FEBRUARY 2019 # 62

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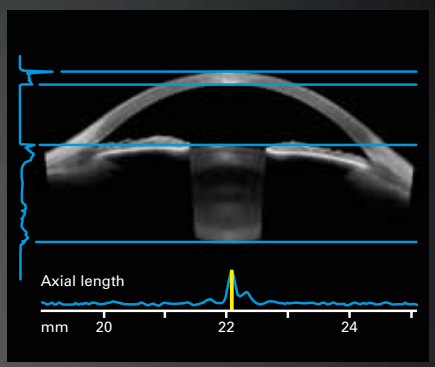

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Image of the Month

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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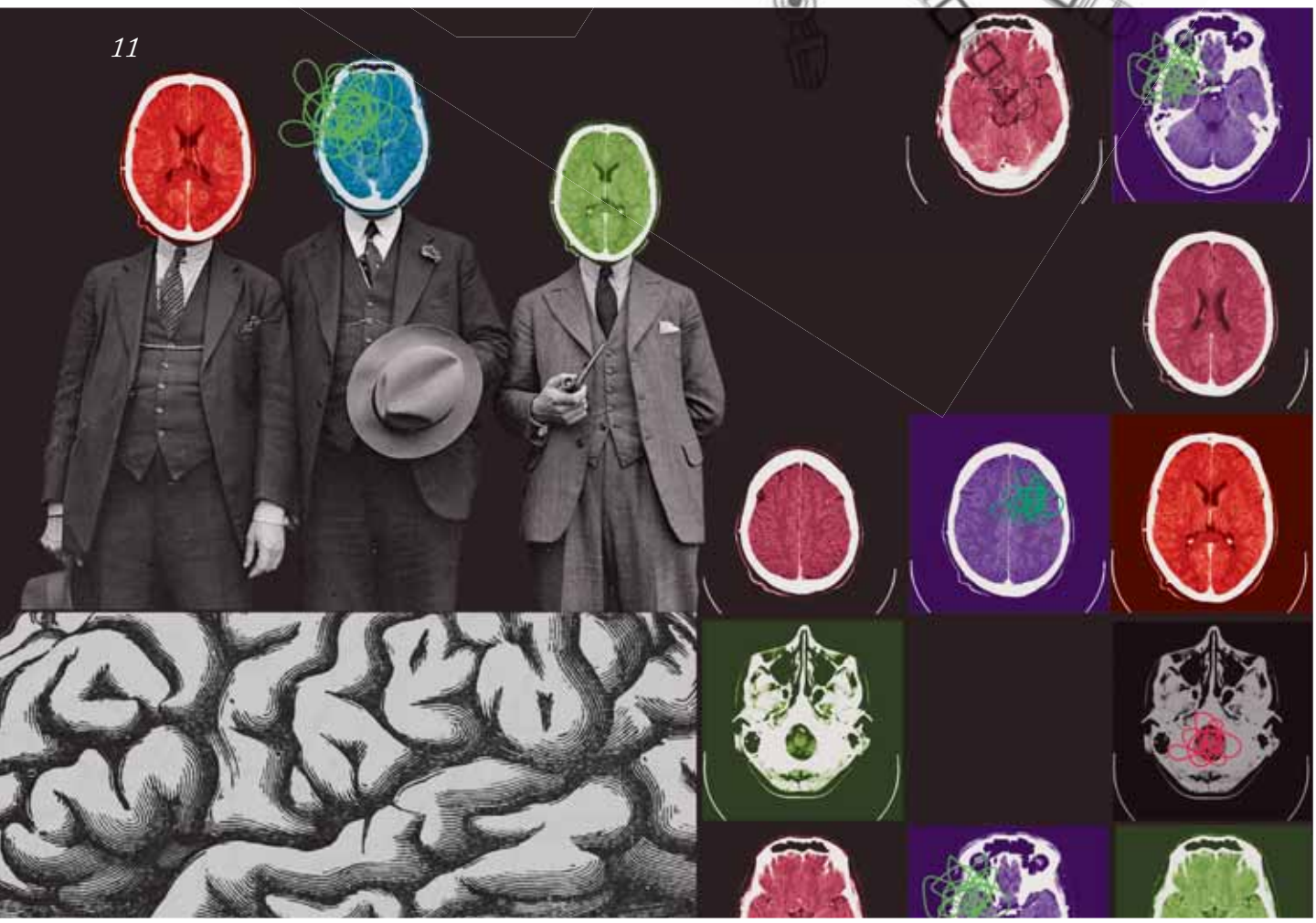
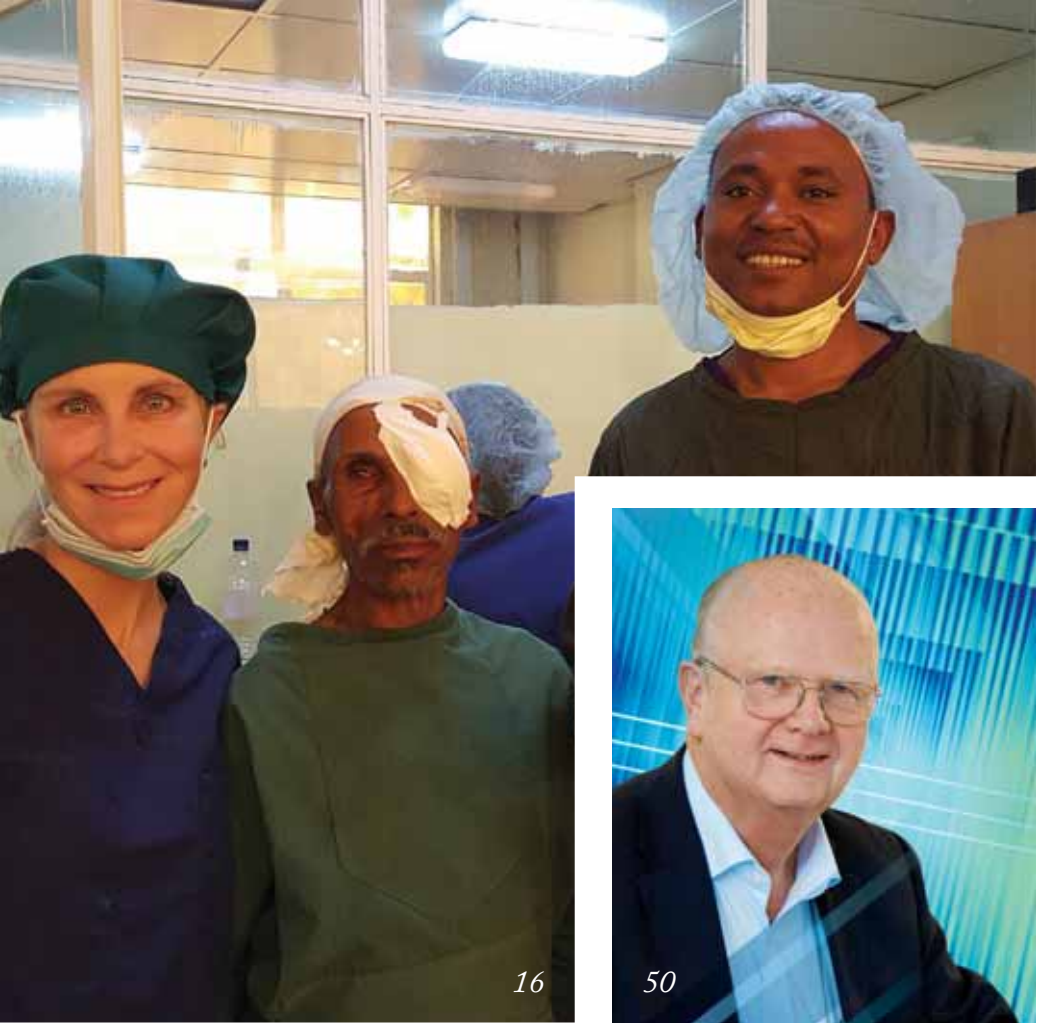


