AUGUST 2018 # 56

the Ophthalmologist™

Good Business

The story of Epipole – a balancing act of doing the right thing and running a sustainable company.

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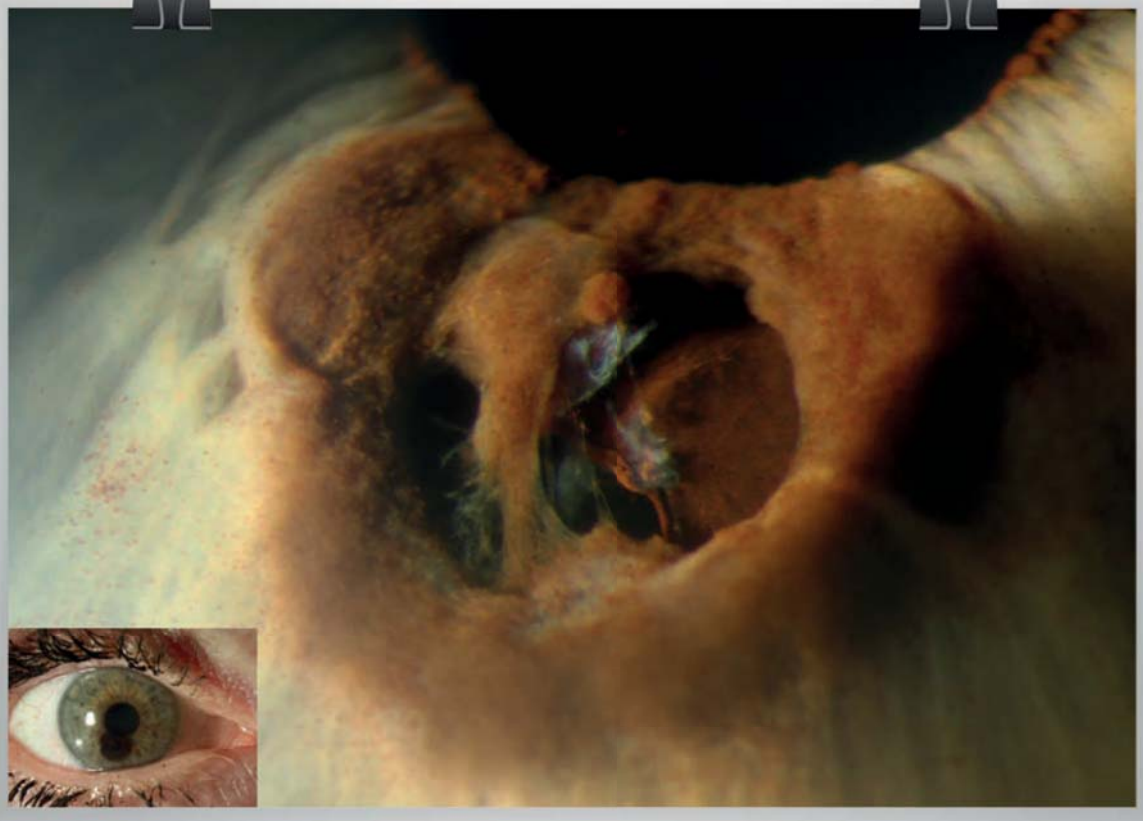

Pele: Goddess of Volcanoes

This image was submitted to us by Houston Sharpe III, an ophthalmic imaging specialist with 10 years of ophthalmic experience in imaging and clinical operations. It shows a high magnification slit lamp image of a large iris nevus, resembling a broiling volcano. Sharpe also acts as Chair of the Scientific Exhibit Committee for the Ophthalmic Photographers' Society.

Credit: Houston Sharpe III, ophthalmic imaging specialist.

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

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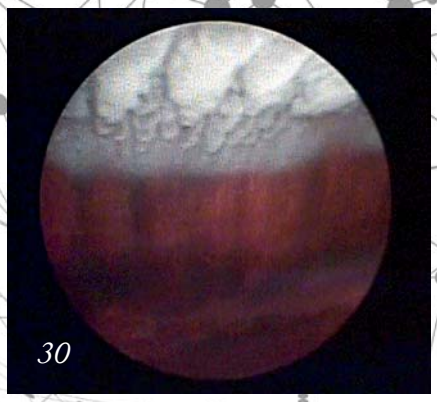

On The Cover

Craig Robertson, Founder of Epipole and cover feature author, holding one of his devices.

