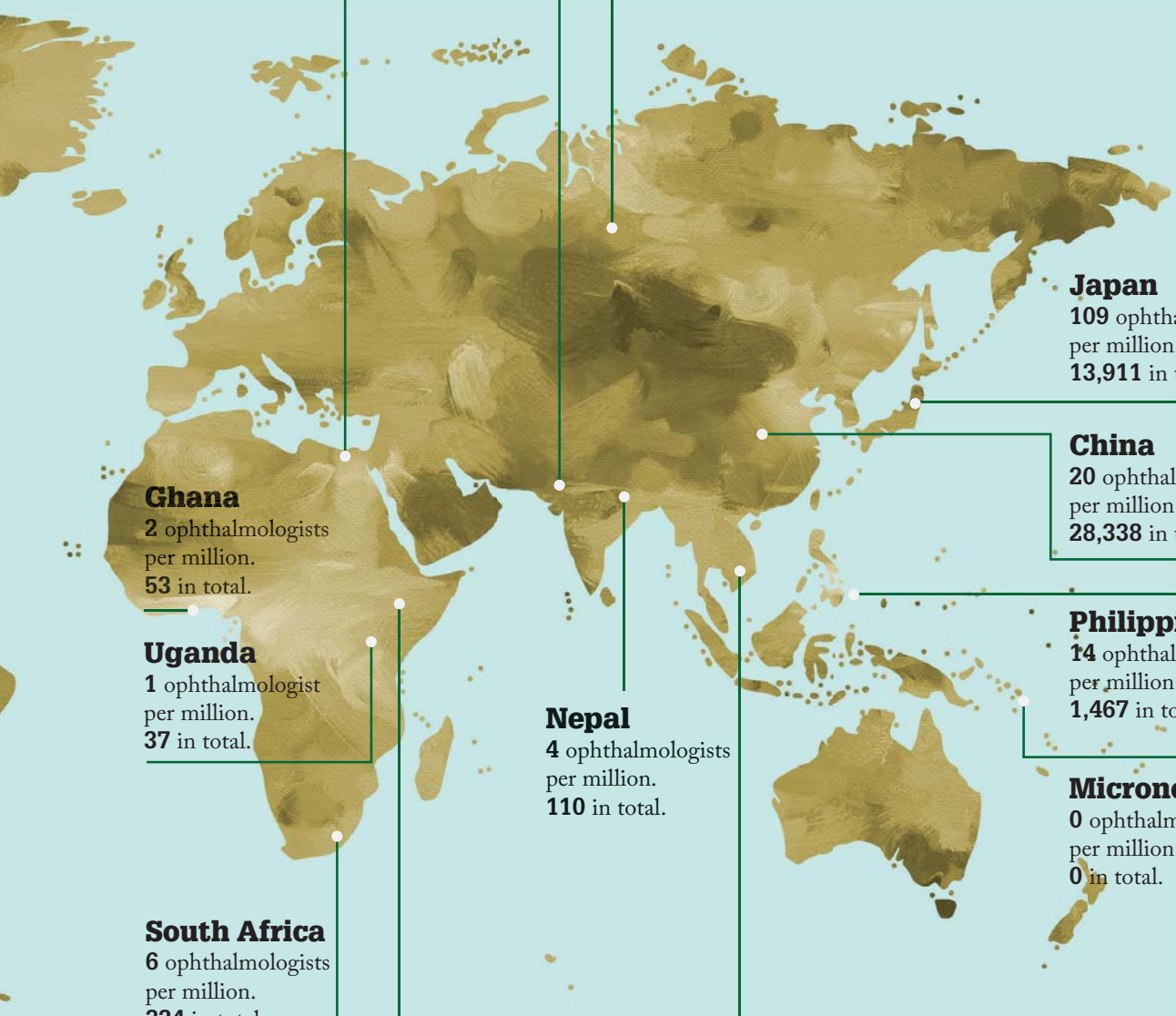


Israel
81 ophthalmologists per million.
650 in total.

Pakistan
10 ophthalmologists per million.
1,860 in total.

Russia
101 ophthalmologists per million.
14,600 in total.

Japan
109 ophthalmologists per million.
13,911 in total.

China
20 ophthalmologists per million.
28,338 in total.

Philippines
14 ophthalmologists per million.
1,467 in total.

Micronesia
0 ophthalmologists per million.
0 in total.

Ghana
2 ophthalmologists per million.
53 in total.

Uganda
1 ophthalmologist per million.
37 in total.

Nepal
4 ophthalmologists per million.
110 in total.

South Africa
6 ophthalmologists per million.
324 in total.

Ethiopia
1 ophthalmologist per million.
103 in total.

Cambodia
2 ophthalmologists per million.
38 in total.

Kevin Waltz…

…and his work in Central America.

What are the most remote locations you've worked in?

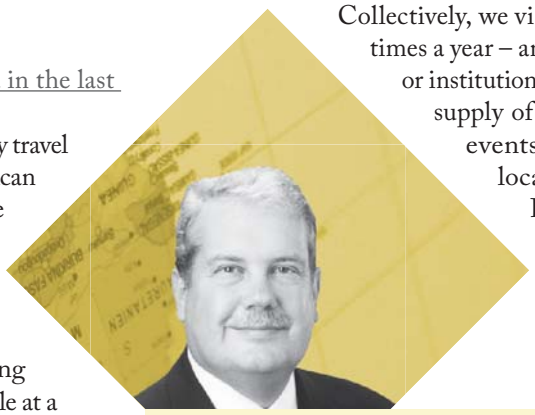
The group I work with is focused on Central American locations, primarily Honduras, with some work being done in El Salvador. I have about ten facilities and groups that I work with at any given time. The most comprehensive of those is the project in Western Honduras, in Santa Rosa de Copan. It is a large group of buildings, which is going to be a dedicated eye center – very much needed in the area, where around a million people require ophthalmic care. Local ophthalmologists are providing the building and the land, and the charity – through cash and equipment donations – are taking care of all the necessary machinery and supplies. Local ophthalmologists are being trained in modern surgical techniques.

How has ophthalmic outreach changed in the last couple of decades?

In the past, ophthalmologists would mostly travel to a certain location and follow the American marine model: go self-contained, hit the ground running, operate, then fold everything and take it back home. These days projects try to follow a model of supporting local doctors, transferring skills or improving existing skillsets, and using the equipment available at a specific location, which provides a much stronger benefit over time – although that is not always possible. The ultimate goal is to set up a facility that can function independently long-term. A great example of this is the Himalayan Cataract Project.

If I go to a remote setting and perform surgeries myself, I might be able to do a few dozen in a year, broken up over several visits, but if local professionals learn the techniques and have the technology available, they can do so much more – and there are several thousand people waiting for their procedures.

It usually takes between five and ten years to set up a facility in a remote location. Modern equipment is often completely different from what local ophthalmologists originally trained on, and it takes time to adjust to a different microscope, a new set of instruments, or a new phaco machine. Local doctors are often experts in traditional cataract surgery, and they can easily take a person from being blind from cataracts to 20/100 vision, time and again, which in itself is amazing, and makes both doctors and patients happy. But if they can learn how to improve these outcomes and give 20/30 or even 20/20 vision to cataract patients, that's on a whole different level. Each intervention should maximize benefits to patients, even if it requires a mindset change and learning some new skills.



"The ultimate goal is to set up a facility that can function independently long-term."

Once set up, how often do you visit these facilities?

Collectively, we visit projects regularly – three or four times a year – and try to connect locals with industry or institutional partners, so that they have a steady supply of equipment. We also help organize events, inviting speakers from various locations, and initiating networking. For the last six years, we have hosted an annual Honduras interest group meeting during the AAO, where doctors from Honduras, other Central American countries, and the US come together. At the last meeting, in Chicago in 2018, we had 64 attendees. I realized some years ago that many people are working in these locations, but they didn't communicate with each other; my goal has been to provide an opportunity for people to get together and learn from each other.

What is the most striking aspect of working in places with limited access to care?

I see many children with cataracts – and, in remote settings this can be a lethal disease, as children with

severe cataracts might not be able to take care of themselves. We try to prioritize these cases and perform phacoemulsification to control the incision and the optical outcome. There are some difficult decisions to be made: a child's cataract surgery is very time consuming, it takes a lot of resources, so you could probably operate on three or four adults in the time it takes to operate on a child. But the potential outcome and quality of life is usually so much greater for a child.

"I have certainly learned to be less wasteful – right down to the little things: if you can use one tissue, why use two?"

What skills have you learned from your time in Central America?

I have certainly learned to be less wasteful – right down to the little things: if you can use one tissue, why use two? Perhaps I don't need to fill a whole syringe with medication, if I'm only going to use half of it? They seem like such small changes, but it means using half the amount over a long period of time, and it all adds up. I have certainly been more respectful of the resources and the environment, and I think it's an important aspect of being a doctor.

What impact do you think these projects – and the volunteers behind them – have on the remote locations?

It's an enormous impact – and in more ways than we usually consider. There are now so many charities working with developing countries, that airlines open new connections! This makes a difference to other people's lives – they are able to see their families and friends more often. Volunteers can make a big difference to local providers – they buy food, stay in local accommodation. Governments impose taxes on international flights, and get a certain amount of money from each person entering the country. If I remember correctly, just in Honduras this amounts to $20-40 million a year in tax revenue from foreign charity workers – a huge economic benefit to the system, on top of the important work and skill transfer that volunteers provide. However, it is extremely important to make sure that all the work that is done is balanced with the existing infrastructure. You should never provide free care in places where local care already functions well – this undermines local professionals, who can't compete with volunteers working free of charge – you wouldn't stand for it if someone came to where you live and work, and offered their services for free. Doing so has the potential to destroy the existing medical economy, and has an impact on patients, who sometimes delay accessing care for years, waiting for volunteers to arrive. Of course, it's a different situation if the area is so remote that there is no care available there at all, but if you can help a local doctor make a living, at the same time helping the population access the best care possible, it is an amazing result, and it makes the whole healthcare ecosystem stronger.

Kevin Waltz is President of Ophthalmic Research Consultants, and Chair, Board of Directors of Central American Eye Clinics.

Emilio Torres-Netto...

...and his work in the Amazon forest.

Tell us more about the challenges of the Amazon...

Unlike other locations around the world, Brazil does have a public healthcare system; the problem for the Amazon riverside settlements is the sheer distance from the nearest city with proper ophthalmic care (12–13 hours away) as well as difficulties in organizing transport. The doctors who work in these remote locations are not specialized in eye care, and patients are often not very well educated; they may not realize why their sight is deteriorating. The project's organizers try to get to the least accessible villages and towns at least once a year.

There are farmers who live in the riverside villages, towns and cities, who must support whole families, even though they lost their sight several years ago. There are multiple projects working on bringing eye care to these remote populations, and often the only way to reach them is by boat. We packed the boats full of equipment: all the latest generation phacoemulsification equipment, IOLs, and anything else we need to create the right environment to perform surgery and offer proper care.

What are the most prevalent diseases?

Cataracts are a huge problem, including congenital cataracts. Some patients have cataracts in both eyes, often with ocular surface diseases. They may wait for up to ten years for surgery. As this is a reversible condition, we tend to focus our time and effort on this. The project I worked on, the Amazonian Project, was designed approximately 30 years ago by Professor Jacob Cohen supported by the Piedade Cohen Foundation. Similarly, Professor Rubens Belfort Junior and Professor Walton Nose, through partnerships with the Institute of Vision and the Federal University of Sao Paulo, were instrumental in the success of the more than 15,000 surgical procedures already performed.

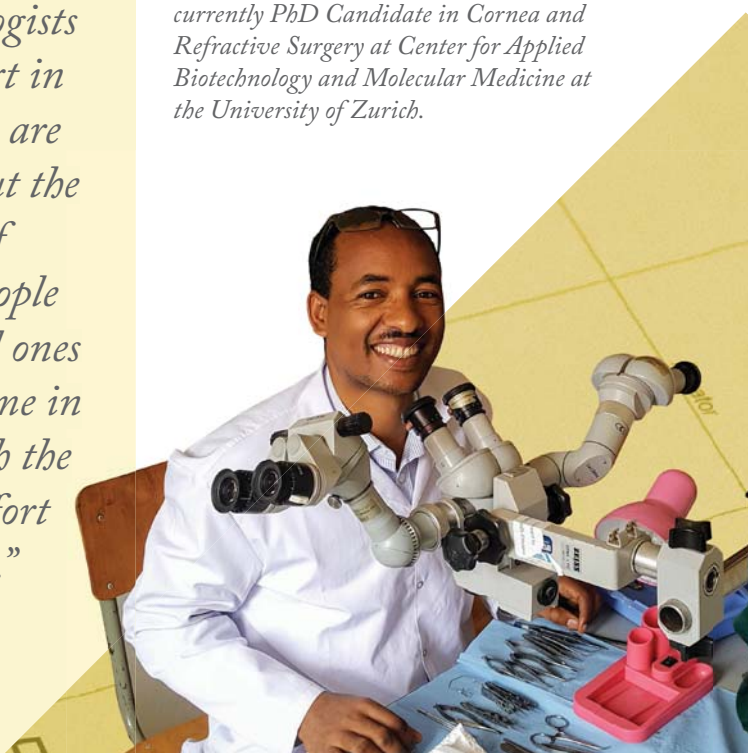
As cases are usually very advanced, and some are quite complicated, it is usually experienced surgeons who get invited to join the project. Unfortunately, there aren't many opportunities to train doctors while we are there, but we do get through a very high number of surgeries with very low complication rates. We mostly use the same equipment as in our day-to-day practice, but occasionally surgeons have to use the extra-capsular technique or fixate the IOL if the patient is aphakic.

We rely on donations as well as working with several industry partners to deliver the best possible practice – from screening and biometry, to performing surgery. Ophthalmologists who take part in these projects are volunteers, but the reward of watching people recognize the faces of their loved ones for the first time in years is so worth the time and effort we put in.

Another condition that produces severe visual impairment in remote locations is corneal infection. Whereas in developed countries it tends to be caused by extended wear of soft contact lenses, in remote locations minor traumas to the cornea, not taken care in a timely manner, may be responsible for visual impairment. The diagnostic dilemma, especially when identification of the underlying pathogen is not feasible, also makes the choice of an appropriate therapy difficult. Our group from Zurich are currently looking into developing the best practices for treating infectious keratitis in the most remote settings.