On The Cover

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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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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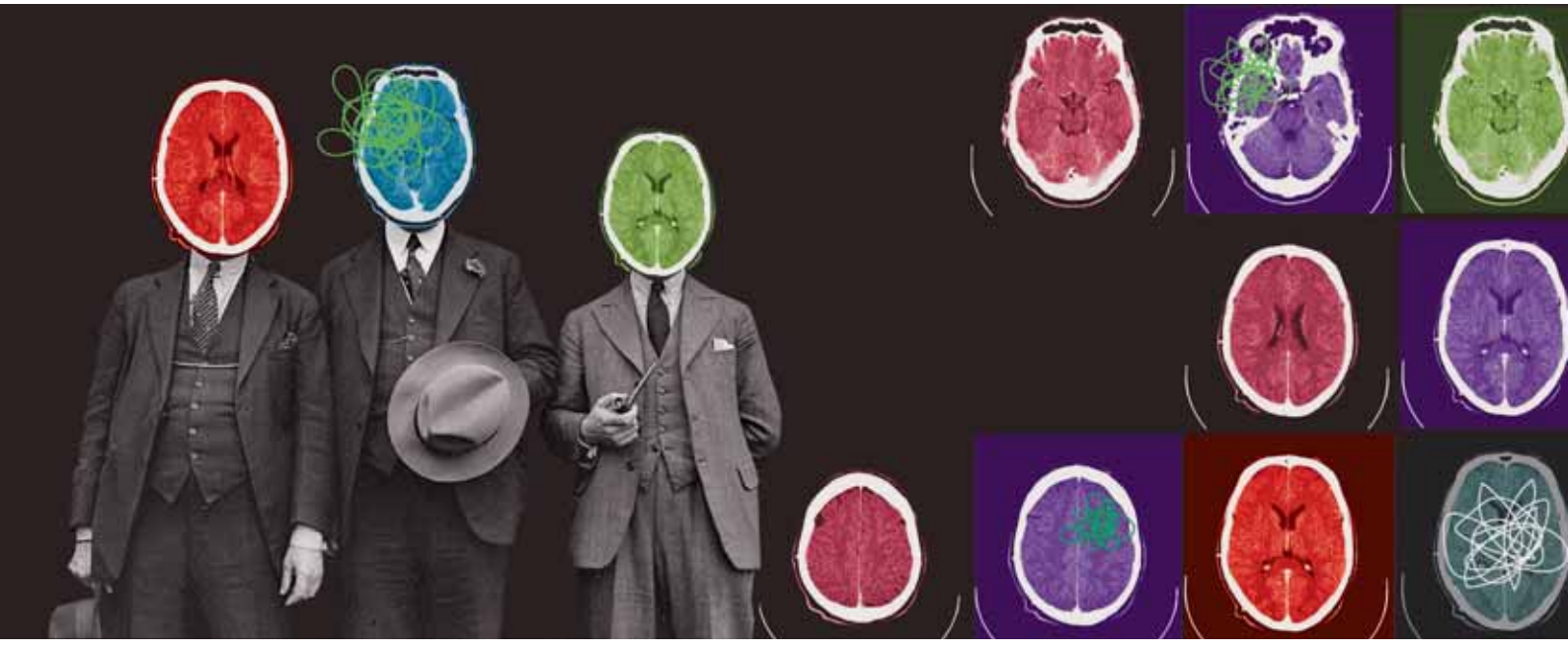

In My View

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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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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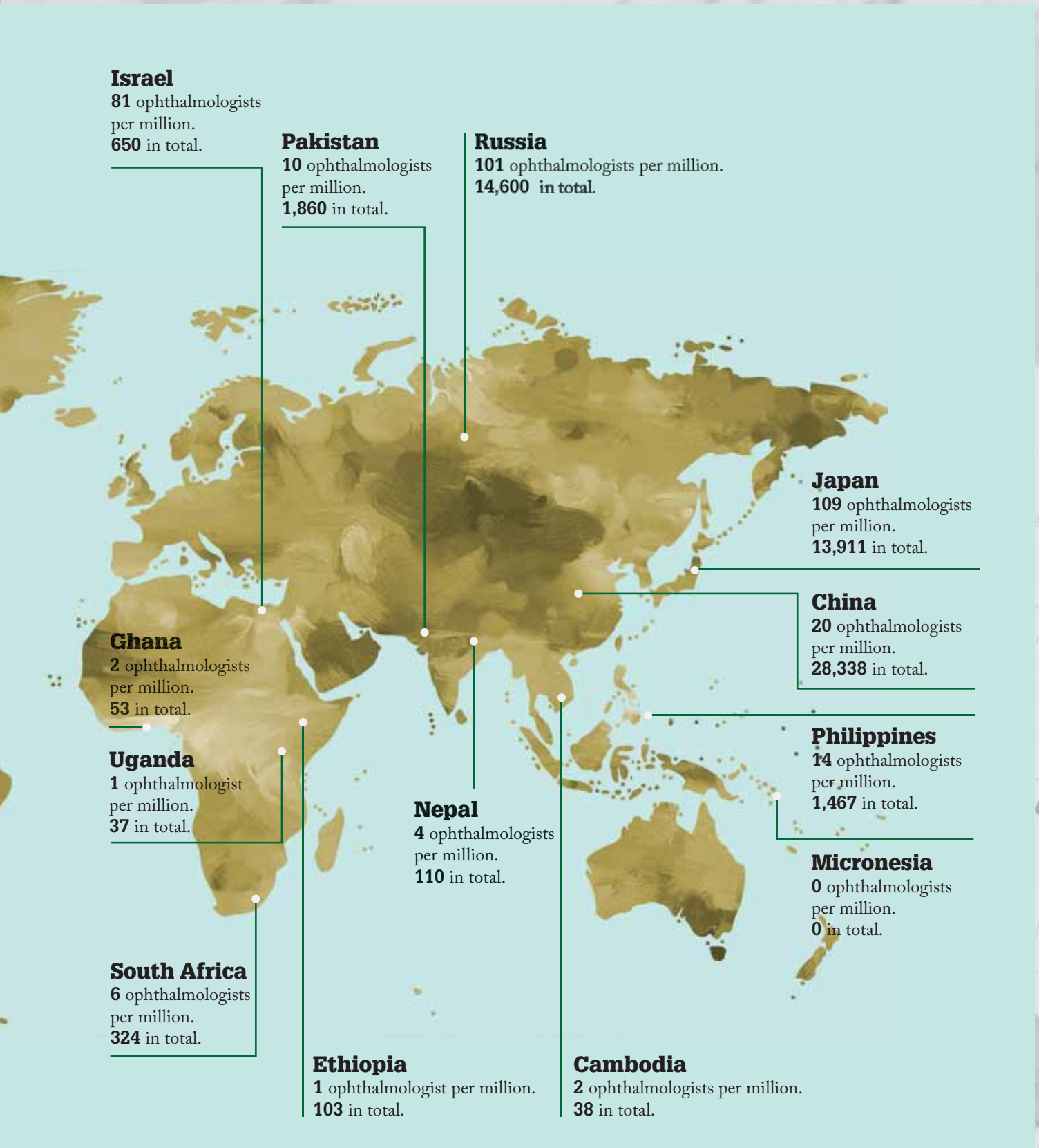

Israel
81 ophthalmologists per million.
650 in total.
Pakistan
10 ophthalmologists per million.
1,860 in total.
Russia
101 ophthalmologists per million.
14,600 in total.
Japan
109 ophthalmologists per million.
13,911 in total.
China
20 ophthalmologists per million.
28,338 in total.
Philippines
14 ophthalmologists 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?