Upfront

In My View

Feature

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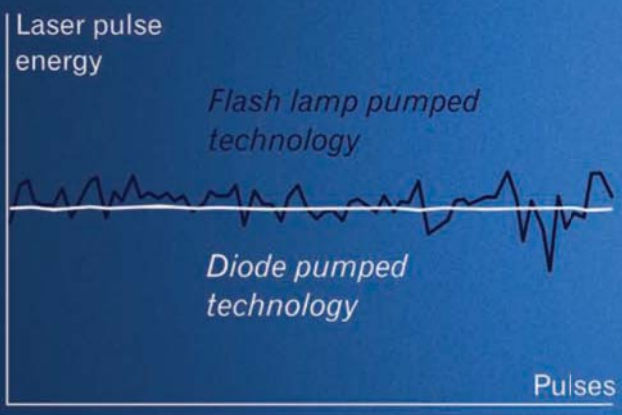

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ISSUE 56 - AUGUST 2018

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Distribution
The Ophthalmologist (ISSN 2051-4093),
is published monthly by Texere Publishing,
Haig House, Haig Road, Knutsford,
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Modern Medicine's Makeunder

What goes up must come down. And what goes forward can always come back to serve the many, not the few

Craig Robertson shares the story of Epipole in our cover feature (page 16) – and it was a tale we were more than keen to tell. Founded to help bring advanced yet inexpensive imaging technologies to neglected countries, Epipole has centered its business model on 'doing good' – but have experienced commercial success along the way.

Clearly, companies need to make money, not only to keep the 'lights on', but also to drive research and development, and to iteratively improve upon technologies and treatments. But it seems to me that, with the wonders of the modern world, there exists the potential for disruptive low-cost solutions that can make a huge difference to those who need it most. And that's precisely what Robertson and his team have focused on; through cunning, perseverance (and not the pursuit of profit), they have adapted high-tech imaging solutions to provide inexpensive and portable fundus imaging devices – and all without compromising quality.

And they're not alone in providing neglected markets with feasible solutions. In our June issue, Sean Ianchulev shared the story of miLOOP, the low cost microinterventional cataract surgery device that is helping to tackle the backlog of global cataract blindness (1). For countries or rural communities where phaco machines aren't readily available – or affordable – the device is proving to be a gamechanger. Many surgeons in more technologically-advanced markets are also praising the device for its simplicity and its effectiveness in hard cataracts. Even the humble ophthalmoscope, which does not come with a prohibitive price tag for many, received a makeunder: back in 2017, William J Williams, Andrew Blaikie and John Sandford-Smith told their wonderful story of Arclight, the $6 ophthalmoscope that is improving eyecare for millions (2).

There will always be a place for advanced technologies that push ophthalmology and medicine into exciting new realms of possibility – as well as the markets and interest to support them. But equally, there is also a place – and, as Epipole exemplifies, a market – for more affordable, more portable, or more efficient solutions that increase the accessibility of healthcare. It delights me to see companies risking it all by driving development in a different direction or by putting a positive spin on the concept of a 'makeunder' – in doing so, they are satisfying unmet needs across the globe.

Ruth Steer
Managing 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

Where Are They Now?

Re-dropping the needle: topical anti-VEGF therapy revisited

In June 2017, we reported on a study that demonstrated topical delivery of anti-VEGF antibodies to the posterior segment, and how the findings showed the potential to release AMD patients from the burden of monthly injections (1). The hero? Cell penetrating peptides (CPPs) that can act as chaperones to facilitate the uptake of anti-VEGF complexes.

In their 2017 publication, the team – led by Felicity de Cogan of the University of Birmingham, Birmingham, UK – showed that CPP-anti-VEGF complexes successfully reached the posterior segment in rat and porcine eyes, and that they could reduce lesion size in a mouse model of choroidal neovascularization (2).