"Ophthalmologists who take part in these projects are volunteers, but the reward of watching people see their loved ones for the first time in years is worth the time and effort we put in."

Emilio Torres-Netto is a cornea, cataract and refractive surgeon trained in several renowned centers in Brazil, USA, France and Switzerland. He is currently PhD Candidate in Cornea and Refractive Surgery at Center for Applied Biotechnology and Molecular Medicine at the University of Zurich.



Barbara Erny…

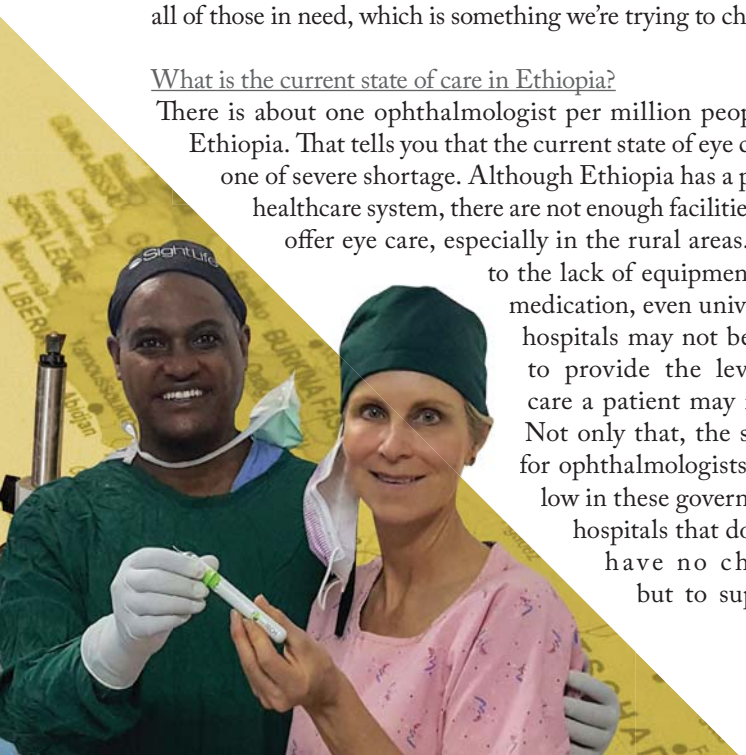
…and her work with the ASCRS Foundation in Ethiopia.

Tell us more about your outreach work.

For the last few years, I've worked with the ASCRS Foundation and its partners, teaching and helping to develop the Ethiopian residency programs. Our aim is to build infrastructure so that eventually Ethiopia will no longer have to rely on outside aid for eye care. We work with our partners to supply equipment and training. To give an example, Orbis and The Himalayan Cataract Project (HCP) have just set up wet labs at each residency hospital in the country. We are supporting the residency directors financially, and collaborating with them to improve educational programs for residents. In March we will be teaching a review course to residents to help them study for the ICO Board Exam. The ASCRS Foundation also supports the Sinskey Eye Clinic, which serves the impoverished, and now provides a rotation for the residents to improve their clinical and surgical skills. Right now, most residency programs – and ophthalmologists – in Ethiopia are based in the big cities. In order to perform surgery in remote areas, a team has to transport all their own equipment; in the south of the country – the poorest, more rural part – that could be a more than a day's drive. Understandably, these regions don't have enough doctors, staff or equipment to provide surgery to all of those in need, which is something we're trying to change.

What is the current state of care in Ethiopia?

There is about one ophthalmologist per million people in Ethiopia. That tells you that the current state of eye care is one of severe shortage. Although Ethiopia has a public healthcare system, there are not enough facilities that offer eye care, especially in the rural areas. Due to the lack of equipment and medication, even university hospitals may not be able to provide the level of care a patient may need. Not only that, the salary for ophthalmologists is so low in these government hospitals that doctors have no choice but to support themselves in private practice at least part-time.



Now that five residency programs are up and running, the number of ophthalmologists in the country is growing quickly. Still, it may be many years before there are enough doctors to serve all of the patients in need of care.

Hundreds of patients come to the public clinics without appointments every day, hoping to be seen. The majority come from remote villages, traveling for hours with their families. Of course, some people can't afford the cost of transport and, unfortunately, have to go without. There simply aren't enough clinics or doctors – and certainly not enough in remote areas.

What are the most common cases you deal with?

You might think that the majority of cases are tropical diseases, but that's not the case. Most residents have never even seen active trachoma, thanks to the great work being done to eradicate it. They certainly do see corneal scarring though, and eyelid surgery for trichiasis is a common procedure. Cataracts is the most common cause of blindness, which is sad and frustrating, as it is treatable with a quick and inexpensive operation.

We tend to see a lot of injuries from farming and other accidents as laborers don't tend to use protective eyewear. Interestingly, a new problem they are facing is one common in developed countries: diabetic retinopathy. To add to the increased severity of eye conditions, there is a constant lack of medications that we take for granted.

Any success stories to share?

Well, almost all cataract operations are success stories. But there are many situations less glamorous, but just as impactful. A man once came to me saying he had to stop working as a radio repair man because he could no longer see the parts. All I did was give him a pair of $1 reading glasses and he could see clearly. It sounds like such a small thing, but those over-the-counter reading glasses gave him the ability to earn an income again. He told me I saved his career, and his whole family.

The number of people blind from cataracts is a huge challenge…

It is estimated that one million people are completely blind from cataracts in Ethiopia. The number of operations per year in all the public hospitals barely makes a dent in that number. NGOs set up remote eye camps and, remarkably, do up to 1,000 operations in a week. Still, this is a drop in a bucket. We can only hope that as more Ethiopian ancillary personnel and ophthalmologists graduate, they will be able to independently provide the care the country needs.

In developed countries, cataract surgery is most often performed using phacoemulsification, but that's not standard for the majority

of Ethiopian facilities. Not only is the equipment extremely expensive to buy, the consumable materials these machines require for each use are also expensive, and can be difficult to obtain in remote locations. Another roadblock is the lack of technicians trained to service the machines. Manual small incision cataract surgery (MSICS) is the standard of care for cataract surgery in Ethiopia and many other developing countries because it's fast, safe, inexpensive and effective.

Cataract surgery isn't just life-changing for the patient. Many young family members have to give up work to care for their blind loved one. Eliminating cataract blindness not only helps the patient and the family – it also improves the health and economy of the entire country.

What advice would you offer to volunteers?

It's not enough to just show up, do a few operations and leave. The goal is sustainable change and that means taking the time to collaborate with local doctors, to "train the trainers." We would like to inspire them to achieve the quality of care we have in developed countries. It doesn't just mean developing their surgical skills; it also means helping with clinical skills, improving training programs, and strengthening infrastructure. Be open to learning from the residents, too. They will have seen severities of disease that you haven't. You also have to respect that people communicate differently in other cultures. Maybe locals won't tell you as much as you'd like them to, or they will say "yes" when you can tell they haven't really understood the question. It is also worth being aware of how different cultures react to pain – do they express themselves with stoicism or grand displays of emotion? By learning side-by-side, working together to offer better care, and encouraging and training doctors on best practices for their patients, you will become a better doctor yourself.

Barbara Erny, MD, is an ophthalmologist and Medical Liaison for International Programs at the ASCRS Foundation.

It's Not About You!

Steve Charles, who has operated in 25 different countries over 42 years, shares his guidelines for ophthalmologists traveling to remote locations:

- Skill transfer and sharing the knowledge with colleagues is vital; they are your partners, so you need to be operating and seeing patients together, using equipment that local ophthalmologists will be using day to day
- Don't just show local ophthalmologists how to perform procedures – tell them when to operate and, often more importantly, when not to operate. The focus should be on mainstream cases, not extreme surgery and overly complicated procedures
- Sustainable development is key – teach those colleagues who will be able to pass the knowledge on, and who can operate on large numbers of patients
- Learn how to set up and operate all equipment, including microscopes and video systems – it will expedite surgery, teach optimal use, and send a non-elitist message
- Put an emphasis on medical ethics and evidence-based medicine
- Use reliable equipment – cheap machines are a false economy
- Use disposables – they save money, provide consistent performance, and prevent infection and inflammation
- Make sure post-operative care is not being neglected
- Don't use the trip as an opportunity to take pictures for building the image of your own practice
- Use appropriate terms: avoid talking about a "mission" or "mentoring" – you are sharing information with equals
- Keep all political and religious views to yourself
- It's best to avoid mixing holidays, sightseeing opportunities or shopping trips with outreach projects
- Avoid exchanging gifts – your money is better spent on equipment or supplies
- If possible, don't bring your team with you – work with local healthcare professionals and share your knowledge with all the OR staff
- Bring books, handouts, copies of your talks on USB drives
- Try to introduce local ophthalmologists to your industry contacts to facilitate acquisition of the necessary equipment
- Organize further visits to the facility and invite your colleagues to visit your practice back home. Keep in touch via email and build long-lasting relationships

Steve Charles is the founder and CEO of the Charles Retina Institute, Memphis, Tennessee, and Clinical Professor of Ophthalmology, University of Tennessee, USA.

Lisa Park…

…and her work with Vision Care USA & Hospital de la Familia.

Tell us more about your outreach work…

I'm primarily involved with two mission organizations, Vision Care USA and Hospital de la Familia. Vision Care is an organization that holds about 30 eye camps per year in 38 countries throughout the world. We have fully portable machines, microscopes and supplies that we can set up in any location that has access to electricity and running water. I work primarily in Africa, teaching phacoemulsification to ophthalmologists in Addis Ababa, Ethiopia and working with the Ophthalmological Society of Ethiopia to develop sustainable eye care systems.

I also volunteer with an organization called Hospital de la Familia, a foundation in California that has built a hospital in Nuevo Progreso, a small town approximately six hours west of Guatemala City. It is equipped so that multi-specialty teams of US surgeons can visit there regularly to provide much needed care.

In many developing countries it is possible to find ophthalmologists in the capital cities where most doctors tend to work. It is in the outlying and remote areas that there is very little access to specialty healthcare.

What are the barriers to universal eye care?

One of the main issues is that eye care is a low priority within healthcare systems in the developing world where much of the emphasis is on infectious diseases and maternal-fetal health, which is understandable. However, what makes eye care unique is that the overwhelming majority of cases of blindness worldwide are reversible with two relatively simple interventions: glasses and cataract surgery. And what makes cataract surgery unique is that it is a definitive treatment that can be delivered with very short follow-up care. Cataracts do not require ongoing treatment and do not recur! The impact of reversing blindness may not be easily measured in terms of mortality rate, but the restoration of sight has an important economic and social impact not only on individual patients, but also on entire families and communities. The main barriers to universal eye care aside from the cost to patients are having doctors who are trained and providing them with reliable equipment and ongoing access to supplies. While going to perform surgery is gratifying, working to help local doctors and their staff develop surgical skills and helping them find reliable sources for equipment and supplies is an important part of the work I do.

"You have to accept that you are going to go to places where you will see horrible things and you will have absolutely no resources to do anything about it."

What skills or traits are needed to work in remote communities?

The most important trait is to be flexible! As ophthalmologists we depend on a great deal of technology, and we become accustomed to certain standards and have expectations of what we need to deliver adequate care. In remote areas you have to be prepared to see patients that you know you could easily treat and think to yourself, "If only I had this piece of equipment, medication etc., I could take care of this." You cannot get frustrated in these situations, but be prepared to think outside the box, be creative and adjust to the clinical scenario at hand. It can be psychologically exhausting, but also amazingly rewarding when things turn out better than you imagine!

What about cultural differences?

We have to understand that what we may believe is good for a patient is not necessarily what they need – and that takes times to learn. I go to the same locations over and over again to try to understand how I can be most helpful. It also helps me develop relationships, which are critically important in this line of work, because we have to build trust in communities to deliver care effectively.

Have you learned any skills you can apply to your everyday practice?

In the US we're accustomed to making everything very streamlined, efficient and uniform, but that's not what it's like out in the field. I've gained the ability to modify my surgical technique for a wide range of clinical scenarios that we don't commonly see in the US. For example, phaco machines in the field are nothing like the machines that we are accustomed to in the US, so understanding the subtleties of machine settings has helped me tremendously and made me more efficient when I get back home. It also goes without saying that when you are in a country where you don't speak the language and whose lifestyle is very different from yours, you must develop the skill to quickly gather clues to assess a patient's visual needs, which is also helpful in my own practice.

"To anybody thinking about volunteering: take the plunge. World blindness is curable; we have the means, we just need to put the resources in place."

Any special cases you can share?

We saw a young boy – 13 or 14 years old – who was blind and disfigured after a penetrating eye injury. As a result, he was ostracized by his community. Our oculoplastic surgeon performed surgery and much to our amazement found an appropriately sized prosthetic shell, making the disfigurement almost unnoticeable. When he came to the clinic for his postop visit, we were so busy looking at this boy (and admiring our own work), we almost didn't realize that his mother was the side crying at seeing her son's new appearance for the first time. It was very emotional, but that's the kind of thing we see again and again.

Any advice to potential volunteers?

To anybody thinking about going: take the plunge. World blindness is curable; we have the means, we just need to put the resources in place. It almost doesn't matter where you go or who you go with, just go – as a community, we can do so much.

Lisa Park is an Associate Professor of Ophthalmology at Columbia University Medical Center and an Attending Ophthalmologist at New York-Presbyterian Hospital.

Tosin Smith...

And her work in Africa – and beyond.

What are the most remote locations you've worked in?

I've done mission work in Africa for over 15 years. I tend to go on two types of trips: either the kind where I treat patients, or the kind where I train doctors. We hold symposia and surgical training, and help create alliances with important companies within the industry, so that they can thrive after we've left. Last year we went to the Tilganga Institute of Ophthalmology in Kathmandu, Nepal and partnered with them, training close to 100 ophthalmologists from all over the country. We also collaborated with the Eye Foundation Hospital in Lagos and Glaucoma Society of Nigeria in a similar model to train local doctors, with the hope they will return to their home regions with the additional skill to treat patients and help train the other ophthalmologists. A lot of the companies have been supportive of our cause. They understand that if you train someone in a particular region, that effect will trickle down and, ultimately, help everyone. Teaching is one of the most important things you can do because it potentially impacts the whole nation.

What are the most common conditions in these locations?

We mostly deal with cataracts and glaucoma, though sometimes your job can be as simple as giving someone glasses to correct a refractive error. On some missions, people wait for hours to be seen because there is no public recourse for the provision of eye care – this might be the only chance they have to get help. It gets really desperate at times.