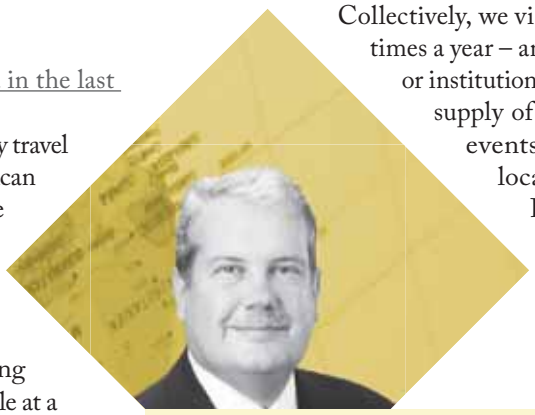
The group I work with is focused on Central American locations, primarily Honduras, with some work being done in El Salvador. I have about ten facilities and groups that I work with at any given time. The most comprehensive of those is the project in Western Honduras, in Santa Rosa de Copan. It is a 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.

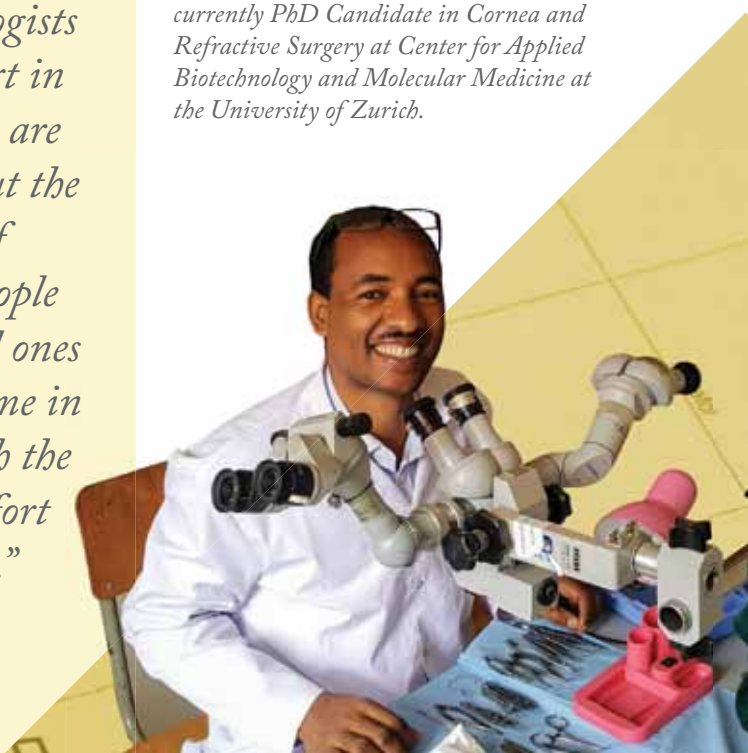
As cases are usually very advanced, and some are quite complicated, it is usually experienced surgeons who get invited to join the project. Unfortunately, there aren't many opportunities to train doctors while we are there, but we do get through a very high number of surgeries with very low complication 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...

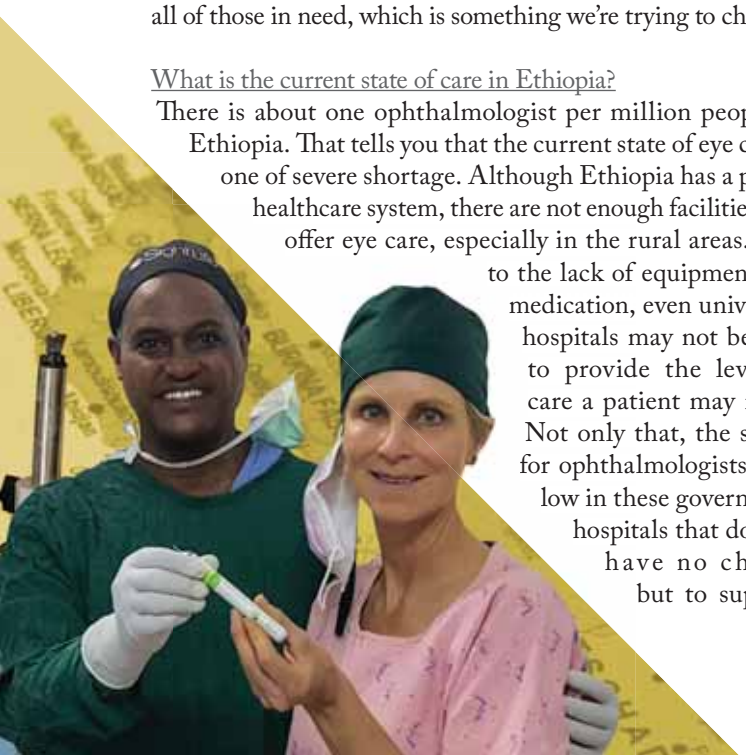
...and her work with the ASCRS Foundation in Ethiopia.

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 on 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.

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Cataract surgery is one of the most ubiquitous procedures in ophthalmology – in fact, it's the most commonly performed elective surgical procedure in the world today. With a strong history of innovation and development, today's cataract surgery offers better outcomes than ever – and this trend is set only to continue. Here, leading ophthalmic companies showcase their latest cataract surgery technology, and explain what these advances mean for you and your patients.

ALWAYS ILLUMINATING

Ultra-reliable red reflex, increased depth of field, and highly accessible settings make the Proveo 8 stand out from the crowd.

Meet Leica's Proveo 8 – a state-of-the-art ophthalmic microscope that enhances cataract surgery workflows by providing the exact image the surgeon needs at every phase of every procedure – all accessed with a simple tap of the footswitch.

When it comes to microscopy in cataract surgery, a stable red reflex is key; by ensuring clear visibility of the lens structure, the surgeon is presented with the best view for a safe procedure. But the significant challenge with conventional systems is that red reflex illumination often diminishes when it's needed most: during hydro dissection, phacoemulsification or cataract extraction.

Now, Leica's new CoAx4 Illumination uses four individual beam paths to overcome this challenge, providing unmatched stable red reflex for all observers; indeed, both the surgeon and the assistant are provided with the ideal contrast for visualizing the capsule, lens, and the anterior chamber structure. Ike Ahmed, Assistant Professor and the Director of the Glaucoma and Advanced Anterior Segment Surgery fellowship at the University of Toronto, Canada, is not shy about the impact of CoAx4 Illumination: "I was captivated by Proveo's unparalleled and consistent red reflex throughout the entire procedure."

Advanced illumination is not the only trick up Proveo's sleeve. Its unique FusionOptics boost depth of field by 40 percent – but without compromising resolution. The result? A much larger 3D visualization – in focus – which provides surgeons with clear anatomical details, right down to very small, delicate structures.

The Proveo has also been optimized for use in busy practices. It includes separate user settings for up to 30 user profiles, a feature that not only recognizes the fact that each surgeon has unique ergonomic preferences for maximum comfort – but it also saves valuable set-up time.

Another time saving and workflow enhancing feature is the Combination Mode, which allows surgeons to pre-define and program specific levels of light, focus and magnification for up to five procedure phases (for example, capsulorhexis, phacoemulsification, irrigation/aspiration, posterior capsule polishing, IOL positioning in cataract surgery). And how are the programmed settings for the next phase activated? "With the Proveo 8, I customize the light settings by a simple click on the foot switch," explains Devesh Varma, Assistant Professor in the Department of Ophthalmology and Vision Sciences at the University of Toronto.