But where are they now? The group have pushed their treatment one step further, and recently shown that topically applied CPP complexes (with either bevacizumab or ranibizumab) can reach the retina in both rabbit and porcine eyes, and have also quantified how much anti-VEGF was delivered (3). Also, Macregen, Inc, now owns the pending patents for the treatment, and a collaboration between the US-based company and the team is in place to develop novel therapies for AMD and other eye diseases. On the collaboration, de Cogan said: "We welcome the commercial investment and expertise from Macregen so we can deliver a structured research and development program that should bring concrete benefits to people with AMD and eye diseases" (4).

With proof of concept studies currently being expedited, and clinical trials set to start as early as Q2 in 2019, how soon might patients be able to "drop the needle?"

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Eat to Beat AMD

Meet the foods halting AMD progression – and those responsible for 'speeding' it up

What do Shanghai and San Sebastian have in common? According to science – more than you think. A team at the University of Auckland, led by Naoko Chapman, has found that Oriental and Mediterranean diets are beneficial for those at risk of AMD.

Their systematic review (1) analyzed 18 studies and found that adherence to a Mediterranean diet – characterized by high consumption of fruits, vegetables, legumes, wholegrains, and nuts – decreased risk of late AMD progression. Similarly, an Oriental diet pattern – which resembles the Mediterranean diet in volume of fruit, vegetables, legumes, tomatoes, and seafood – decreased association with early and advanced AMD prevalence. In contrast, the high-glycemic Western diet pattern – categorized as having a high intake of red meat, high-fat dairy products, processed meat, fried potatoes and refined grains, as well as alcohol consumption of more than two units per day – increased association with early and advanced AMD prevalence.

"When I started this research I was looking for a simple answer," says Chapman. "However, the evidence showed that there were multifactorial influences of diet and food intake on the incidence and progression of AMD." The upshot? "Health professionals need to check that their own views of what constitutes a healthy diet are consistent with the evidence base, and help patients consider – what might be for some far-reaching – changes in diet".

These findings add weight (no pun intended) to existing research that has focused on modifiable risk factors, such as diet and antioxidant supplementation, to protect against AMD. And the evidence keeps mounting. Researchers at the University of Sydney, Australia, assessed the dietary intake of flavonoids in 2,856 adults aged 49 years and younger, with 2,037 followed up 15 years from baseline (2). They found each 1 standard deviation (1-SD) increase in flavonoid intake – the bioactive compounds found in tea, chocolate, red wine, fruit, and vegetables – was associated with a reduced likelihood of AMD. Furthermore, study participants that reported eating ≥1 orange – a key source of flavanones – per day were found to have a reduced risk of late AMD 15 years later compared with those who didn't consume oranges at baseline (odds ratio: 0.39; 95% CI, 0.18–0.85).

So how many oranges are needed to prevent the onset of AMD? Apparently, as little as one a week. Bamini Gopinath, lead author on the associated study (2), says, "We were not hugely surprised that certain flavonoids were protective against the risk of AMD, but what did surprise us is that oranges, which contribute to the intake of a particular flavonoid subclass – flavanone – were so strongly protective against late AMD."

Gopinath's study provides further evidence that flavonoids could be capable of not only reversing oxidative stress and inflammation-associated damage, but also improving vascular function and thus, possibly the clinical features of AMD. "Dietary modifications can not only slow the evolution of established AMD, but represent one of the only means of delaying the onset of the condition," she says. "Therefore, paying attention to what we're eating could help to minimize our risk of developing AMD."

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The Pitter-Patter of Tiny Diagnoses

A simple yet accurate model could help streamline ROP screening

Every year, retinopathy of prematurity (ROP) affects between 400 and 600 infants in the US (1). ROP continues to be a leading cause of strabismus, amblyopia, and severe near-sightedness in premature babies – and can lead to total vision loss, if not diagnosed and treated quickly. And therein lies the problem: the current model has low specificity for predicting which premature infants are most at risk of severe ROP; only 5–10 percent of those selected for a screening examination go on to receive treatment. But that looks set to change – thanks to a new model that boosts accuracy while maintaining, or even improving upon, sensitivity (1).