Any experiences that stand out?

There are lots, but one struck a particular chord with me. We were in a village in Africa and a woman came to us for an eye exam. She was in her 40s and already completely blind from glaucoma. I checked her eyes knowing there was nothing we could do to help her. She wailed when I told her. After a while, we managed to calm her down and explain that her life wasn't over just because she was blind. It's a difficult conversation to have because she's in a place where there is no support for the visually impaired – even now she was being cared for by her daughter. I said to her: "Your daughter is here, let me take a look her, too." I found that this young girl, probably no older than 22, had glaucoma as well. Her pressure was high and, medically, her situation wasn't far behind her mother's – and she had absolutely no idea. We were able to help her, but we didn't make it in time for her mother. I can think of a happier story from a 50-year-old NGO in Mombasa, Kenya, called The Lighthouse for Christ. When you walk through the gates, you see a big stack of wooden walking sticks. That's because patients come in blind with cataracts, led by a family member holding on to the proximal portion of the stick while the patient holds on to the distal portion as they are led around. When they come out after their cataract surgery, seeing for the first time in years, they don't need the stick anymore, so they add it to the pile. It's testament to the life-changing work that is being done out there.

What skills have you been able to transfer to your everyday practice?

I've learnt to be more efficient, a lot less wasteful, and to improvise when needed. There are many skilled surgeons out there that make the most of the resources available to them, and do a beautiful job. To put things into perspective, I was once in a government hospital in Owerri, Nigeria and noticed the staff didn't use the slit lamp very much, they used a pen light instead. That seemed odd to me, so I pulled the slit lamp out and started using it. Every time I stepped away from the slit lamp, somebody would come over and turn the light off. I couldn't work out why so after a while, I asked: "What are you doing?" The woman replied: "If the bulb burns out, we may not get another one to replace it." I had to sit down for a second to think over her remark. You go home with a completely different mindset and skillset.

Any additional words of advice?

You don't have to go half way across the world to offer help, you can do it in your own city! For instance, there are several organizations in the Dallas, Fort Worth area, both governmental and non-governmental, that serve the community – such as Grace for Impact, or Project Access Dallas run by the Dallas County Medical Society. The Cure Glaucoma foundation also has access to care programs, while The Division for blind services of the TDARS is run by the state. At a national level, the American Academy of Ophthalmology and American Glaucoma Society have their own assistance programs that provide free eye screening and exams to people without insurance and help fund surgery when needed – and they're always looking for volunteers.

If your worry is about the cost, there are grants available to support this type of work, including one funded by New World Medical, which offers an annual grant to individuals or organizations who want to fund their outreach work at different levels. Many companies in the ophthalmic industry will support missions and provide medication and instruments to help your cause. If your preference is a more global approach, find an organisation that travels and join their effort by volunteering in a capacity that you feel most comfortable.

There are many programs out there; all you need to do is find the perfect fit for your current life situation.

Tosin Smith is a glaucoma specialist at Glaucoma Associates of Texas (GAT) in Dallas. She oversees the Cure Glaucoma Foundation, Dallas, Texas, USA.

the Ophthalmologist™

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In Practice

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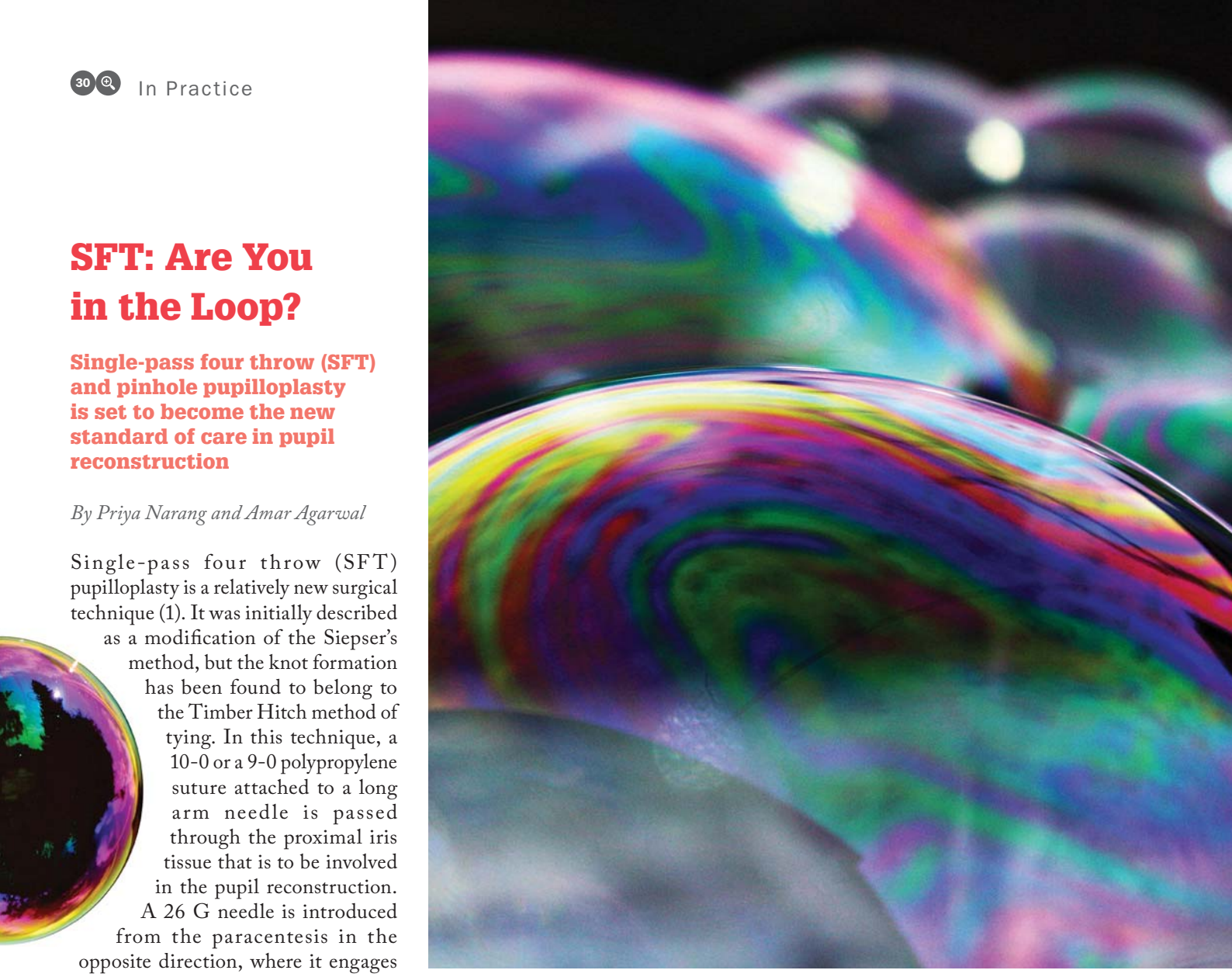
SFT: Are You in the Loop?

Single-pass four throw (SFT) and pinhole pupilloplasty is set to become the new standard of care in pupil reconstruction

By Priya Narang and Amar Agarwal



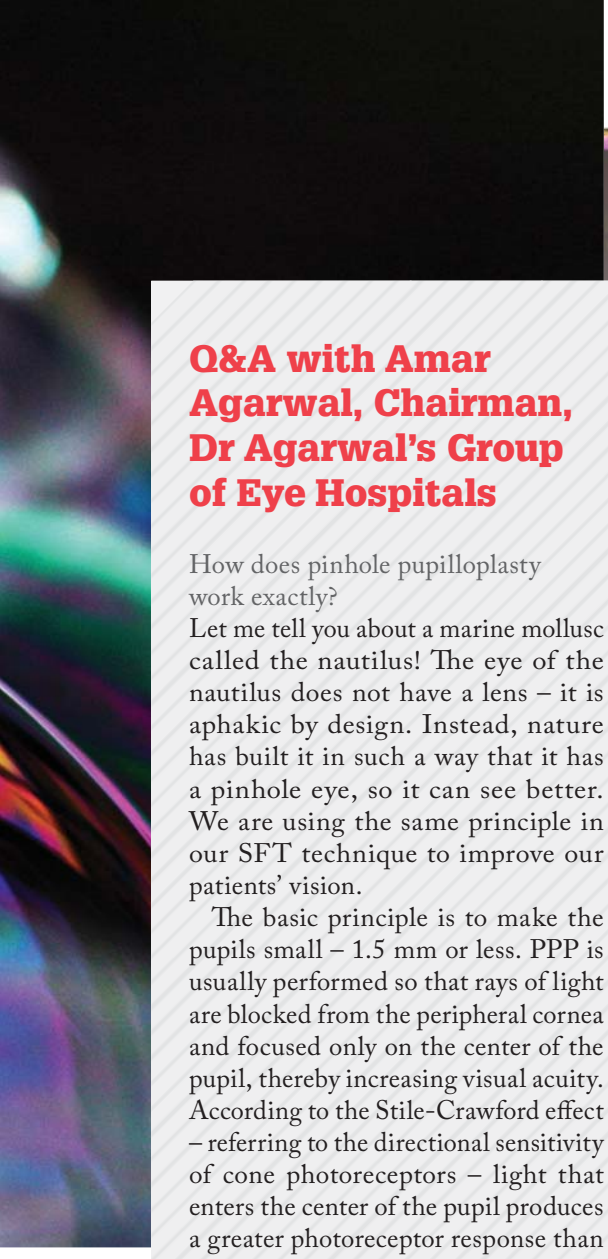
Single-pass four throw (SFT) pupilloplasty is a relatively new surgical technique (1). It was initially described as a modification of the Siepser's method, but the knot formation has been found to belong to the Timber Hitch method of tying. In this technique, a 10-0 or a 9-0 polypropylene suture attached to a long arm needle is passed through the proximal iris tissue that is to be involved in the pupil reconstruction. A 26 G needle is introduced from the paracentesis in the opposite direction, where it engages the distal iris tissue to be approximated (Figure 1 A). The 10-0 needle is then passed in to the barrel of the 26 G needle, before it is withdrawn from the eye. A Sinskey's hook withdraws the loop of the suture (Figure 1 B) and the suture end is passed from the loop four times, thereby taking four throws (Figure 1 C). Both the suture ends are pulled, and the loop slides inside the eye, thereby approximating the pupillary edges together (Figure 1 D). A micro-scissor is introduced inside the eye and the suture ends are cut. The helical structure created due to the loop approximation forms a self-locking and a self-retaining knot inside the eye.

A recent study has demonstrated

At a Glance

- *SFT is an alternative method of pupilloplasty, requiring the surgeon to pass the suture end through the loop four times*
- *Compared with current pupilloplasty methods, it offers faster visual recovery and reduced postoperative inflammation*
- *Reconstructing the pupil this way prevents patients from glare, photophobia and untoward images formed due to reflection of light*
- *PPP with SFT is suitable for patients with a range of visual disorders – from high astigmatism and corneal injuries to post-penetrating keratoplasty.*

"But reduced postoperative inflammation and faster visual recovery are not the only benefits of the technique."



Q&A with Amar Agarwal, Chairman, Dr Agarwal's Group of Eye Hospitals

How does pinhole pupilloplasty work exactly?

Let me tell you about a marine mollusc called the nautilus! The eye of the nautilus does not have a lens – it is aphakic by design. Instead, nature has built it in such a way that it has a pinhole eye, so it can see better. We are using the same principle in our SFT technique to improve our patients' vision.

The basic principle is to make the pupils small – 1.5 mm or less. PPP is usually performed so that rays of light are blocked from the peripheral cornea and focused only on the center of the pupil, thereby increasing visual acuity. According to the Stile-Crawford effect – referring to the directional sensitivity of cone photoreceptors – light that enters the center of the pupil produces a greater photoreceptor response than light that enters the periphery.

What makes it so effective?

Its simplicity. Every optician, optometrist and ophthalmologist uses a pinhole. You don't have to be a very skilled surgeon to do it, and there are no expenses involved. All you need is a suture and a microscope light to establish a visual axis.

What advantages does SFT have over other methods?

The beauty of this whole procedure is its speed – it takes 10 minutes at most. Compare that with the alternatives: both penetrating and pinhole IOL are significantly more time-consuming. But what if you don't have the IOL, or you do have it, but don't have FDA approval? By choosing pinhole pupilloplasty, these problems are negated.

And the results?

We've had phenomenal success so far. We have done around 20 cases, which is a large number for such a new technique, and our first case was a patient with astigmatism of 24 dioptres who had a patch graft during small incision cataract surgery. Four days after SFT PPP, the patient's vision had improved to 6/12. We have made sure to operate on patients with different conditions, such as corneal ring segments and corneal injuries, and combined it with IOL implantation to experiment with extended depths of focus.

Which patients are suitable for this operation?

Patients with:

- high astigmatism
- corneal injuries
- highly abberated corneas
- post-penetrating keratoplasty
- intra-corneal ring segments…

It is an extremely versatile technique!

Does it work on phakic patients?

It does, but I suggest making them pseudophakic first – removing the cataract and implanting the IOL before you do the pinhole pupilloplasty to avoid damaging the crystalline lens.

Are there any repercussions to having smaller pupils?

Not at all. For argument's sake, let's say the patient developed detachment a few years after the operation. If you want to treat them surgically, all you need to do is treat the iris with a Yag laser, and the pupil will dilate, so you can examine them as usual. As for field effects and contrast sensory, those aren't affected at all from what we have seen. All in all, SFT is a simple, cost-effective procedure, which can be done by every ophthalmologist in the world – without any long-term implications.

the scope of pupillary dilation after SFT (2), allowing posterior segment surgeons to visualize the fundus and perform any retinal procedures that may be needed in future. SFT is also faster and easier to perform than current forms of pupilloplasty, including both the modified Siepser's and McCanell methods. These procedures are more time intensive, requiring more than two passes to be made from the anterior chamber – as well as additional manipulation of the iris tissue – whereas only a single pass is needed with SFT. But reduced postoperative inflammation and faster visual recovery are not the only benefits of the technique.