And there's no need for users to reset all the major functions of the microscope (zoom, focus, light and XY) to zero – the Proveo 8 performs the task automatically, resulting in further time savings.

As a busy cataract surgeon, you want to make better-informed decisions – fast. By simplifying access to exactly the right image at exactly the right time, the Proveo 8, with its host of advanced features, helps avoid interruptions and streamlines your workflow.

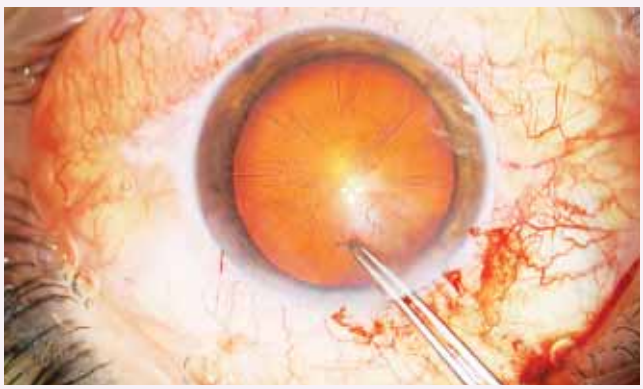

Figure 1. CoAx4 illumination provides a stable red reflex during capsulorhexis.

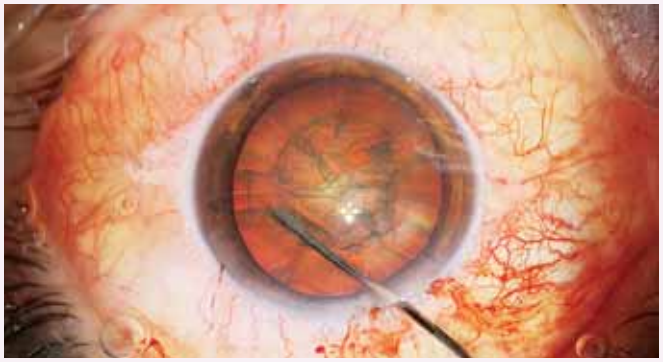

Figure 2. Hydro dissection with excellent and stable red reflex illumination during challenging conditions.

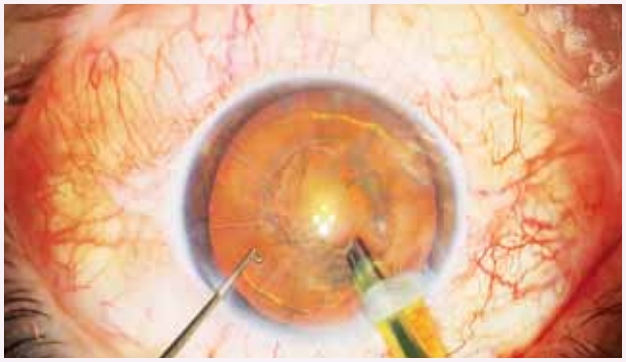

Figure 3. Throughout the Phaco process, the new Proveo 8 provides unparalleled optical visibility with contrast, color rendition and crispness, making it a powerful tool when dealing with challenging cases.

Figure 4. During cortex removal, there is no need for adjustments to light settings for higher values or refocusing, thanks to the transparent Leica optics and unique FusionOptics technology.

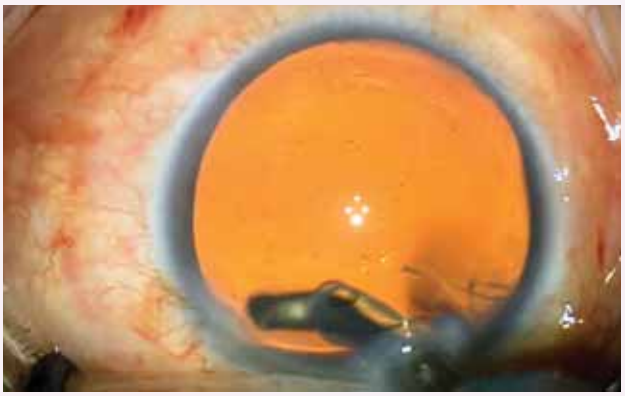

Figure 5. Posterior capsule polish, with excellent resolution.

Figure 6. During IOL preparation, simply tap the assigned foot switch button to activate the Quick Focus. The Optic Carrier moves to a pre-programmed focal plane to help the user to quickly prepare the IOL before placement.

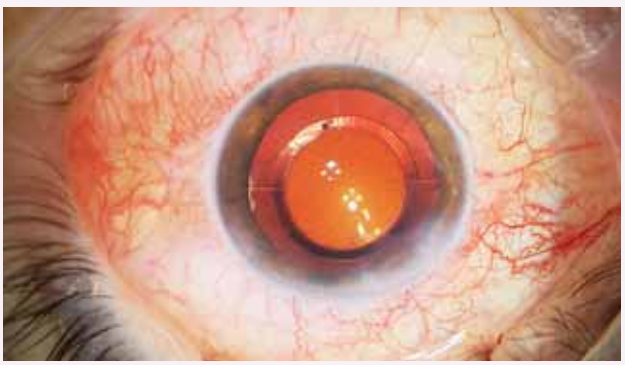

Figure 7. IOL placement is made easy, with the option of coming back to the initial focal plane to place the IOL available with just one tap.
Images courtesy of Dr. Fabio Dornelles, Porto Alegre, Brazil.

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FROM INTELLIGENCE COMES PERFECTION

The AI-driven Hill-RBF 2.0 pushes the boundaries of accuracy in IOL predictions

HAAG-STREIT DIAGNOSTICS

Standard keratometric and topography machines tend to yield varying degrees of inaccuracies when it comes to assessing corneal astigmatism. But in today's competitive healthcare climate, any amount of inaccuracy is simply not good enough. Patients want perfection. If surgeons are to achieve truly accurate IOL predictions – even in torical applications – a new approach is needed. Enter the Hill-Radial Basis Function (Hill-RBF) 2.0.

Unlike theoretical formulas, the Hill-RBF 2.0 selects IOL power using AI-driven pattern recognition rather than effective lens position. Based entirely on data, and so free of calculation bias, it works by analyzing and processing real-world data collected by leading cataract surgeons. The powerful combination of artificial intelligence and data extrapolation results in highly accurate IOL predictions – 94.8 percent within ±0.5 D in all eyes, to be precise. To make sure that figure is as accurate as possible, the Hill-RBF also runs a reliability check. If it does not have sufficient data to make an accurate prediction of IOL power, it informs the surgeon. The benefits are two-fold: greater confidence for surgeons and better postoperative outcomes for patients.

So what makes the Hill-RBF 2.0 so accurate and effective? The first reason is simple: intelligent design. Hill-RBF 2.0 is the only approach that uses adaptive learning and an enormous dataset – three times larger than that of the previous version. Currently encompassing more than 12,400 eyes, the number will continue to grow in the coming years as more surgeons add to the dataset. And as the likelihood of similar eyes increases, the accuracy of IOL predictions increases too.

The second reason behind the accuracy of Hill-RBF 2.0 is its use of the Abulafia-Koch algorithm, which is how it compensates for the posterior corneal astigmatism effect. The formula, based on a regression model created by Doug Koch and Adi Abulafia, works on the premise that post-operative astigmatic outcomes can be optimized by calculating total corneal astigmatism with corrected magnitude and meridian, using anterior curvature-based corneal measurements. And research confirms it. In a study into predicted refractive astigmatism, standard calculators reported errors between 0.55 and 0.75 diopters – while the Hill-RBF reported errors of just 0.07 (1). It's just one study of many that demonstrate Hill-RBF 2.0's ability to reduce error and increase the accuracy of IOL predictions, even in torical applications.