"Prior approaches were successful but limited by development studies that were too small, resulting in overfitted models and relatively complex calculations," says Gil Binenbaum, who led the study. "But despite these limitations, we suspected we could combine successful ideas from each group of investigators into a more effective approach." And thus, a hybrid model was born.

Together with a multi-hospital team he analyzed 7,483 premature infants born in 29 hospitals in the US and Canada between 2006 and 2012 in a retrospective cohort study. Infants included were at risk of ROP and had a known ROP outcome. "We knew we had to use as large a cohort as possible so that we could develop a new model that is easy to use and more accurately identifies all premature infants who are at high-risk of developing severe ROP," said Binenbaum (2).

The study identified six key criteria that could be used to determine whether a child should receive a screening examination for ROP: birth weight (BW) below 1,051 grams (about 2.3 pounds), gestational age (GA) at birth younger than 28 weeks, hydrocephalus, and slow weight gain during three time periods between the ages of 10 and 40 days. Using these six criteria, they were able to correctly predict 100 percent of infants with "type 1 ROP" – those requiring treatment – while reducing the number of premature infants who would undergo examinations by 30.3 percent.

Binenbaum added, "The criteria we developed were highly sensitive; in fact, they were slightly more sensitive that the current screening guidelines, and yet they were much more accurate than the current guidelines."

Current ROP screening criteria – based on BW, GA at birth, and a third, poorly defined screening criterion for heavier, older infants – relies on the judgement of the neonatologist. Under these guidelines, 70,000 infants are examined annually in the US – 69,400 more than have the disease. As these recommendations have the potential to significantly reduce the number of eye examinations being performed, could they ease the burden for parents, nurses, and doctors, who are already dealing with other issues associated with premature birth?

"Using these modified screening criteria could potentially reduce the number of babies who need to be examined by almost a third, which would be beneficial for those infants, and allow us to focus all our efforts on treating those who are at high risk for retinal detachment and blindness," says Binenbaum. "The next step is to validate these encouraging results in a second large clinical study before actually using the new criteria in practice."

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Reading Between the Lines

Are deficits in visual function more frequent in children with developmental dyslexia?

Developmental dyslexia (DD) is a common learning disability, estimated to affect between 5 and 10 percent of the US population (1). Although researchers agree on its origins, there are still facets of the disorder that are not fully understood – including whether visual processing deficits are more prevalent in children with DD. Now, an observational study involving 29 school-aged children with DD and 33 typically-developing (TD) children has attempted to provide an answer (2).

"We set out to initially determine whether visual function deficits are in fact more prevalent in children with developmental dyslexia", says Aparna Raghuram, who led the study. "Establishing that such differences exist would be essential as a basis for any further studies to evaluate whether treating vision makes sense."

Participants spent two hours undergoing psychoeducational testing, comprehensive eye examinations, and visual function measures – assessing vergence, accommodation, and ocular motor tracking. Ocular motor tracking was evaluated two ways – with a printed test and infrared eye tracking – and all parametric analyses for the vision measures were adjusted for age and sex.

Children with DD exhibited more deficits in peripheral visual function – specifically vergence, accommodation, and/or ocular motor tracking – than the non-randomized group of TD children: 23 children (79 percent) in the DD group had deficits in one or more domain of visual function, compared with 11 children (33 percent) in the TD group ($p<0.001$).

"This study provides evidence that visual function deficits are prevalent in children with DD" says Raghuram. "Hence, it would be premature for clinicians and educators to discount a potential role for visual function in some children with DD until more is known. By the same token, however, our findings do not establish that visual deficits are the primary cause of dyslexia, even if visual deficits play a role."

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In My View

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

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

Contact the editor at edit@theophthalmologist.com

V for DME

More recent research suggests that vitrectomy works in DME – and that it might be the cost-effective treatment we're looking for

By J. Fernando Arevalo, Edmund F. and Virginia B. Ball Professor of Ophthalmology, Wilmer Eye Institute, Baltimore, MD, USA

Diabetic macular edema (DME) is a major cause of visual impairment. It is currently treated with anti-VEGF therapy – but it might not stay that way for much longer. As private insurers and national health care systems struggle to manage the escalating costs associated with monthly anti-VEGF therapy, it is obvious that a long-lasting, reasonably priced treatment for DME is needed – and I think vitrectomy could be the answer.