SFT has been found effective for a number of conditions – including patients with Urrets Zavalia syndrome who present with raised IOP and persistent pupil dilation (3). As SFT pulls peripheral iris tissue, it prevents secondary angle closure, breaking the formation of peripheral anterior synechias and inhibiting the mechanical

blockage (4). SFT has also been found effective in selected cases of secondary angle closure, along with silicon oil induced glaucoma (5). Because the knot formation associated with SFT is almost parallel to the surface of the iris (6), it is beneficial for patients undergoing endothelial keratoplasty as the manipulation involving graft unrolling occurs in the center of the pupil area where the knot is present. Studies have also found SFT useful in treating patients with higher order corneal aberrations (7). The pinhole pupil is 1.5 mm in size, and as such, blocks the stray light emanating form the peripheral cornea and decreases the overall aberrations of the optical system of the eye.

In summary, SFT is the latest variant amongst pupilloplasty procedures with a very effective implementation for performing a pinhole pupilloplasty (PPP). Studies have reported a statistically significant difference in the Chord MU values after performing PPP using this technique, along with an improvement in visual acuity. SFT is easy to perform, with the added advantage of requiring minimal intervention inside the anterior chamber. Importantly, reconstructing the pupil this way prevents patients from glare, photophobia and untoward images formed by reflection of light.

Amar Agarwal is Chairman of the Dr Agarwal's Group of Eye Hospitals in Chennai, India.

Priya Narang is the Director and Chief consultant at Narang Eye Care and Laser Centre in Ahmedabad, India.

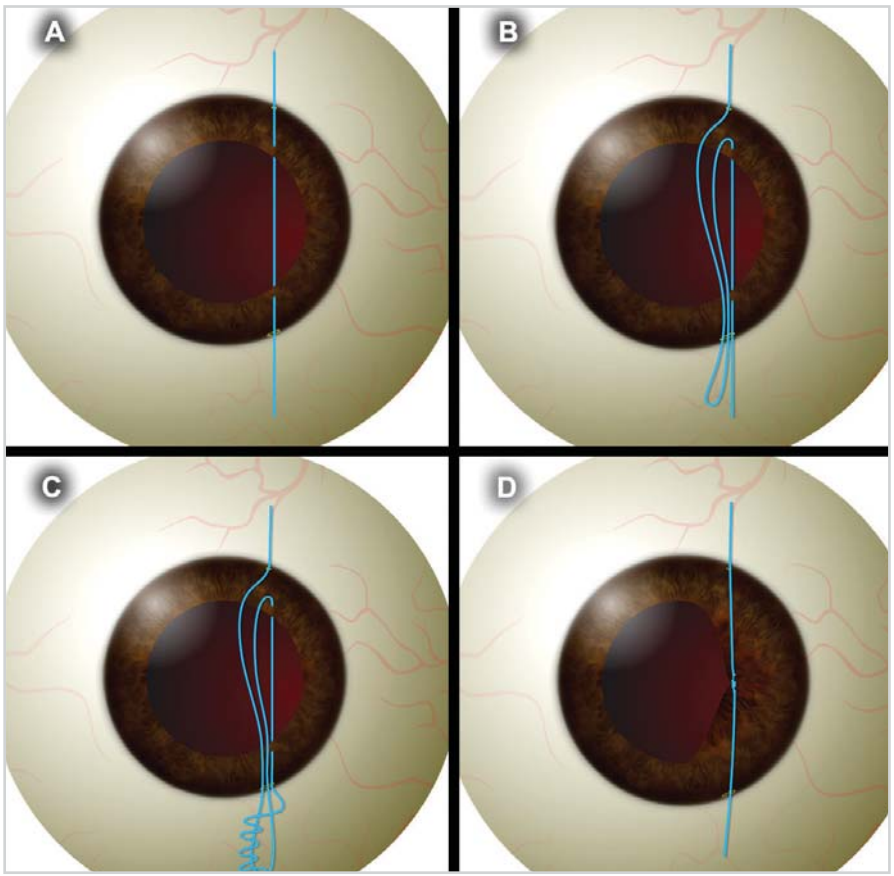


Figure 1. Surgical technique of single pass four throw (SFT)
A – The 10-0 suture is passed through the proximal and distal iris tissue.
B – A loop of suture is withdrawn from the anterior chamber with a Sinskey's hook.
C – The suture end is passed through the loop four times.
D – Both the suture ends are pulled and the loop slides inside the eye approximating the iris tissue.

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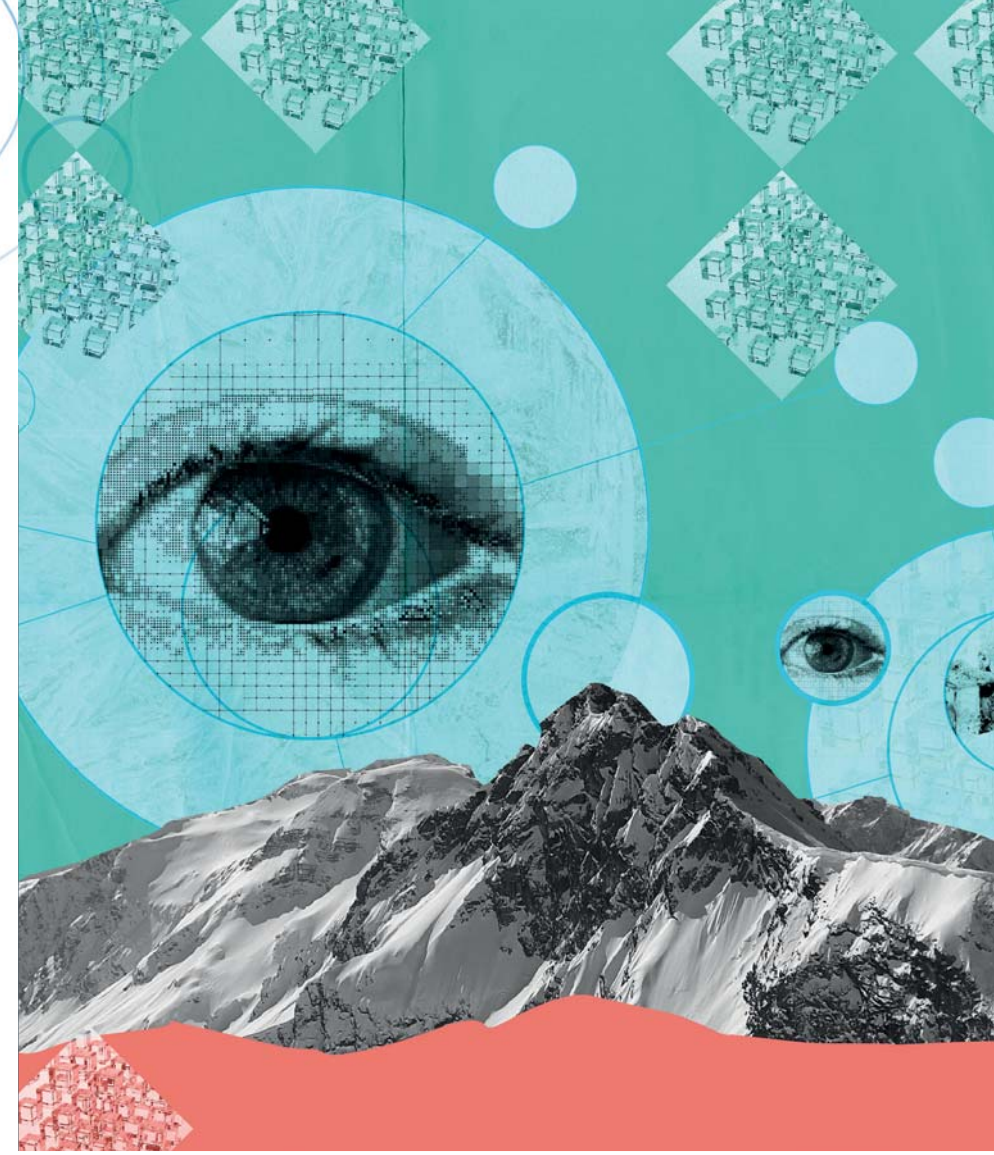
The Process Is the Product

When it comes to treating ocular surface disease, cryopreservation best retains the key healing characteristics of amniotic membrane.

By Mark S. Milner



Years before the now ubiquitous "dry eye center of excellence" emerged as a pervasive practice model, I was treating large numbers of ocular surface disease (OSD) and dry eye disease (DED) patients, and like many others, recognized how complex this disease is. Treating these patients inspired the creation of the Cornea, External Disease, and Refractive Society (CEDARS) Dysfunctional Tear Syndrome Algorithm, which I developed along with my colleagues Kenneth Beckman and Jodi Luchs on behalf of the CEDARS Dysfunctional Tear Syndrome Panel.

The foundation of the CEDARS algorithm is that we base treatment on diagnosis rather than severity. The CEDARS algorithm separates dysfunctional tear syndrome into diagnostic categories (aqueous deficiency, blepharitis, and so), which then guide treatment. We use testing to arrive at a diagnosis and the diagnosis to guide our treatment plan, keeping in mind that the patient may have more than one diagnosis. Finally, we treat the coexisting pathologies with a logical, step-wise approach (1). The formula goes hand-and-hand with what I have learned from these challenging patients for more than two decades: i) OSD is a multifactorial disease that often requires multiple forms of treatment; and ii) patients typically get some relief with a first-line treatment, but it's usually the second or even third intervention that achieves our treatment goals.

My success with cryopreserved amniotic membrane (CAM) tissue has led to its inclusion in the CEDARS algorithm. Throughout the years, I have seen CAM tissue evolve from a last-ditch initiative reserved for only the most recalcitrant OSD and DED patients – in other words, a treatment based solely on severity – to a quick and simple in-office procedure that is frequently relied upon to augment other therapies for patients at various stages of disease severity. CAM tissue is a staple in my practice; I use it to treat common corneal pathologies associated with OSD, such as superficial punctate keratitis, filamentary keratitis, recurrent corneal erosion, corneal ulcers, neurotrophic keratitis, neurotrophic ulcers (Figure 1), exposure keratitis, and Sjogren's syndrome. In my hands, CAM provides these patients with relief for many months.

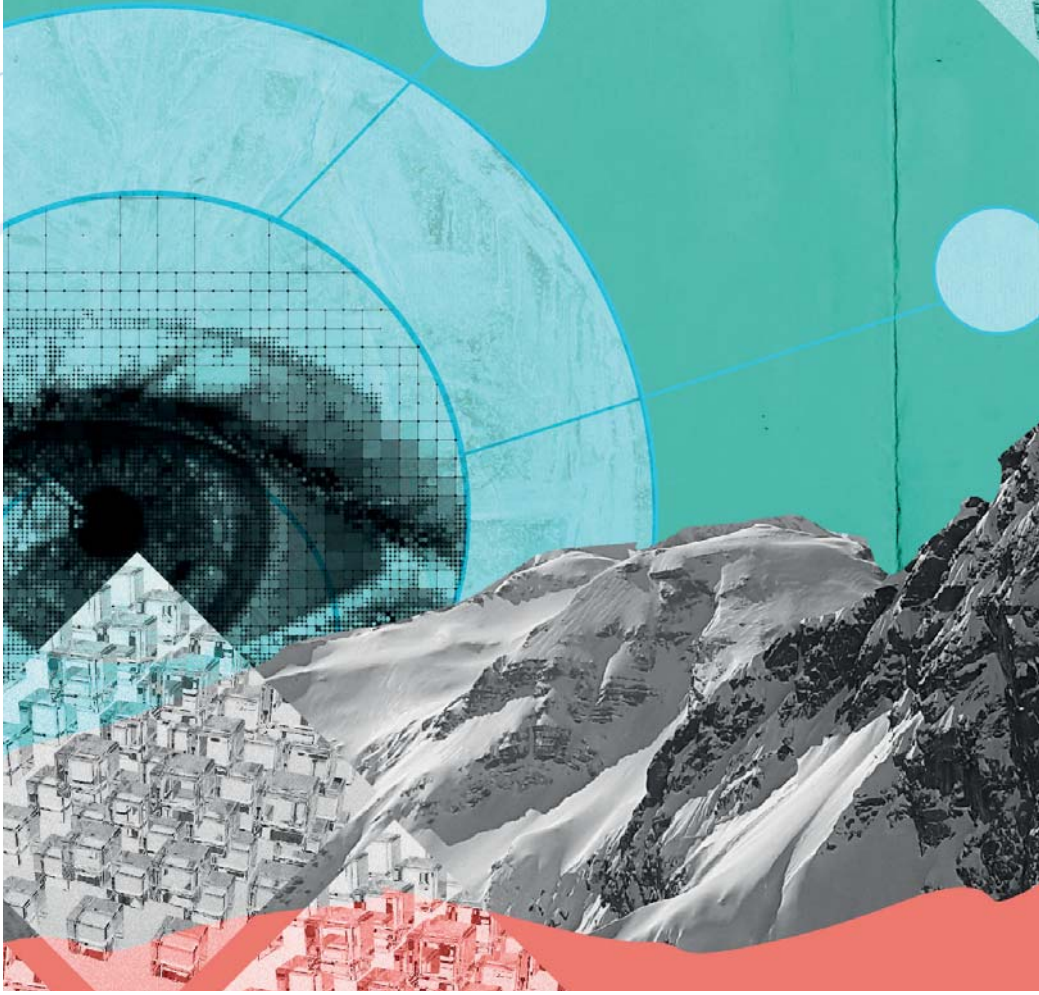
At a Glance

- *The CEDARS algorithm was created as a response to great numbers of patients being treated for ocular surface disease and dry eye*
- *Testing is used to get a diagnosis and develop a treatment plan based on the diagnosis rather than severity*
- *Cryopreserved amniotic membrane tissue can be used to treat common corneal pathologies associated with OSD.*

Frozen or dehydrated?

Not all amniotic membrane tissue is the same. The key distinction lies in how

"I think of HC-HA/PTX3 as the "secret sauce" that adds exactly what is needed by complex OSD patients, who comprise a hefty portion of my patient base."



CAM tissue and dehydrated extracellular membrane derived from human amniotic tissue are processed. Cryopreserved AM (PROKERA, Bio-Tissue) is kept frozen and brought to room temperature just before placement. Dehydrated AM (AmbioDisk, IOP Ophthalmics/Katena, BioDOptix, DermaSciences, Aril, BlytheMedical) is stored at room temperature and must be rehydrated for clinical use. Cryopreservation allows the tissue to maintain the structural and biological integrity of the membrane by retaining the extracellular matrix components: heavy-chain hyaluronic acid (HC-HA)/pentraxin 3 (PTX3), which is associated with anti-inflammatory, anti-scarring, and regenerative properties (2). In contrast, dehydration breaks down HC-HA/PTX3 to pro-inflammatory low molecular weight hyaluronic acid, and the structural integrity is lost (3). I think of HC-HA/PTX3 as the "secret sauce" that adds exactly what is needed by complex OSD patients, who comprise a hefty portion of my patient base.