Doesn't every ophthalmologist have the same goal: to provide the best possible care to their patients? With the Hill-RBF 2.0, available exclusively on the Lenstar 900 from Haag-Streit, the goal is made achievable. By harnessing an AI-powered, data driven approach, surgeons can feel more confident that they are recommending the best IOL for their patients – and, as the dataset continues to grow, so too will confidence levels.

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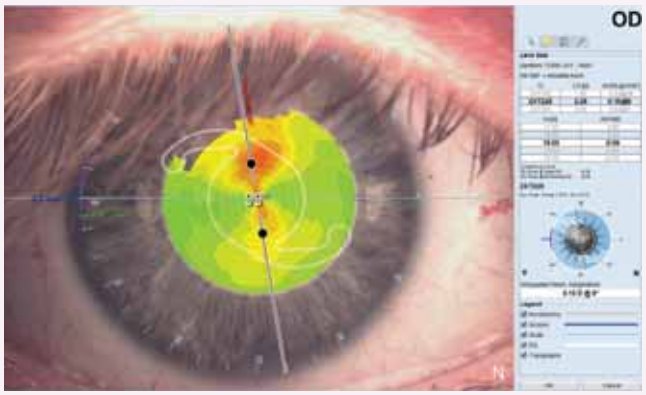

IN SAFE – AND SIMPLE – HANDS

The Faros™ platform from Oertli delivers the surgery outcomes you truly desire with easyPhaco® technology and the unique SPEEPMode™.

By combining proven technology and smart innovation, as well as renowned technical support, Faros™ – the latest surgical platform from Oertli – delivers a new standard for ophthalmologists performing cataract, glaucoma and vitreoretinal surgeries.

Pedro Moreira, from Trás-os-Montes e Alto Douro Hospital Center, Vila Real, Portugal, recognizes the winning combination: "Experiencing the Faros platform and the unique Oertli technical support enables me to achieve the best surgery outcome for my patients, enjoying the safety and the simple handling provided."

The Faros surgical platform certainly benefits from proven technology: easyPhaco® provides unprecedented chamber stability, efficient fragment aspiration and perfect emulsification, from soft to dense lenses. But it also introduces the new SPEEPMode™ – an innovation that allows easy but precise control of both flow and vacuum.

The cutting-edge dual-pump system at the heart of the platform is based on a fluidics system that does not rely on electronics or sensor systems, but instead commandeers the always-reliable laws of physics, making it is less prone to errors. The peristaltic pump system delivers the finest control with absolute precision to the surgeon – but is also

oertli SWITZERLAND

capable of delivering significant power, when needed. The pump wheel can also be triggered instantly and can be used for fine manipulation in the anterior and posterior segment. In SPEEPMode, the same precise flow can be set to a constant value, where it is actively regulated by the Faros platform. Whatever the mode of operation, the system's light and clearly readable display of the control field show the precise operating settings and values.

Even the dual-linear foot pedal itself exhibits the attention to detail and first-class quality you would expect from Oertli. Designed to increase comfort but also to sensitively follow the surgeon's commands, the pedal is extremely robust, waterproof and follows a compact format. Moreover, it can be programmed individually for up to 50 surgeons working in the same environment, and has four auxiliary buttons that can be used for bottle height adjustment, change of pump, light and air, and other assignment options.

In all aspects of the Faros platform, reliability and safety are the name of the game. As Qasim Qasem, from Imperial Healthcare Institute, Dubai, UAE, notes, "The Faros is reliable, efficient and delivers what is required in straightforward and complex cases."

Designed for safety in irrigation and aspiration, the "Quick Tips" have an extended shaft length to enable better sub-incisional access. And the reduced aspiration opening creates better occlusion power and allows perfect stability of the anterior chamber. Put simply, in combination with SPEEPMode, Quick Tips offer the highest degree of safety.

Meanwhile, the HF capsulotomy tip makes capsulorhexis amazingly simple by using high-frequency energy; the capsule bag can be melted easily – and fully – without any of the usual tearing with forceps and needle.

In operative treatment of glaucoma, Faros brings about significant added value in micro-invasive glaucoma surgery (MIGS). High Frequency Deep Sclerotomy (HFDS) creates direct access to the Schlemm's canal from the anterior chamber, thus avoiding outflow resistance of the trabecular meshwork. Despite the short intervention time, excellent long-term results are achieved while the complication rate is very low.

In summary, the Faros platform is designed with reliability, safety and improved performance at its core. But in doing so, it does not neglect the need to save time and money – it is ready for operation in just seven seconds, speeding up preparation for surgery. All instruments are perfectly integrated into the surgical system. Most consumables are available as single use or reusable instruments.

The overall result? Carlos Leon, Centro Oftalmológico Leon, Guatemala City, Guatemala, says, "The Faros™ provides precision and confidence in every procedure."

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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.

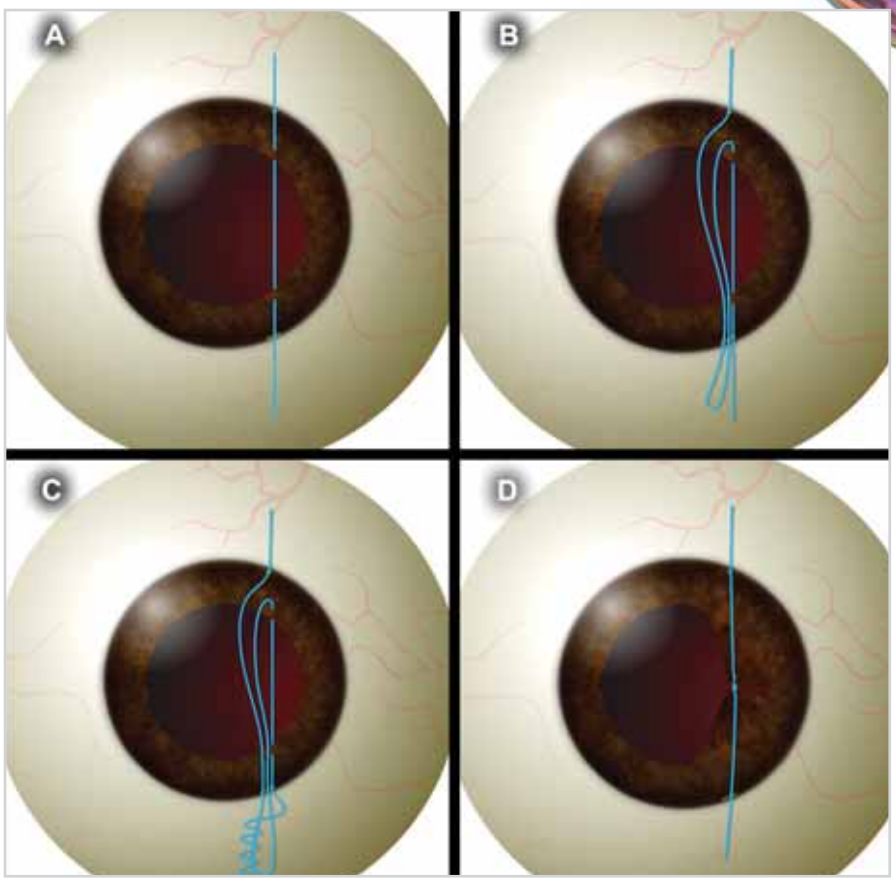

Figure 1. Surgical technique of single pass four throw (SFT)
A – The 10-0 suture is passed through the proximal and distal iris tissue.
B – A loop of suture is withdrawn from the anterior chamber with a Sinskey's hook.
C – The suture end is passed through the loop four times.
D – Both the suture ends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

A recent study has demonstrated 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

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.*

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.