Vitrectomy removes traction, eliminates vasoproliferative factors, and improves oxygenation. But despite several retrospective and prospective studies showing that vitrectomy significantly decreases DME, it is not yet supported by good clinical evidence. Many of the existing studies lack consistent enrollment criteria, control groups, and standardized measurements of visual acuity (VA), as well as the use of more advanced OCT technology.

The DRCR.net study is one such example; it showed that vitrectomy effectively decreases DME, but only eyes with vitreomacular traction experienced an average of 3 letters improvement in VA (1). The trial, however, only enrolled "eyes that in the estimation of the investigator would not benefit from any other therapy." In other words, the use of vitrectomy was a last resource. Another study by the DRCR.net included eyes without vitreomacular traction, and found that average central subfield thickness improved from 412 µm to 278 µm at 6 months but median VA remained unchanged at 20/80 (2). Greater improvements in VA occurred in eyes with worse initial VA and epiretinal membranes. Older trials, including those performed by the DRCR.net, have used time domain (TD)-OCT to evaluate the macula; however, though TD-OCT is proficient at accurately and reproducibly measuring macular thickness, it is incapable of evaluating outer retinal morphology.

But things are looking up. More recent trials have attempted to correlate the integrity of the external limiting membrane (ELM) and IS/OS lines, as visualized by spectral domain (SD)-OCT, with visual improvement after vitrectomy. Eyes with significant pre-vitrectomy defects in the ELM and/or IS/OS often experience favorable resolution of macular edema but do not actually achieve improved VA. In a retrospective analysis of eyes that underwent vitrectomy for DME, those with intact IS/OS lines improved by an average of 13.3 letters whereas those with IS/OS defects improved by only 3.9 letters (3). Therefore, outer segment findings on SD-OCT may be used to select patients who would be expected to do well visually after vitrectomy. In another study by Adelman et al., retina specialists from 29 countries provided clinical information on 2,603 patients with macular edema, including 870 patients with DME (4). They found that treatment with vitrectomy and ILM peeling alone resulted in better visual improvement when compared with other therapies.

In my view, vitrectomy for DME has not been adequately studied in eyes that still have the potential for visual improvement. To truly understand the potential of vitrectomy as a therapy for DME, a multi-center, prospective trial on preoperative SD-OCT is needed. If vitrectomy were shown to be as effective as ranibizumab or

aflibercept therapy, it would offer economic advantages too, as expenditure associated with vitrectomy management of DME are generally "front loaded" – meaning two-year costs may be only 1/10 of those incurred by anti-VEGF therapy. But we can only enjoy these benefits with the appropriate clinical research – and I look forward to seeing what might be revealed in the next few years.

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What's the Frequency?

The promise of round-the-clock IOP monitoring in glaucoma care: a Pandora's box?

By L. Jay Katz, Professor of Ophthalmology, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA, USA

At the present time, IOP remains the only clinically proven modifiable risk factor for glaucoma, and IOP measurements are vital for diagnosis and for judging the adequacy of therapy by reaching a target IOP. Daily diurnal IOP fluctuations are well-recognized – with particularly large 'swings' occurring in glaucomatous eyes. Although peak IOP has been definitively correlated with disease progression, and IOP fluctuation may be a separate risk factor for glaucoma, practicality has limited tonometry to a 'split second' in-office determination with patients in an upright position. Is this really an adequate sampling of IOP to drive clinical decisions?

An additional concern is the revelation that supine, nocturnal IOP is generally higher then upright, daytime IOP readings. Studies have also raised questions about activities that may lead to large IOP elevations, such as yoga, playing wind musical instruments, and sleeping on one side. There are also concerns about medical therapy inducing troughs and spikes in IOP as drug effects wane; consistent adherence with drug therapy; and the ineffectiveness of certain drugs at night. In other diseases, such as systemic hypertension and diabetes mellitus, there have been welcome advances in providing 24-hour measurements for advanced care, and it is great to see that those models have spurred a potential restructuring of glaucoma management.