CAM has multiple benefits. First, it retains all the hard-working anti-inflammatory mediators that initiate regenerative healing. Second, it is "self-retained," which means that it maintains placement on the cornea via a polycarbonate ring secured to the membrane. Dehydrated AM, on the other hand, needs a bandage contact lens (CL) to keep it in place.

In my experience, dehydrated tissue tends to get lost very quickly; sometimes it slips out from under the CL, and other times it crinkles up in the corner of the eye. The CL introduces other issues, such as increased risk of infection or hypoxia. In addition, there are certain OSDs that actually benefit from the polycarbonate ring of CAM; for example, with Stevens-Johnson syndrome or chemical injuries, the ring acts as a symblepharon ring to prevent scarring, which you do not get with the combination of dehydrated AM and a CL.

Reversing the Cycle

DED involves a defect in the neuronal feedback loop. DED patients have decreased corneal sensation, which initiates the process of shutting down the lacrimal gland. The lacrimal gland becomes inflamed and produces T-cells and cytokines; these inflammatory mediators are then secreted in the tears and end up damaging the ocular surface, which causes more of a neurotrophic effect and a decrease in nerve impulses. A message is sent to the brain that a problem exists, which shuts down the lacrimal gland and perpetuates the cycle.

By regenerating nerves, we can potentially reverse the cycle. Research suggests that in addition to stimulating active healing, CAM initiates corneal nerve regeneration (4, 5). In a prospective, controlled study comparing PROKERA Slim with conventional treatment in patients with moderate-to-severe DED, PROKERA Slim promoted a lasting effect by increasing corneal nerve density. The same study also showed rapid reduction of symptoms, pain, and corneal staining in patients treated with PROKERA Slim.

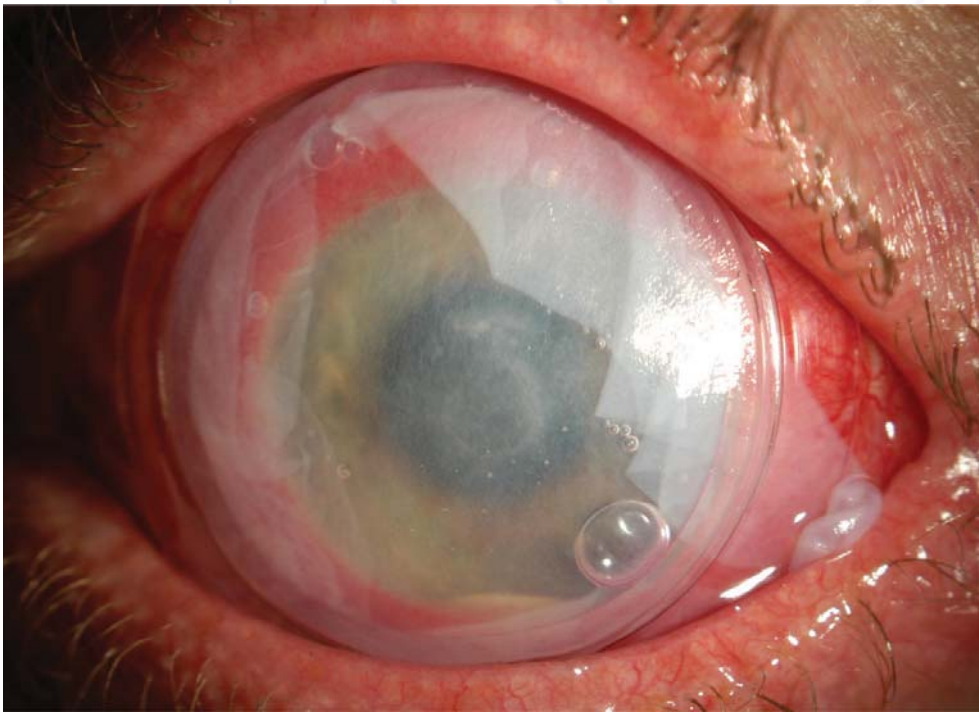


Figure 1: Neurotrophic ulcer with a PROKERA cryopreserved amniotic membrane in place.

PROKERA's lasting effect was reproduced in a larger retrospective study of 100 moderate-to-severe DED patients who were not responding to maximum conventional therapies; 88 percent demonstrated improved corneal staining scores along with a notable reduction in the severity of their DED symptoms (6).

More recently, in a small retrospective case series of patients who received PROKERA Slim or PROKERA Clear for acute treatment of neuropathic corneal pain, sustained pain control was demonstrated in 80 percent of treated eyes for more than 9 months after a single placement (7). And even when left in for only 6 or 4 days, there was a 72.5 or 63.1 percent reduction in pain, respectively. The fact that the researchers were still seeing improvement in nerve sensation and nerve regeneration at 9 months is impressive and coincides with what I have seen in my practice.

With studies touting results that match my own clinical experience, I am convinced that CAM is a game-changer when it comes to managing patients with OSD and DED.

Mark S. Milner, MD, is associate clinical professor at Yale University Medical School, Department of Ophthalmology, and cofounder and co-medical director of Precision LASIK Group, Cheshire, CT.

Disclosures: Speaker consultant for Allergan, Bausch & Lomb, Shire, TearScience, Sun, Ocular Science, Bio-Tissue, Avedro, Omeros, Valeant, and EyeVance. Research performed for Kala, EyeGate, Biotherapeutics, Aldeyra, and Icare and has ownership interest in RPS, EyeVance, and Percept Corp.

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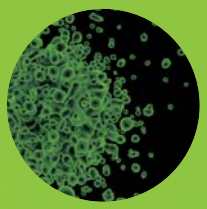

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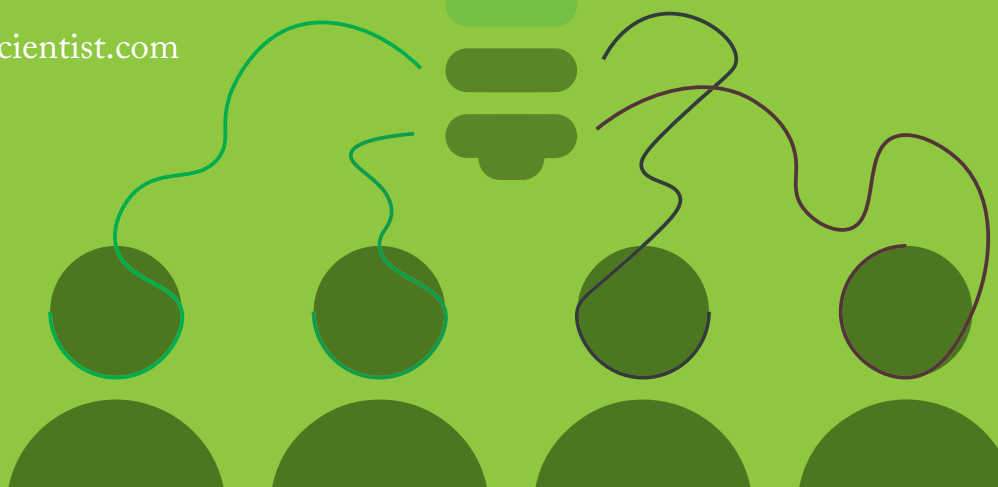


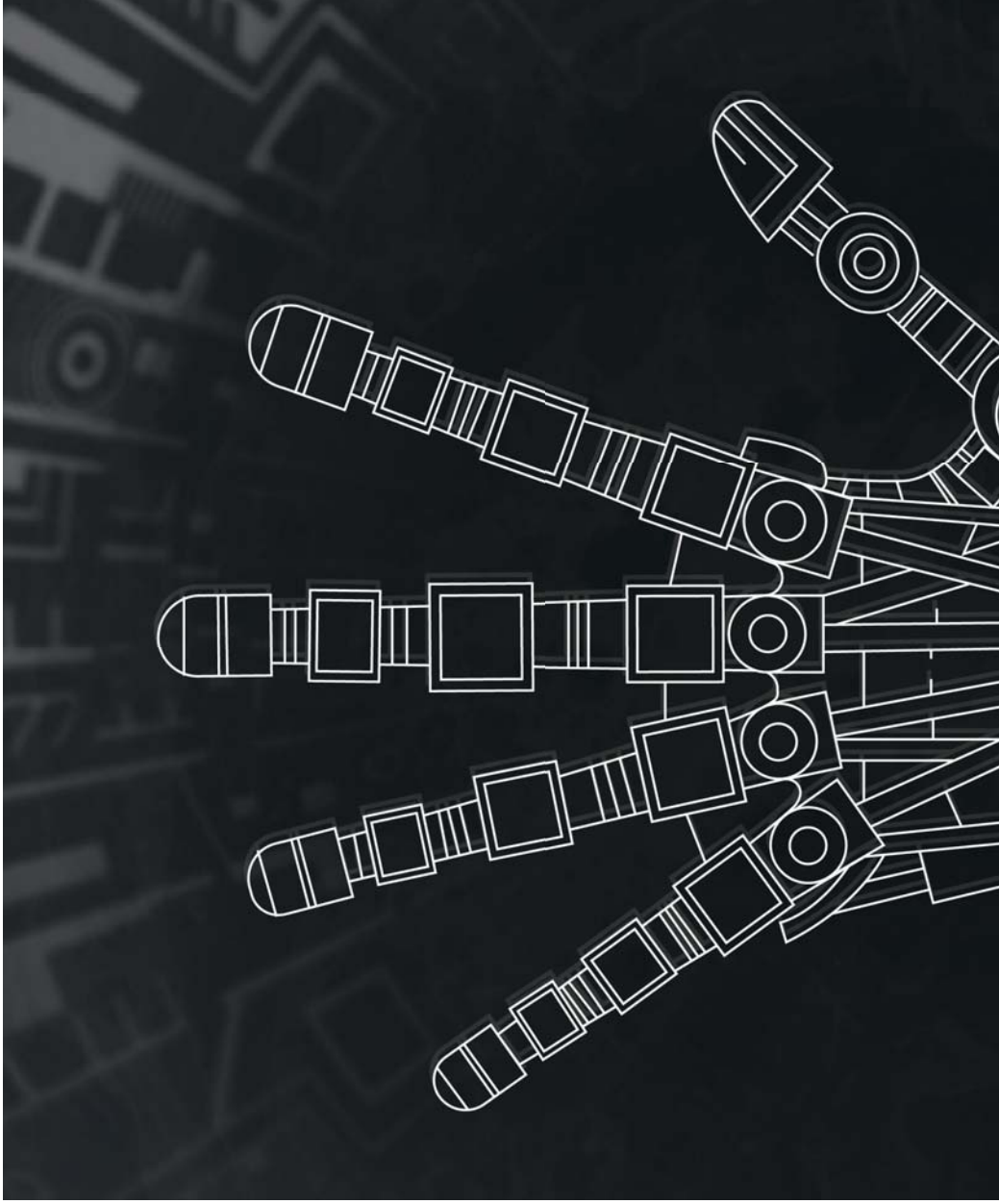
NextGen

Research advances
Experimental treatments
Drug/device pipelines

Robot Dreams

The UK's NIHR recently awarded £1,000,000 to a project led by Research Scientist, Christos Bergeles, and Consultant Ophthalmic Surgeon, Lyndon da Cruz. It is a highly collaborative project linking King's College London, University College London, and Moorfields Eye Hospital. The expectation? To bring new precision to retinal surgery.

By Christos Bergeles and Lyndon da Cruz



At King's and MEH, part of our remit is to develop clinically-relevant technology that will enhance the National Health Service's capabilities. Developing a novel robotics system to enable very precise retinal manipulations is a great example. The idea is to improve operating room technology and – in particular – bring it up to speed with cell therapy, so that regenerative medicine for the retina can achieve its full potential.

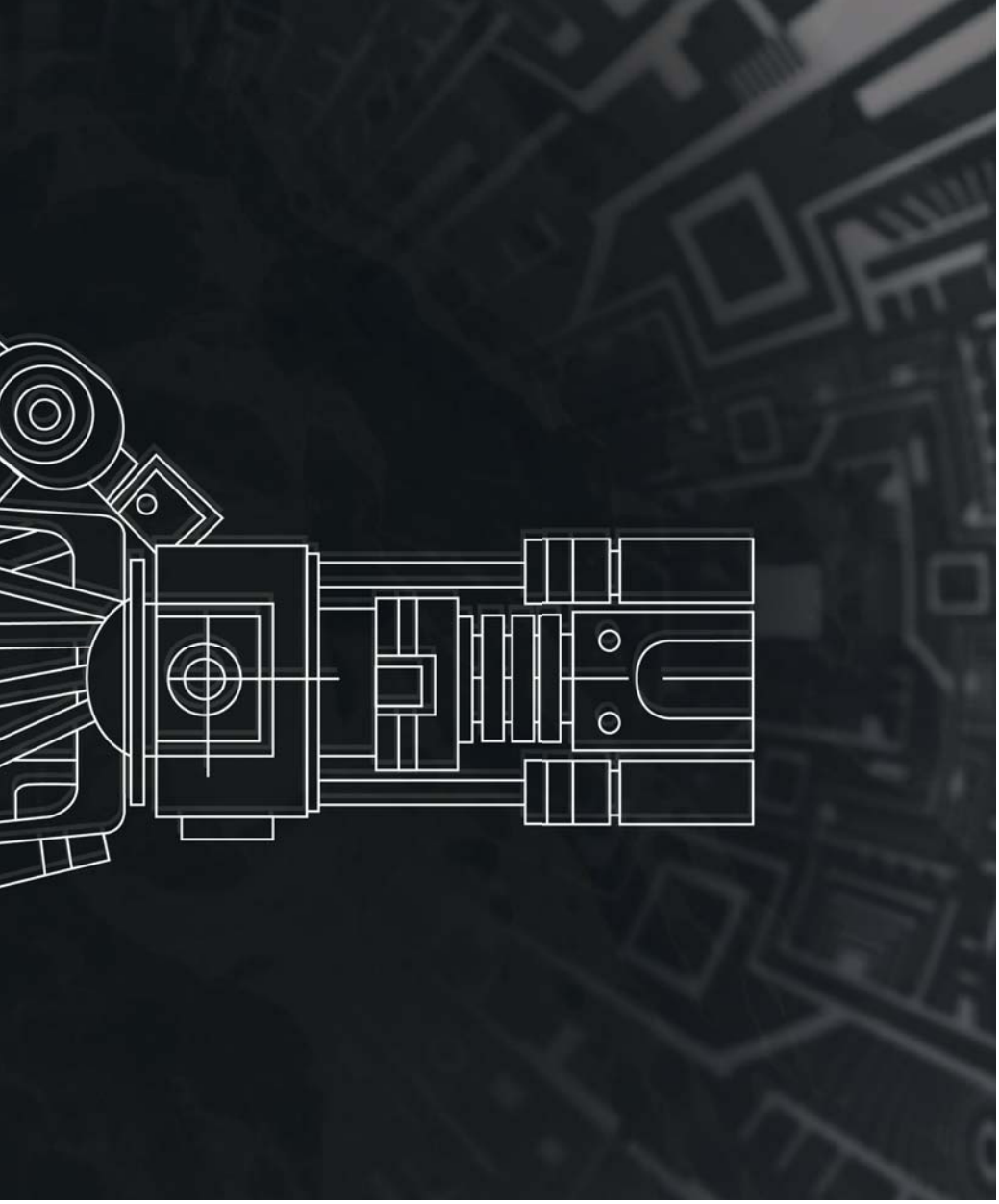
At a Glance

- *The challenge for retinal cell therapy is positioning the therapeutic cells very precisely into the correct retinal layers*
- *A collaborative project team is working on developing a device that provides the surgeon with delivery tubes capable of multiple orientations and flexibility of operation*
- *The human factor is important to the researchers, who have been involving patients, and the broader public, in discussions about medical robotics*
- *Patient representative, Douglas Tredget, shares his experience of being part of the robotics project.*