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.

(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.

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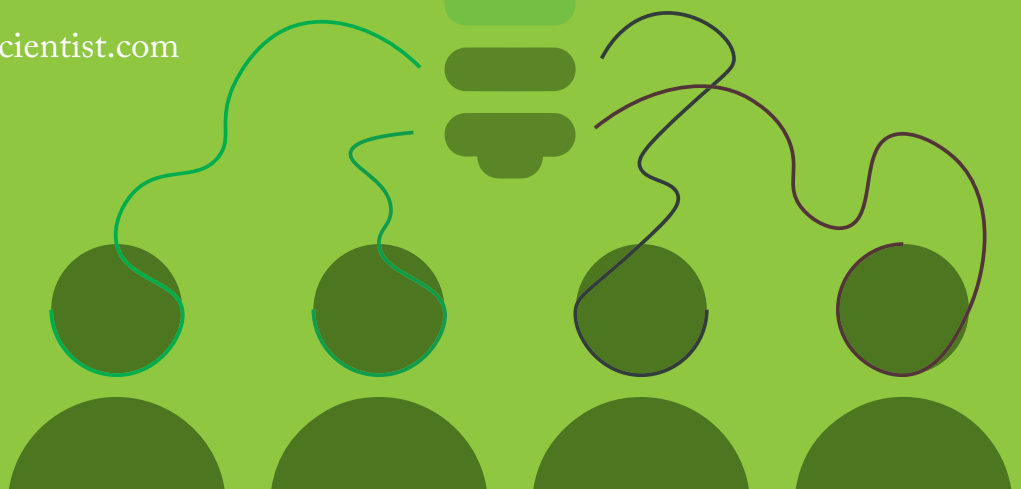


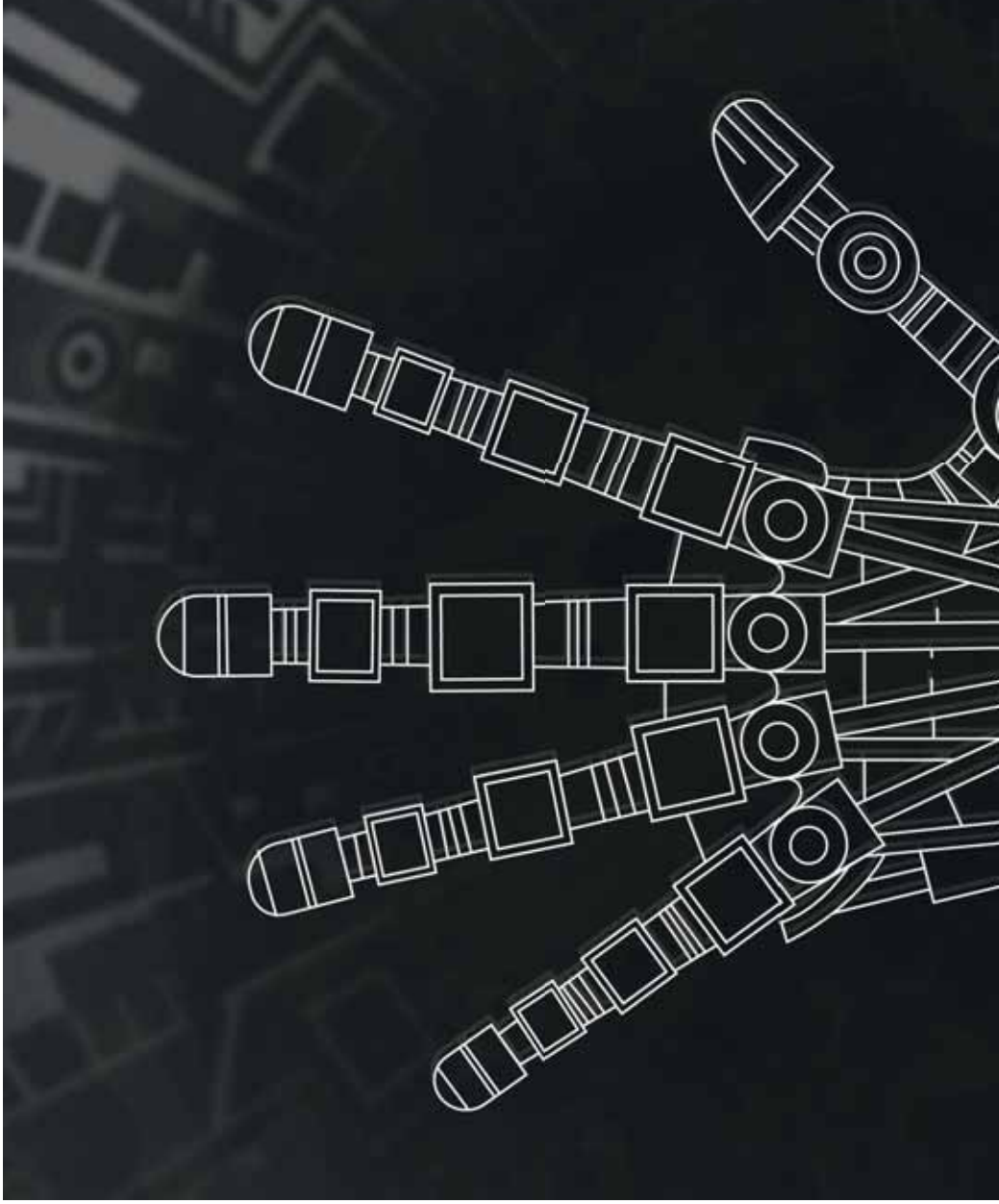
NextGen

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.