Attempted methods to generate more IOP information have included performing in-office tonometry measurements at different times of the day and sleep laboratories dedicated to serial tonometry over 24 hours. But these options are of limited value since they are impractical for most, preventing widespread adoption into clinical practice. Fortunately, there are emerging, innovative methods on the horizon that promise a larger sample of IOP measurements through home tonometry and telemedicine (1).

Patients can now be instructed on the home use of the iCare rebound tonometer without any need for corneal anesthesia. The majority of patients have been able to master the instrument and obtain meaningful measurements that are reasonably close to the gold standard Goldmann tonometry values. In one study, use of the Icare tonometer led to an adjustment in therapy in over 50 percent of patients (2). Another available tool is the Triggerfish contact lens, which has imbedded strain gauges that are able to detect relative changes in IOP (but not in mmHg). Studies using the contact lens verified peak IOP times during surveillance and documentation of a response to therapy. Both the iCare tonometer and Triggerfish contact lens have gained international approval by regulatory agencies. Implantable IOP sensors that are surgically placed in the eye have also been developed, and early clinical trials have been conducted (3). Thousands of IOP measurements are possible daily, and that information may be transmitted to a computer or smart phone; the specific IOP data and its presentation in a meaningful, useful manner will evolve.

There may be initial resistance raised about the amount of IOP data, the additional work needed to interpret that data, and questions raised about reimbursement. However, rapid assessment of response to therapy, nonadherence and extent of IOP fluctuations are reasonable expectations. Such information will undoubtedly enable clinicians to offer more rapid and timely adjustments in therapy. The promise of novel 24-hour IOP monitoring technology – whether home tonometry or IOP sensors – will revolutionize and optimize glaucoma care with a triple win: fewer office visits, more cost-effective care – and better outcomes for patients.

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GOOD BUSINESS

In a sector strongly driven by shareholder value, is 'doing the right thing' a sustainable business model?

By Craig Robertson

I took an unusual route into ophthalmology. After training in mathematics, I worked on artificial intelligence (AI) optimization before moving into medical devices. The transition was kicked off by a conversation with the Optos Chief Technical Officer David Cairns; their product development programs needed the kind of mathematical expertise I could offer. In fact, I was predisposed to work in ophthalmology because, as a young person, I'd seen my grandmother go blind due to diabetic complications. The speed of her sight loss was shocking, and the experience never left me – and so it became a powerful motivator in my efforts to improve the management of diabetic retinopathy (DR).

I joined a small prototyping team at Optos, and stayed there for several years working on some incredibly advanced devices. I learnt a lot – Optos is a bit like a University – but, after a while, I began to wonder about the company business model. True, Optos was making the best devices on the market – but as a major PLC, its core aim was to enhance shareholder value, so it focused on the territories that returned the most revenues. Commercially, that makes perfect sense, but I couldn't help asking myself: what about

Box 1: The epiCam M

- 1.3 megapixel camera
- Covers 52 degrees in a single shot, with over 100 degree reach
- Operates in amber spectrum (590 nm), which can help differentiate between oxygenated and deoxygenated blood
- No reflex from surface of retina or cornea
- Main application: DR

Craig Roberston holding an epiCam fundus camera

the other 194 territories on Earth? Once I'd posed that question, there was no going back. I left Optos on a Friday, seven years ago, and started Epipole the following Monday. My aim? To build inexpensive ophthalmic imaging devices for neglected populations.

Life isn't always a beach

My first job was to track down Bob Henderson, a retired engineer who had invented the key Optos instrumentation. Eventually, I found him in Ko Samui in Thailand – though asking him to return to Dalgety Bay on the Scottish coast felt like I was pushing my luck, he came back. Suddenly, Epipole was a team of two. Having buy-in from one of the finest optical engineers in the world was a great boost for me, but when I showed Bob a sketch of my idea for a low-cost fundus camera, he just looked at it and said: "No." And that was the start of two guys shutting themselves away in a tiny pitch-black optics room for months on end.