Regenerate the degenerating

What made us commit to the project? In brief, an opportunity and a challenge. The opportunity is to help cure diseases that cause blindness. Today, gene and stem cell therapies have the potential not just to delay but also to reverse degenerative eye diseases – this is borne out by recent work on gene therapy for choroideremia and cell therapy for age-related macular degeneration (1). However, for retinal cell therapy to reach its full potential, therapeutic cells must be able to be positioned very precisely into the correct retinal layer – and this is the challenge we take on.

Current systems for delivering cells to the retina simply have not caught up with the advances – and requirements – of cell therapy. In fact, delivery systems such as manually-operated needles remain somewhat crude and limited by the physical capabilities of humans in terms of precision and tremor. This in turn limits the development of cell therapies. It is frustrating that the therapeutic cells exist but cannot be delivered to the 10-micron zone in the retina where they are needed. The technology to enable such precision does not currently exist. We realize that we are at the limits of what the human hand can achieve, and this is impeding the translation of cell and molecular therapies into the clinic.



Augmented reality for effective image-guided ophthalmic surgery

Claudio Ravasio, a PhD student, is developing systems to enhance the surgeon's intra-operative view of the retina. Theodoros Pissas, a PhD student, identifies critical landmarks on optical coherence tomography angiography images.

- Integration of images of different retinal layers will assist intra-operative manipulations
- Based on near-real time, 'inverse realism' computer-generated images, the system will combine optical microscopy and pre-operative optical coherence tomography (OCT) images
- Surgeons will access augmented images via 3D screen or head-mounted display
- Integration with robotic operating system will enable surgeons to position device tip very accurately
- It will reduce training time, increase safety, simplify navigation, increase precision

Beyond dexterity

The realization that the human hand may hold back advances in cell therapy led the two of us, to initiate this collaborative project. The combination makes an ideal team, one of us leading the engineering component, while the other leads the clinical surgical translation aspect. Our fundamental aim is to enable precise and reliable micro-scale retinal surgery for cell therapy.

In more detail, the problem we face is not just one of scale, but of relative scale. Consider: the status quo of retinal surgery involves a linear instrument that enters the eye through the sclera, the white of the eye; thereafter, any surgical manipulations require the instrument to pivot around that entry point. Assume, for the sake of argument, that the depth of the eye – from scleral entry point to retina – is 1 cm, and the target zone is 10 microns (0.01 mm). And that equates to a thousand-fold difference in size between the instrument length and the target zone. In other words, the surgeon is attempting the equivalent of hitting a one-meter target with a one-kilometer pole! The disparity between distance and required precision was a key problem for us to overcome.

Our solution? In effect, to move the pivot point closer to the target – essentially, to provide the linear instrument with a flexible tip. Briefly, our device comprises a linear outer tube containing smaller, deformable inner tubes (Figure 1), fabricated from a memory material (NiTi CC). The inner tubes can be pushed out of the end of the device; once outside, their tips take on the shape in which they were fabricated. Similarly, upon retraction they deform so as to fit into the outer tube. The tips are designed to facilitate micro-incisions and delivery of viable cells. In addition, the tips can be rotated as required to assist with precise cutting and targeted implantation. The device therefore provides the surgeon with delivery tubes capable of multiple

Hardware integration and telemanipulation

John O'Neil, alumnus post-doctoral researcher, developed electromechanical control and feedback systems

- Desk model prototype: electric motors advance and retract internal tubes within delivery device
- Surgeon controls tube movements via a joystick system
- Forthcoming: control system that gives surgeon physical feedback through hand-held joysticks

Figure 1. Main components and architecture of the robotic system. An actuation system transmits motion to the flexible tip through an array of concentric cylinders (like pistons). This way, the actuation system is decoupled from the tip, and enables changing the tip during surgery.

orientations and unparalleled flexibility of operation.

Helping hands

Our project has involved several individuals focusing on different elements of the technology. Initial tasks included development of custom software to achieve the required device tip flexibility, and development of novel actuation components and stabilisation constraints. Ongoing work includes perfection of image processing systems to better guide the surgeon (Sidebar 1), and construction of advanced electromechanical control and feedback systems (Sidebar 2). And before all of this innovation, we had to cover a lot of background work; for example, to ensure that we were completely familiar with anatomical landmarks of the eye and how they can guide surgery.

As with any translational project, problems arose as development proceeded. Throughout, we have had to consider many aspects: the sterility of the device; how to drape the instrument; components that should be single use; and the cost implications of all the above. Safety is key, of course – we must allow for the unexpected, and ensure that if there is any kind of intra-operative failure, the device can be fully controlled and carefully retracted at all times. Nobody wants to see a medical robot run amok! All these aspects must be managed, and they add to the project timelines. Fortunately, we've had no major problems, and the funders remain happy with our progress.

That said, with robotic systems you can theorise as much as you like, but you won't know if they work until you build them. We are now making prototypes for evaluation in model systems, such as plastic eyes. The resulting data will allow us to improve the device and bring it closer to clinical application. And as we expect this surgery to be performed under local anesthesia, we are also going to develop image stabilisation algorithms to cancel out patient movements – not just breathing, but also head movements. Vitreoretinal surgery is now normally done under local anesthesia, and we want to stick as closely as possible to existing practices!

Real-world impact

The increased precision permitted by our system will assist conventional retinal surgery to some extent – for example, it will make retinal membrane peeling or vessel cannulation a little faster and safer. However, conventional surgery is already highly reliable, so the improvement afforded by our system would only be incremental – say, a move from 90 to 95 percent efficacy. The real importance of our system will be in enabling forms of surgery that are at present impossible – namely, the precise localised delivery of gene or cell therapies to any individual retinal layer.

As well as optimizing the engineering and surgical effect, we are trying to maximise our real-world impact by involving patients, and the broader public, in discussions about medical robotics. It is important for researchers – and clinicians – to be aware of the human factor, no matter how exciting the technology. Understanding people's hopes and fears and incorporating these into research is why patients like Douglas Tredget (see interview on the next page) are so valuable. Not only do they offer tremendously helpful insights through lived experience, but they can quickly raise issues that could otherwise take us years to recognise.

We are very happy with the progress we have made – the project has been running for about one year now, and has attracted financial support over and above the original National Institute for Health Research (NIHR) grant. It has just grown and grown, which makes everybody happy, including the original funders. Above all, we look forward to making a real difference to patients with degenerative disorders of the eye. The days of therapeutic delivery by handheld needle are numbered!

How the patient sees it

Douglas Tredget is the Macular Society patient representative on the King's/UCL/ Moorfields Eye Hospital robotics project.

Figure 2. Christos Bergeles, Douglas Tredget and Lyndon da Cruz.

What is your experience of AMD?
I was diagnosed with AMD in 1998. After noticing a blurred spot in the vision of one eye, I contacted my local ophthalmologist, who sent me to the West Kent Eye Hospital. Subsequently, I was referred to Professor Bird and Dr Tufail at Moorfields Eye Hospital, London. Currently I am being treated by Tim Jackson at King's College Hospital, London.

In the last five years, I have joined the Kent Association for the Blind (KAB); I do voluntary work for them and have befriended a gentleman with AMD at a more advanced stage than mine. I also participate in bridge games for partially sighted people, again at KAB, and I know a number of other AMD patients via my local Macular Society.

Why did you get involved with the Macular Society and this robotics project?
I joined the Macular Society to keep abreast of research and to participate in clinical studies. For example, I have been involved with investigations into the effects of diet, aspects of facial recognition, and methods of vision assessment. Recently, the Society asked me if I would be interested in this robotics project. I agreed, and the project leaders – Christos Bergeles and Lyndon da Cruz – got in touch with me and explained the project aims and timelines. They also introduced me to the other members of the team.

Since then, I've been sitting in on the robotics project quarterly progress meetings, where different members of the team present their work and new research results. Sometimes the researchers demonstrate the robot prototypes they are working on. Following these meetings, I write summary articles for Sideview (the magazine of the Macular Society) about different aspects of the research.

What do you think about the technology and its potential impact on patients' lives?
There are many AMD research projects, but to me this one seems the most likely to succeed. In the first trial of stem cell therapy for AMD (1), about three years ago, Lyndon da Cruz and Pete Coffey (UCL) showed that stem cell implantation into the macular resulted in quantifiable improvement of symptoms. As Lyndon explained at the first project meeting, the biological aspect of this therapeutic approach was sound, but the surgical aspect – the actual delivery of the stem cells – was impeded by human limitations. It was just too difficult for routine application. As Lyndon put it, the macular has many fine layers, a bit like an onion – and we need to deliver the stem cells between these layers, without causing too much damage in the process. It is hoped that robotic systems will be able to carry out this delicate procedure more safely and reliably than manual approaches.

What aspects of the technology most interest you?
The power of computing to bring accuracy and standardization to complex operations! In my own profession, I have had first-hand experience of the ability of computers to increase speed and reliability, and I am excited and encouraged by their application to retinal surgery.

Disclaimer
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Christos Bergeles works at the Robotics and Vision in Medicine Lab, School of Biomedical Engineering and Imaging Sciences, King's College London

Lyndon da Cruz works at the NIHR Biomedical Research Centre, Moorfields Eye Hospital and University College London

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Looking Back, Moving Forward

Reflecting on our January feature – A Year in Ophthalmology Research: 2018 – glaucoma specialist Paul Singh walks us through the publications, approvals, and advances driving ophthalmology onward

As a glaucoma specialist, I've really enjoyed seeing the significant advancement and proliferation of technology over the last few years, both in diagnostics and treatment. And 2018 was no exception. We have seen approvals for new topical glaucoma medications, approvals of new MIGS devices, and recent publications demonstrating new technologies that make it easier to identify glaucoma patients much earlier in the disease.

Over the last few years, there has been an emphasis on earlier detection – and understanding which patients are at higher risk of glaucoma progression. A landmark 2018 study looked at the role of corneal hysteresis (CH) as a risk factor for developing glaucoma. (1) With increasing age, both the cornea and the lamina become more rigid and less resilient. The Reichert ocular response analyzer (ORA) (Ametek Reichert Technologies, Depew, NY, USA) measures CH and has been associated with progressive visual field worsening in glaucoma patients. Though earlier studies have demonstrated the link between low CH, glaucoma and response to topical medications, I consider the paper by Carolina Susanna and colleagues to be a landmark study as it is one of the first prospective and longitudinal studies to support the role of CH as a risk factor for developing glaucoma. In our clinical practice, we often use CH to help decide i) if we should initiate treatment in a glaucoma suspect, and ii) how aggressive the treatment should be, regardless of disease severity; after all, the study showed that lower CH measurements were significantly associated with increased risk of developing glaucomatous visual field defects over time.

Along the lines of earlier detection of glaucomatous optic neuropathy, another article published in 2018 caught my attention (2). Glaucoma patients are often diagnosed and treated when irreversible loss of visual function has occurred. Early detection – and therefore appropriate early treatment – are clearly best for such patients. A novel technology called Detection of Apoptosing Retinal Cells (DARC) allows real-time in vivo quantification of apoptosing cells through the use of a fluorescent biomarker and a confocal scanning ophthalmoscope. A recent Phase I clinical trial evaluated the safety of DARC and its ability to detect retinal apoptosis in glaucoma patients and healthy volunteers. Results demonstrate the potential benefits of DARC in the early detection of glaucoma.

In more detail, DARC uses an intravenous injection of an infrared fluorescently labeled ANX (ANX776), followed by retinal imaging using specific wavelengths with the use of a commercially available confocal scanning laser ophthalmoscope (cSLO) and indocyanine green angiography settings. In the Phase I trial, half of the enrolled subjects were eight

"With increasing age, both the cornea and the lamina become more rigid and less resilient."

At a Glance

- *Paul Singh explores two of the most important studies in glaucoma research in 2018, dealing with the role of corneal hysteresis as a risk factor for developing glaucoma, and with DARC, a new technology used for quantification of apoptosing cells*
- *2018 saw the approval of several MIGS devices, including the iStent Inject, Hydrus microstent and the iStar MINIject*
- *Approval and commercialization of new medications and drug delivery systems has considerably changed the landscape in 2018.*

healthy volunteers and the other half were eight patients with progressive glaucoma. Although the trial was designed primarily to assess the safety and tolerability of ANX776 in patients, it showed that the DARC count was significantly increased in glaucoma patients, compared with healthy volunteers. Furthermore, the DARC count correlated with increasing rates of glaucomatous progression. Phase II trials are underway.