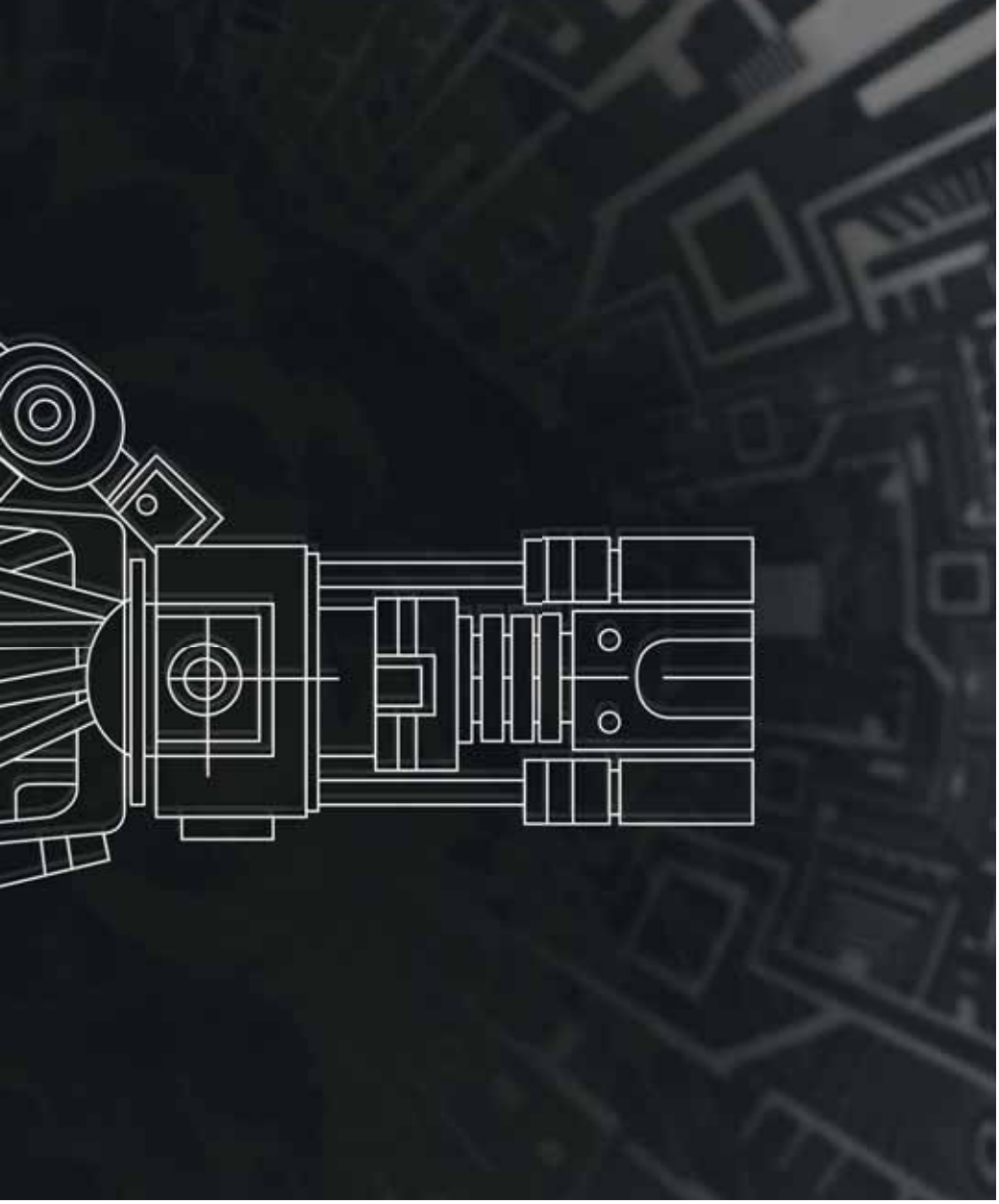
At a Glance

- *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
The research was funded by the NIHR Invention for Innovation Programme. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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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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

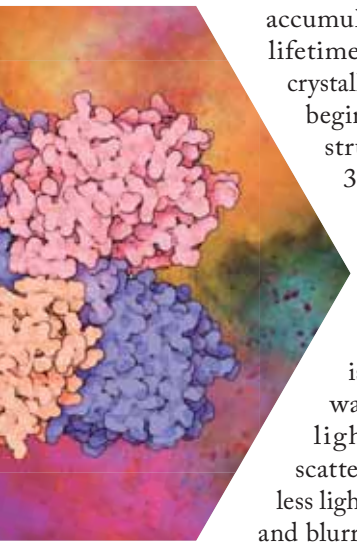
- *Over time, crystallins stick together to form aggregates – leading to the formation of cataracts*
- *Wild-type (undamaged) crystallin promotes aggregation of the mutant version – without itself aggregating*
- *Evidence of oxidation–reduction between molecules disproves the long-held theory that crystallins 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.*

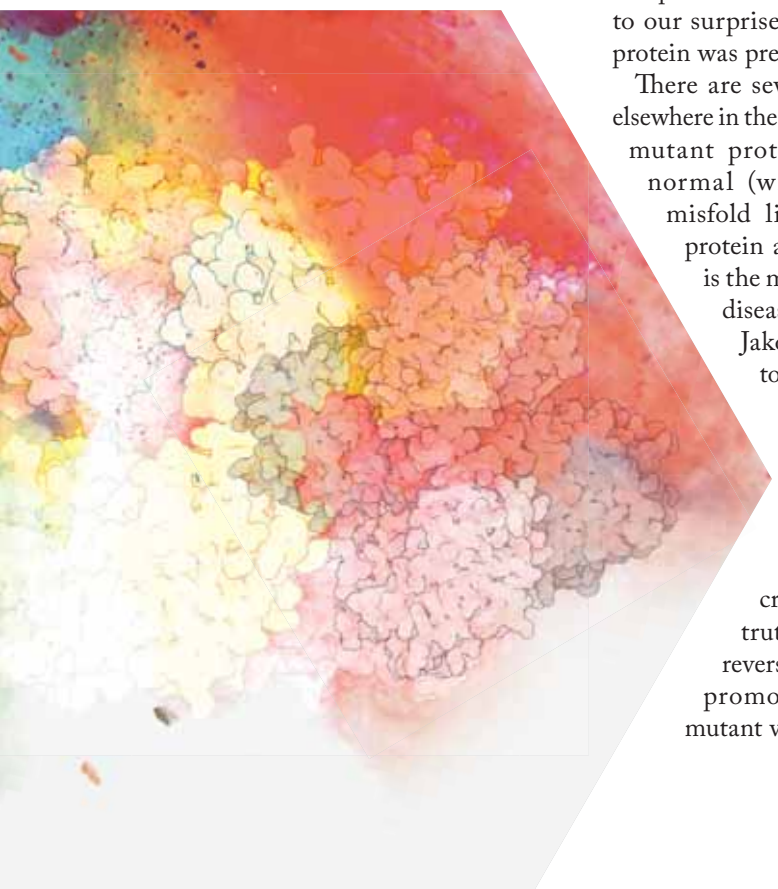
What led you to study crystallin proteins?

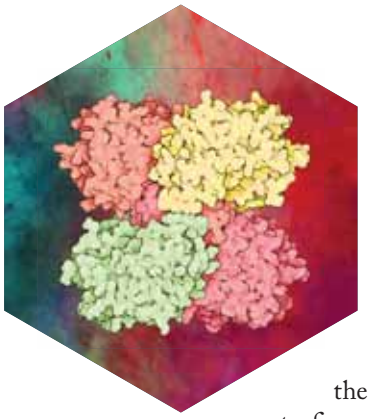
The eye lens proteome is fascinating because it has evolved to minimize light scattering. That means it must resist aggregation because protein aggregates (clumps of many molecules of a protein) scatter visible light. Yet, the protein molecules in the core region of the lens are synthesized before birth 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.

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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

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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.

References

1. *E Serebryany, JA King, "Wild-type human γD-crystallin promotes aggregation of its oxidation-mimicking, misfolding-prone W42Q mutant", J Biol Chem. 290, 11491-11503 (2015). DOI: 10.1074/jbc.M114.621581.*
2. *E Serebryany, JC Woodard et al., "An internal disulfide locks a misfolded aggregation-prone intermediate in cataract-linked mutants of human γD-crystallin", J Biol Chem, 291, 19172-19183 (2016). DOI: 10.1074/jbc.M116.735977.*
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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.