It wasn't easy. We were trying to solve problems which, for all we knew, might have been unsolvable; many ideas that seem great on paper are confounded when they meet biological tissue. Perhaps the hardest thing about building an ophthalmoscope is that the illumination and the optical axis are on top of each other – all the system wants to do is send reflex back to your sensor! We worked on that problem for about a year and, just as we started to question our sanity, we finally made a series of discoveries that fixed the issue. It was a hugely cathartic moment for us, and opened up the way to device prototyping.

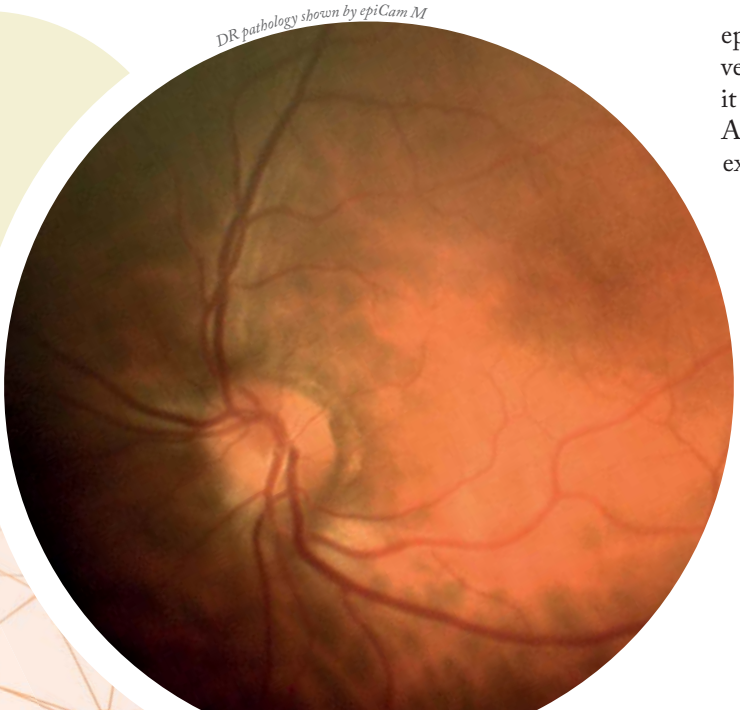
Aiming high – and small, and wide

Our first fundus camera, the epiCam M (see Box 1), was conceived to improve the diagnosis of DR. We designed everything about this device from the ground up – the chassis, the optics, the electronics, firmware, software – everything. Nothing similar had been done before, so we were inventing as we went along – and we set ourselves a couple of ridiculously severe engineering constraints.

Firstly, we wanted to diagnose DR with a high degree of sensitivity – specifically, by detecting very small microaneurysms (below 10 µm). I didn't realize how large that hurdle was until we started work! Secondly, we wanted the device to be suitable for any community where DR is an issue, from remote parts of South America to rural China. And that limits size. If you're taking it to rural communities, it must be portable. It also restricts the price: a rural doctor making $6,000 a year won't buy a $30,000 camera.

The result was better than we could have hoped for: not only did we limit the size and price of the device for our markets, but we also met and exceeded our technical goals. To control camera costs and dimensions, we designed an electronics board (which in itself is something of a work of art!) that permits us to download data via a USB cable and display on a separate screen. Hence, the device does not need a large battery, or a screen, or a computer – the camera body needs only to house the optics. In terms of performance, we achieved a detection limit of about 8 µm at the back of the eye – which is plenty because microaneurysms are only 'problematic' when they reach 30–40 µm. We also provided the device with a very wide reach – well over 100 degrees horizontally and vertically, which can help detect pathologies that might be missed by other devices. Indeed, examination of my own eyes with epiCam M identified a congenital hypertrophy of the retinal pigment epithelium (CHRPE) in the periphery, which a market-leading competitor device could not detect. Being able to look around the eye and see pathology beyond 45 degrees, instead of relying on a static view, makes a huge difference. Furthermore, the unique video capability we have incorporated allows observation of the retina in real time as a living tissue. It also supports efficient triage – the doctor can very rapidly examine all around the fundus, which can help make a real difference to clinical practice. The video capability also encourages novel basic science; for example, some are using epiCam M to study blood flow through the eye – you can see vessel dilation and contraction in real time. Others have used it to observe hypoxic changes in the fundus at high altitude. As well as diagnosing DR, the device is also capable of examining related applications, such as the tortuosity of blood vessels, and observing cholesterol platelets. Anecdotally, we have been told by users that it has been useful in a wide range of other systemic conditions.