MIGS approvals in the USA

As we have seen, the MIGS space has grown tremendously over the last few years. And 2018 saw the approval of two new MIGS devices. The iStent Inject, which gained FDA approval in the summer, now allows for the implantation of two 0.23 mm x 0.36 mm microstents through the trabecular meshwork (TM) into the Schlemms canal. These devices optimize the natural physiological outflow of aqueous humor by creating two patent bypasses through the trabecular meshwork. The iStent inject cohort achieved a 31 percent mean IOP reduction, or 7.7 mmHg, in unmedicated IOP from an unmedicated mean baseline IOP of 24.8 mmHg to 17.1 mmHg. Also, at 24 months, the overall rate of adverse events for the iStent inject cohort was similar to cataract surgery alone.

Another MIGS approval was the Hydrus microstent. The device not only bypasses TM resistance, but also scaffolds approximately 90 degrees of the patient's Schlemms canal. The FDA's approval was based on the 24-month results from the largest MIGS trial to date: HORIZON. The study included 556 mild-to-moderate glaucoma patients randomly assigned to undergo cataract surgery with or without the microstent. More than 77 percent of patients with the implant exhibited a significant decline in unmedicated IOP, compared with 58 percent of the control group. On average, the device reduced IOP by 7.5 mmHg, approximately 2.3 mmHg more than the cataract surgery-only group. Safety was similar to the cataract-only group.

Both of these devices appear to be effective at eliminating or reducing medications, compared with cataract surgery alone. Reducing the medication burden is a key factor when analyzing the effectiveness and overall benefits of MIGS devices.

Since the withdrawal of the Cypass stent, there has been a void in the

supraciliary space. Fortunately, there are two other devices undergoing trials, one of which finished enrollment in its IDE trials back in 2017. The iStent SUPRA prospective, randomized clinical trial includes 36 sites and 505 subjects with mild-to-moderate primary open-angle glaucoma and cataracts. Subjects were randomized to receive either iStent SUPRA in combination with cataract surgery or cataract surgery alone. The study has a 24-month primary outcome measure of a 20 percent or greater reduction in intraocular pressure (IOP) from baseline.

Another company, iStar Medical, recently published one-year results of its first-in-human MIGS trial for the MINIject device in a standalone setting. The iStar MINIject system has a medical grade silicone device with precision-pore geometry in a soft, flexible, tissue-friendly material. The company claims exceptional biointegration of the device with surrounding tissue colonizing the porous structure, while preserving in vivo drainage efficacy. The STAR-I trial is a prospective, open, international, multi-center study in which MINIject was implanted in 25 patients with mild-to-moderate primary open angle glaucoma uncontrolled by topical hypotensive medication. Minimal encapsulation was observed, as shown by the absence of a continuous surrounding fibrous capsule, continuous macrophage, and a continuous fibroblast layer. After one year, the STAR-I trial in a standalone setting demonstrated an average 32.6 percent IOP reduction to a mean of 15.6 mmHg at one year. In addition, 75 percent of patients were able to discontinue topical medication usage and remained medication-free at one year. There were no serious ocular adverse events and no patients required subsequent glaucoma surgery. There was minimal change in mean ECD between baseline and one year. The company will start enrolling subjects in the US sometime in the middle of 2019 for the refractory population.

Medication approvals and commercialization

With the introduction of MIGS, mechanism of action has started to gain more and more traction. We are now paying more attention to outflow resistance and addressing the site of pathology. With this in mind, the approval and commercialization of two new pharmaceuticals was a significant advance in 2018. Both Rhopressa (netarsudil ophthalmic solution 0.02 percent) and Vyzulta (latanoprostene bunod 0.024 percent) were approved for the reduction of intraocular pressure. These drugs are unique as they both demonstrate activity that helps improve outflow through the conventional outflow pathway (the primary site of resistance in POAG patients). There is a possibility these drugs may decrease further pathology in the conventional outflow pathway and may also have a synergistic role with MIGS devices. The added benefit of these eye drops is that they are qd dosing. The introduction of both these new medications and the proliferation in micro-invasive glaucoma surgery have truly inspired a renaissance in the field.

Drug delivery has been a hot topic in the last few years. Three approvals in the cataract surgery space this year have spurred excitement among my colleagues. Dexycu, INVELTYS, and Dextenza are steroid medications that have been approved to reduce postoperative pain and/or inflammation. Dexycu is the first long-acting intracameral product approved by the FDA for treating inflammation following cataract surgery injecting a proprietary drug delivery technology (Verisome) dexamethasone under the iris at the end of the case. In approval studies, a single dose of 5 mcL of Dexycu (equivalent to 517 mcg of dexamethasone), a dose

equivalent to 342 mcg of dexamethasone, or a vehicle placebo was administered by the physician at the end of the surgical procedure. The percentage of patients with anterior chamber clearing at day 8 was 20 percent in the placebo group, and 57 percent and 60 percent in the 342 and 517 mcg treatment groups, respectively. The percentage of subjects receiving rescue medication of ocular steroid or nonsteroidal anti-inflammatory drugs was significantly lower on days 3, 8, 15, and 30 in the 342 and 517 mcg treatment groups, compared with placebo.

INVELTYS (loteprednol etabonate) 1 percent ophthalmic suspension is the first ocular steroid approved for twice-daily dosing for post-op pain and inflammation; other ocular postoperative topical steroids are approved for four times daily dosing. INVELTYS uses mucus-penetrating particle (MPP) technology to improve penetration into target tissues of the eye. The technology has demonstrated a greater delivery of the drug into ocular tissues versus current loteprednol etabonate-containing drugs. Data from two Phase 3, multicenter, randomized, double-masked, placebo-controlled trials showed a greater proportion of patients treated with Inveltys having complete resolution of ocular inflammation at day 8 (24 percent vs 13 percent) and day 15 (50 percent vs 27 percent), and complete resolution of pain at day 4 (43 percent vs 25 percent), day 8 (56 percent vs 36 percent), and day 15 (69 percent vs 48 percent) versus placebo (P for both <0.01). In addition, treatment was well-tolerated with no treatment-related serious adverse events reported. INVELTYS will be available as a 1 percent suspension in 5 mL bottles.

Dextenza (dexamethasone ophthalmic insert 0.4 mg) is the first FDA-approved intracanalicular insert to deliver dexamethasone to treat postoperative ocular pain for up to 30 days with one treatment. The device releases drugs into the anterior segment for three to four weeks, and may obviate the need for topical steroids. In two randomized, vehicle-controlled phase 3 studies, a statistically significant number of patients who received Dextenza were free of pain eight days after cataract surgery compared with patients in the vehicle control group. In addition, safety was demonstrated in the two phase 3 studies, as well as a third randomized, vehicle-controlled phase 2 study. Ocular Therapeutix applied for transitional pass-through payment status and intended to apply for a J-code before the January 2019 deadline.

Literature reveals that up to 31 percent of cataract patients have had difficulty inserting drops, and 92 percent used improper techniques. Many of our patients deem the post-op drop regimen the main cause of discontent post cataract surgery. These three approvals benefit patients by decreasing compliance issues and dosing errors associated with the current common post-op regimen of relying on the patient placing drops more frequently following cataract surgery.

In August 2018, the FDA approved the first drug for the treatment of neurotrophic keratitis, Oxervate (cenegermin). Although the prevalence of neurotrophic keratitis is low, it can be a devastating disease. The safety and efficacy of Oxervate, a topical eye drop containing cenegermin, was studied in a total of 151 patients with neurotrophic keratitis in two, eight-week, randomized controlled multi-center, double-masked studies. All eye drops in both studies were given six times a day in the affected eye(s) for eight weeks. In the first study, only patients with the disease in one eye were enrolled, while in the second study, patients with the disease in both eyes were treated bilaterally. Across both studies, complete corneal healing in eight weeks was demonstrated in 70 percent of patients treated with Oxervate, compared with 28 percent of patients treated without cenegermin (the active ingredient in Oxervate).

Industry news

Omidria (phenylephrine 1 percent and ketorolac 0.3 percent intraocular solution) received a two-year reinstatement of pass-through status by the CMS that went into effect on October 1. It was important to allow access to the drug until a permanent code is established. The two-year extension was passed into law in March as part of the Consolidated Appropriations Act of 2018. It will remain in effect until October 1, 2020. Omidria is the only FDA-approved product for use during cataract surgery or IOL replacement to maintain pupil size by preventing intraoperative miosis, and to reduce postoperative ocular pain.

Zeiss' acquisition of IanTECH was an exciting announcement at the end of 2018. IanTECH is well known for its nuclear disassembly device, the miLOOP, and the company has been working on a new technology to disassemble and remove the cataract from start to finish, without the use of cavitation and phaco energy. The device will likely force the whole industry to re-evaluate the cataract surgery process from a cost, flow, and physics perspective. The Zeiss acquisition also reaffirmed the company's desire to get more involved in the treatment side of the cataract surgery, rather than diagnostics alone.

I. Paul Singh is President of The Eye Centers of Racine & Kenosha, Wisconsin, USA. Singh reports that he is a consultant for Ellex.

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The Crystal Maze

Uncovering the complex biochemistry behind cataract formation

By Phoebe Harkin, in conversation with Eugene Serebryany

Crystallins are the collection of structural proteins found in the lens of the eye that help to focus light onto the retina. We know that over our lifetimes they can accumulate damage, losing their native structure and sticking together to form aggregates – one of several mechanisms that causes cataracts. But how exactly does this happen – and can it be stopped? Eugene Serebryany, a Post-Doctoral Fellow at the Department of Chemistry and Chemical Biology at Harvard University, USA, wants to find out. In 2015, Serebryany and his Harvard-MIT team made the crucial discovery that wild-type (undamaged) crystallin promoted aggregation of mutant (damaged) versions – without itself aggregating (1). Chemical bonds between sulfur atoms within the protein (disulfide bonds) were found to play a role in aggregation (2). Most recently, the team found that crystallin protein molecules engaged in oxidation–reduction reactions with one another – disproving the long-held assumption that crystallins are inert (3).

We spoke to Serebryany to find out more about the role of crystallins in cataract formation.

At a Glance

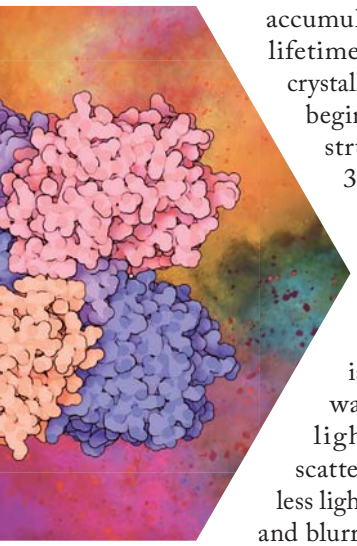
- *Over time, crystallins stick together to form aggregates – leading to the formation of cataracts*
- *Wild-type (undamaged) crystallin promotes aggregation of the mutant version – without itself aggregating*
- *Evidence of oxidation–reduction between molecules disproves the long-held theory that crystallins are inert*
- *Non-surgical therapies for cataracts could improve eye health for millions who currently don't benefit from surgery*
- *Researchers are pursuing several potential drug candidates to inhibit aggregation, including two lipid-based treatment approaches.*

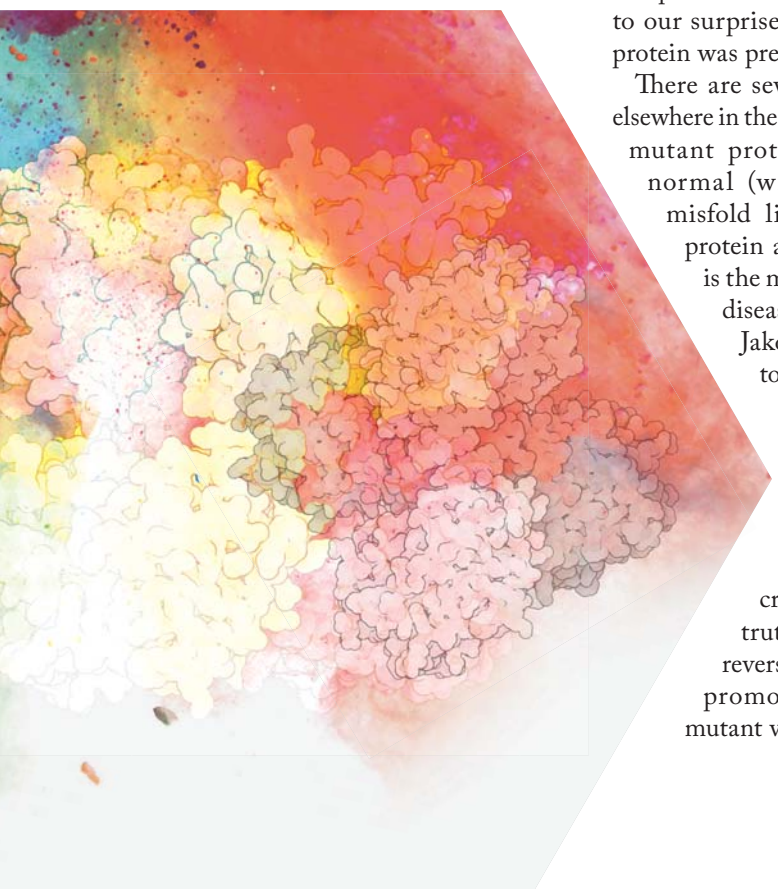
What led you to study crystallin proteins?

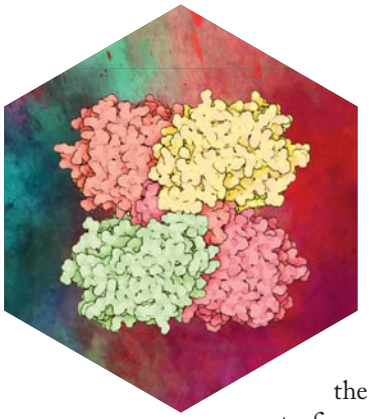
The eye lens proteome is fascinating because it has evolved to minimize light scattering. That means it must resist aggregation because protein aggregates (clumps of many molecules of a protein) scatter visible light. Yet, the protein molecules in the core region of the lens are synthesized before birth and never replaced thereafter. These protein molecules are undergoing an aging process even before we are born, and they continue to accumulate various kinds of damage throughout life. The biochemistry and biophysics of this highly concentrated solution of highly aged proteins, and how they have evolved to resist aggregation, has been of huge interest to many researchers over the years. One of them was my PhD adviser at MIT, Jonathan King, who first introduced me to these fascinating molecules. Our current work in the Shakhnovich group at Harvard builds directly on those earlier studies.