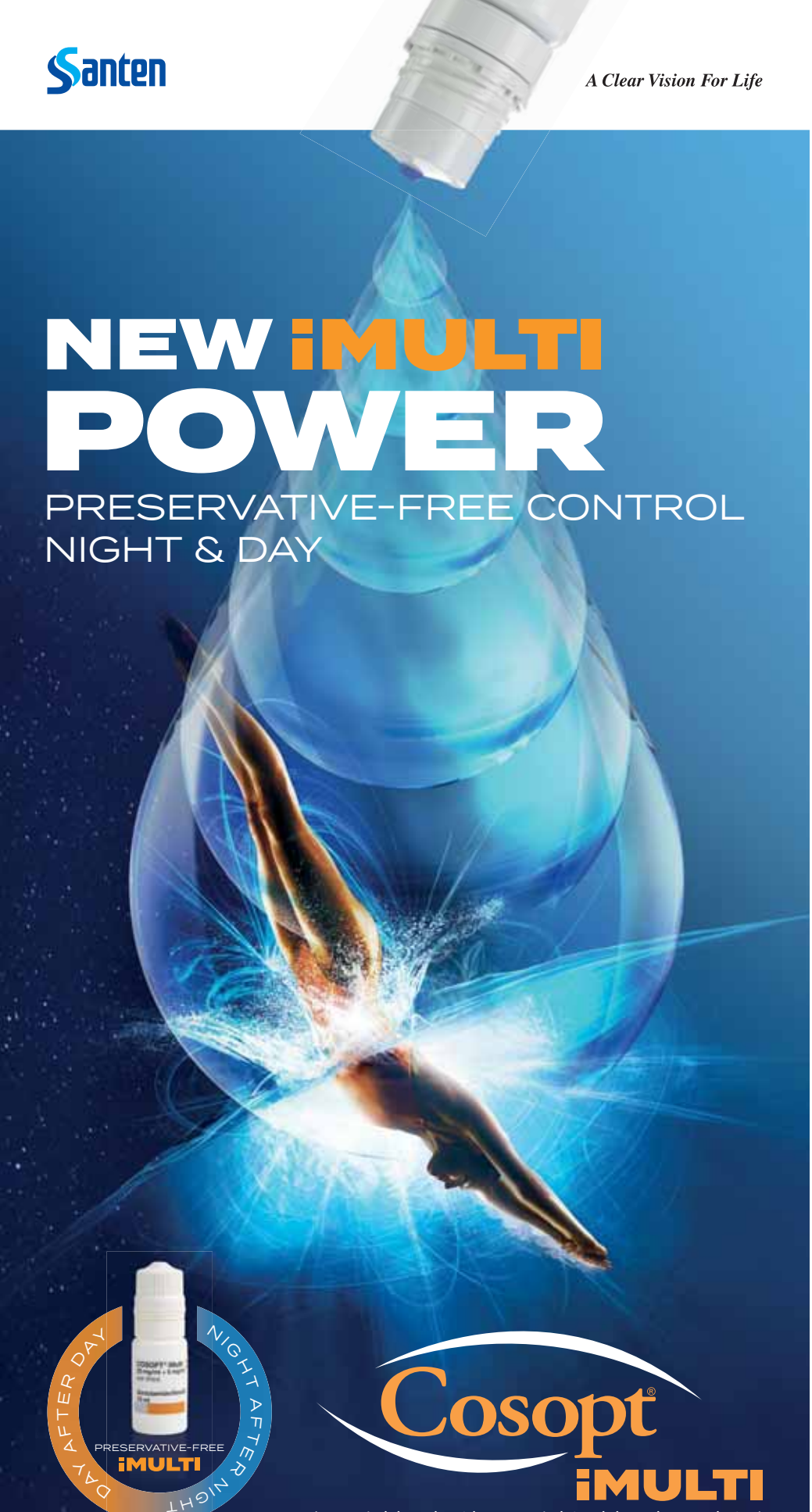
"For me, learning how to learn was one of the most important lessons at university."

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.

Santen

A Clear Vision For Life



Abbreviated Prescribing Information

Product Name: COSOPT® Preservative-Free 20 mg/ml + 5 mg/ml, eye drops, solution, single-dose container. COSOPT® iMulti 20 mg/ml + 5 mg/ml eye drops, solution.

Composition: Each millilitre contains 20 mg dorzolamide (22.26 mg dorzolamide hydrochloride) and 5 mg timolol (6.83 mg timolol maleate). Please refer to the Summary of Product Characteristics (SmPC) for a full list of excipients.

Indication: Treatment of elevated intra-ocular pressure (IOP) in patients with open-angle glaucoma, or pseudoexfoliative glaucoma when topical beta-blocker monotherapy is not sufficient.

Posology and Method of Administration: One drop of COSOPT in the conjunctival sac of the affected eye(s), two times daily. If another topical ophthalmic agent is being used, administer COSOPT and the other agent at least ten minutes apart. COSOPT is a sterile solution that does not contain preservative. Safety in paediatric patients less than 2 years of age has not been established. Please see the SmPC for use in children of more than 2 years.

Contraindications: Hypersensitivity to any component of this medicine, reactive airway disease, including bronchial asthma, or a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, sick sinus syndrome, sino-atrial block, second- or third-degree atrioventricular block not controlled with pacemaker, overt cardiac failure, cardiogenic shock, severe renal impairment (CrCl <30 ml/min) or hyperchloraemic acidosis.

Warnings and Precautions: The same types of adverse reactions found with systemic administration of beta-blockers or sulphonamides may occur, these include severe reactions seen with sulphonamides such as Stevens-Johnson syndrome and toxic epidermal necrolysis. In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and therapy with other active substances should be considered. Patients should be watched for signs of deterioration and adverse reactions. Beta-blockers should only be given with caution to patients with first degree heart block. Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution. Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. Use with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk. Use with caution in patients with hepatic impairment. Concomitant use of dorzolamide with oral carbonic anhydrase inhibitors is not recommended. Use of two topical beta-adrenergic blocking agents is not recommended. Caution in patients subject to spontaneous hypoglycaemia or with labile diabetes. These signs and symptoms of acute hypoglycaemia and hyperthyroidism may be masked. Caution in patients with corneal diseases. The anaesthetist should be informed when a patient is receiving timolol as beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. Though no acid-base disturbances have been observed with COSOPT (preserved formulation), patients with a prior history of renal calculi may be at increased risk of urolithiasis. Patients with acute angle-closure glaucoma require therapeutic interventions in addition to ocular hypotensive agents. This medicinal product has not been studied with acute angle-closure glaucoma. Corneal oedema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intraocular surgery while using dorzolamide. Precautions should be used when prescribing in these groups of patients. Patients with a history of contact hypersensitivity to silver should not use COSOPT iMulti as dispensed drops may contain traces of silver from the container. This medicinal product has not been studied in patients wearing contact lenses. There is limited experience with COSOPT in infants and children. Please refer to the SmPC.

Interactions with Other Medicinal Products: There is a potential for additive effects resulting in hypotension and / or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, catecholamine-depleting drugs or beta adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, quanethidine, narcotics and monoamine-oxidase (MAO) inhibitors. Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol. Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

Pregnancy and Breast Feeding: Do not use in pregnancy or during breast-feeding.

Driving and using machines: Possible side effects such as blurred vision may affect some patients' ability to drive and/or operate machinery.

Undesirable Effects: (Refer to SmPC for complete information on side effects). The side effects observed with COSOPT or one of its components include: headache, depression, burning and stinging, conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing, eyelid inflammation, eyelid irritation, iridocyclitis, signs and symptoms of ocular irritation including blepharitis, keratitis, decreased corneal sensitivity and dry eyes and visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), ptosis, bradycardia, syncope, sinusitis, dyspnoea, dysgeusia, nausea and dyspepsia, urolithiasis, signs and symptoms of systemic allergic reactions, including angioedema, urticaria, pruritus, rash, anaphylaxis, asthenia/fatigue, hypoglycaemia, cardiac arrest, heart block, AV block, cardiac failure, chest pain, palpitation, oedema.

Overdose: Treatment should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Special Precautions for storage: Do not store above 25°C.

Price: COSOPT Preservative-Free 60 x 0.2mL single-dose containers £28.59; COSOPT iMulti 1 x 10ml bottle (60 days treatment) £28.00.

MA Holder: Santen Oy, Niittyhaankatu 20, 33720 Tampere, Finland.

MA Numbers: COSOPT Preservative-Free PL 16058/0015 COSOPT iMulti PL 16058/0025

Legal Category: POM

Date of Prescribing Information: September 2018.

Job Code: NP-CSPTPF-UK-0005

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Santen UK Limited (Email: medinfo@santen.co.uk or telephone: 0345 075 4863).

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