Of course, as fascinating and unique as crystallins are for their own sake, they also have important implications for public health. Their aggregation – when it does eventually occur – causes cataracts, which affect tens of millions of patients.

Some people falsely assume that modern surgery has solved the problem of cataracts. In fact, millions of patients around the world never benefit from the surgery, either because they can't afford it, because they live in areas where it is not available, or because surgery is contraindicated for them. Moreover, the total cost of cataract surgeries performed worldwide already adds up to tens of billions of dollars per year, and as the global population ages, cataract prevalence will rise dramatically. A non-surgical therapy would be of great benefit, and that is the ultimate goal of our research.







What is the role of crystallins in causing cataracts?

Proteins from the crystallin family make up the lion's share of all protein molecules in the cells of the eye lens. Since they are never replaced, at least in the lens core region, they accumulate damage over a lifetime. Eventually these crystallin protein molecules begin to lose their native structure (the normal 3D arrangement of atoms) and stick together to form aggregates. Once the aggregates reach a size that is comparable to the wavelength of visible light, they begin to scatter light, resulting in less light reaching the retina and blurring of the resulting image. Because blue light has the shortest wavelengths, it gets scattered the most, so the colors we see also change, becoming yellower.

How has your work contributed to our understanding of lens crystallins?

It's worth clarifying that the lens is not, itself, a crystal; it is referred to as "crystalline" solely because of its glass-like transparency (and hence also the name of the proteins, "crystallins"), but the cytoplasm of lens cells is gel-like, as in most other cells. Regardless, the initial observation that we reported in 2015 (1) was striking: mixing mutated protein with normal, unmutated protein led to rapid aggregation and a spike in light scattering. We were able to use gel electrophoresis, and more recently mass spectrometry, to separate the components of the aggregates and saw, to our surprise, that only the mutant protein was present there.

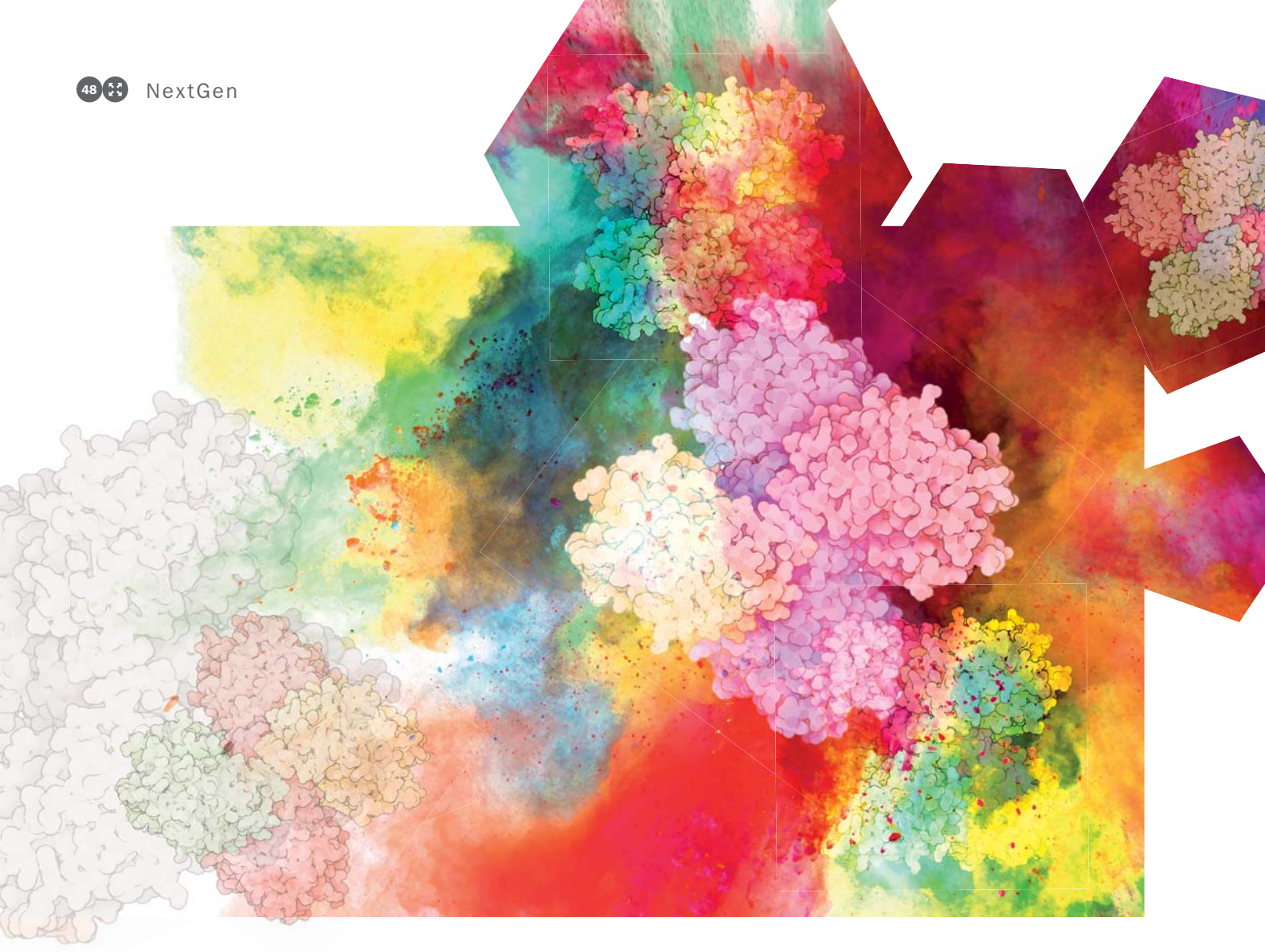
There are several health conditions elsewhere in the body in which misfolded mutant proteins cause otherwise normal (wild-type) proteins to misfold likewise – the mutant protein acts as a template. This is the mechanism behind prion diseases (such as Creutzfeldt-Jakob disease), and it leads to aggregation of both the mutant and the wild-type molecules. Our initial hypothesis was that a similar phenomenon could exist in eye lens crystallins. However, the truth turned out to be the reverse: a wild-type crystallin promoted aggregation of a mutant version of itself, without itself aggregating.

This new phenomenon was intriguing, but its mechanism remained totally mysterious. My collaborators and I have devoted the past several years trying to figure it out. The search for this mechanism led us to another surprise: a chemical reaction was taking place between these crystallin protein molecules, a process of oxidation¬–reduction (3). We also believe there is a second aggregation-promoting mechanism at work, which we are now studying.

"Our initial hypothesis was that a similar phenomenon could exist in eye lens crystallins. However, the truth turned out to be the reverse."

You describe the chemical reaction as being like a "hot potato competition" – could you explain that?

We found that the crystallin proteins can pass disulfide bonds among themselves, from one molecule to another to another. These disulfide bonds are formed when



two atoms of sulfur within one protein molecule react with each other. (This chemical reaction releases electrons, making it an oxidation reaction.) The disulfide bond can then be transferred to another pair of sulfur atoms on a second molecule of this protein. In chemical terms, molecule 2 releases electrons that are received by molecule 1, so molecule 2 is oxidized and molecule 1 is reduced. These transfers of disulfides can be passed back and forth for a long time if the two molecules are equivalent.

How does that cause aggregation?

There are multiple reactive sulfur atoms in each molecule of gamma-crystallin. In wild-type protein, most of those sulfur atoms are hidden and therefore not available for this kind of chemical reaction. The situation changes if a mutation or another form of damage causes the protein's structure to "loosen up", exposing more sulfur atoms. We previously showed (2) that if a pair of sulfur atoms that is normally hidden becomes exposed and forms a disulfide bond, the protein becomes trapped in an aberrant structure and becomes sticky, leading to aggregation. Studies by our colleagues in the Monnier and Fan groups at Case Western Reserve University strongly suggest that this type of chemistry underlies gamma-crystallin aggregation in the lenses of cataract patients.

Now we can connect the dots. Disulfide bonds are passed around among crystallin molecules like a hot potato: if they land on a damaged protein molecule that, due

"The main challenge will not be finding peptides that can inhibit aggregation, but rather delivering such peptides to the most vulnerable cells of the lens."

to its looser structure, displays sulfur atoms that it should have kept hidden, then this damaged molecule gets trapped in a sticky non-native structure, and forced to aggregate. The disulfides do no great harm to the structurally sound crystallin molecules, and may even be protective, but they drive the structurally weakened molecules into aggregates that scatter light – hence, the aggregates in our experiment only contained mutant (damaged) proteins.

Can we stop proteins from aggregating?

The cells of the core region of the eye lens cannot make new protein molecules, nor can they actively degrade them. Peptide-based drugs would be expected to be rapidly broken down and metabolized in any other part of the body, but not in the nucleus of the lens. Although we haven't yet reported any results with potential peptide drug candidates, we are pursuing several that we believe could inhibit aggregation by affecting both structure and chemistry. We anticipate that the main challenge will not be finding peptides that can inhibit aggregation, but rather delivering such peptides to the most vulnerable cells of the lens. Peptide drugs tend to be large molecules, and we don't yet know if they will penetrate the tissue in sufficient quantities. If not, all is not lost – the Arora group at New York University has already shown that it is possible to mimic peptide drugs with much smaller non-peptide ones, if necessary.

What do these findings mean for the future of cataract research?

They advance our understanding of the mechanisms behind what is likely the most common type of cataract (though there are other types with clearly distinct mechanisms). Still, there is much more work to be done. Efforts to treat cataracts therapeutically have grown in number and made waves in recent years; at least two distinct lipid-based treatment approaches are now being pursued, for example. No drugs have been approved so far, and ultimately, a combination of drugs might be needed. But the more we learn about the biochemistry and biophysics of cataract formation, the wider the space of therapeutic possibilities will be.

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Engineer, Leader, Family Man

Sitting Down With… Rainer Kirchhübel,
CEO, OCULUS Optikgeräte GmbH

What is your background – and how did you begin your career at OCULUS?

I studied mechanical engineering and company business operation in Stuttgart, Germany, in the 1970s. During that time, I already worked for OCULUS because my father, Kurt Kirchhübel, was the CEO. He joined the family-owned company in 1947 and jointly chaired it with his cousin Wilhelm Mager, until Wilhelm's death in 1956. As a student, I used to help build up the exhibition booths for the major shows in Germany! Even back then, I had decided to join OCULUS for good; I wanted to help develop new products and introduce them to the market.

What innovations stand out from your father's time?

My father developed many interesting products over the years, such as the Synoptophore for amblyopia training and measurement with Curt Cüppers, a University of Giessen professor. And, in cooperation with Heinrich Harms and Elfriede Aulhorn – two professors at the University Eye Clinic Tübingen, he developed the Tübingen Perimeter to examine static perimetry for detection of early Glaucoma stages for the first time. Kinetic perimetry was standard at that time. (Incidentally, I was later involved in building the first OCULUS Automatic Perimeter – also in cooperation with the University Eye Clinic Tübingen).

Can you share some career highlights?

Together with our R&D team – and Manfred Spitznas, former director of University Eye Clinic, Bonn, and Josef Reiner, former director of Highschool of Optometry, Cologne – I initiated the development of the SDI/BIOM system (the Stereo Diagonal Inverter and Binocular Indirect Ophthalmo Microscope) in 1985. It's a highlight because I believe we set the standard for wide-angle viewing and vitreoretinal surgery with this system – and, today, OCULUS Surgical is very strong in this field. I was also closely involved in developing a new generation of trial frames, the UB 4 (we're now on the UB 6), for which we won design prizes. And in 1995, we started our Keratograph business, which is also very successful worldwide.

What's the secret to success when starting in a new market?

With any new product and in any new market, we first have to comprehensively study the scientific background. Next, we must find areas of potential improvement – and then take the right steps to bring those advances to the field. We introduced the Pentacam in 2003 but, when we started this project in 1999, I remember very clearly our R&D Director at the time, Gert Köst (who had the basic idea for the instrument) saying: "This product will either lead us to big opportunities – or it will fail!" In the end, we succeeded; today, I like to think that it sets the worldwide standard in screening the complete anterior segment of the eye. And it's another big highlight for me.

Is OCULUS still very much a family business?

Absolutely! I work closely with both my sons: Christian is already CEO at OCULUS, and is currently responsible for sales. At the beginning of his career, he made significant improvements to our building and introduced a state-of-the-art workflow. Matthias, my other son, studied mechanical engineering, just like me; he is responsible for our new optic production. And last, but by no means least, Rita Kirchhübel has not only been responsible for national and international marketing for more than 25 years, but she's also my wife!

Can you share any details of current projects?

Myopia progression is becoming a serious problem worldwide. We are working hard to introduce a compact screening device that enables testing of all major aspects of this disease, including autorefraction, keratometry and axial length. It is called the Myopia Master.

"For me, learning how to learn was one of the most important lessons at university."

Do you have any advice for future CEOs – including your successors?

Always listen to the market! Meet colleagues and key opinion leaders regularly and never stop learning. For me, learning how to learn was one of the most important lessons at university. If you have an important decision to make, always sleep on it first, and use your common sense. Look after your health – and the health of all your team members. Enjoy quality time with family and friends. The next generation at OCULUS is already very much involved in the business, and they are ready to continue growing our healthy base with intelligent products.

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ATTENTION: Reference the Directions for Use for a complete listing of Indications and Important Safety Information. **INDICATIONS:** The TECNIS® 1-Piece Lens is indicated for the visual correction of aphakia in adult patients in whom a cataractous lens has been removed by extracapsular cataract extraction. These devices are intended to be placed in the capsular bag. **WARNINGS:** Physicians considering lens implantation should weigh the potential risk/benefit ratio for any conditions described in the TECNIS® 1-Piece IOL Directions for Use that could increase complications or impact patient outcomes. The TECNIS® 1-Piece IOL should not be placed in the ciliary sulcus. **PRECAUTIONS:** Do not reuse, resterilize, or autoclave. **ADVERSE EVENTS:** In 3.3% of patients, reported adverse events of cataract surgery with the 1-Piece IOL included macular edema. Other reported reactions occurring in less than 1% of patients were secondary surgical intervention (pars plana vitrectomy with membrane peel) and lens exchange (due to torn lens haptic).

*Compared against AcrySof® IQ (SN60WF), HOYA AF-1™ FY-60AD and enVista® IOLs (MX60).

Reference: 1. Data on file. Chromatic aberration of the TECNIS® Symfony IOL. Johnson & Johnson Surgical Vision, Inc. Santa Ana, CA.