"We were trying to solve problems which, for all we knew, might have been unsolvable."



DR pathology shown by epiCam M

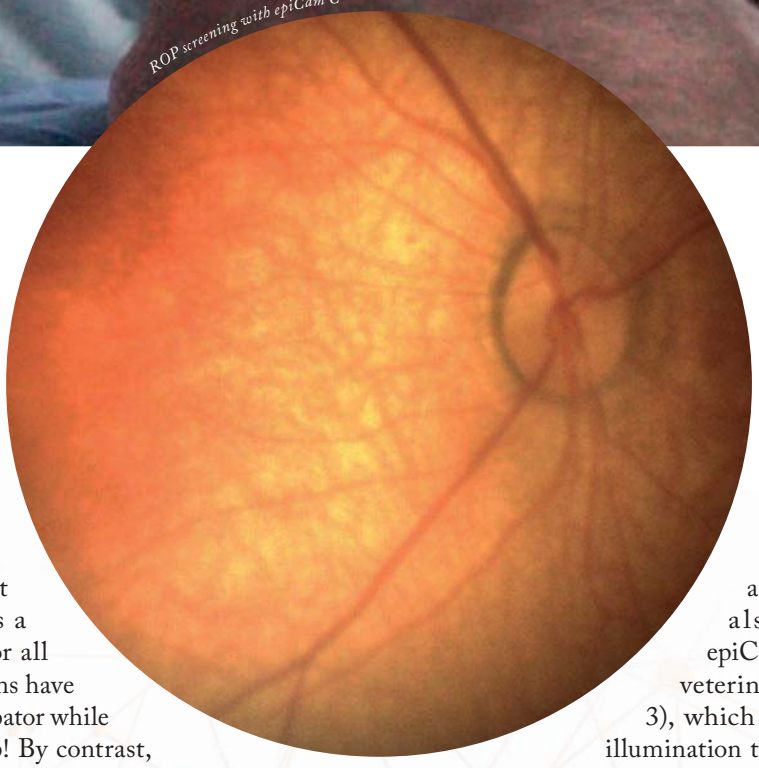
Next generation

While we were developing the epiCam M, I continued seeking feedback from as many clinicians as I could speak with. And I kept hearing about the need for a better system of diagnosing and monitoring retinopathy of prematurity (ROP). This serious pathology can lead to a lifetime of blindness, and is increasing in frequency with the number of surviving premature

BOX 2: The epiCam C

- 5 megapixel camera
- Similar wide reach as epiCam M, but covers 45 degrees per shot
- Operates in full color, red-free and green-free modes
- Like epiCam M, it records video from which still images can be extracted
- Main applications: general ophthalmology, pediatrics

The epiCam C in use on a neonate



ROP screening with epiCam C

neonates. Listening to this feedback, we started developing a second device specifically aimed at ROP: the epiCam C (see Box 2). The device is based on non-contact technology: with a working distance of 13 mm, our device doesn't touch the infant at all, so an examination is a less stressful experience for all concerned. In fact, clinicians have used our device in the incubator while the child is actually asleep! By contrast, other devices on the market are full-contact and require extensive preparation time. We knew it was important to move away from that strategy.

Furthermore, epiCam C is a full-color, video rate ophthalmoscope, making it applicable to general ophthalmology indications as well as pediatrics. We've also made a variant of epiCam C – the epiCam V – for veterinary applications (see Box 3), which benefits from low power illumination that can be adjusted to suit the reflectivity of the tapetum – the reflective

choroid layer found in most animals. Incidentally, some of the comparative work we see from zoo vets – looking at retinas of Sumatran tigers and Bengal eagle owls and vicunas and monkeys – is just fascinating.

Testing times

One of the problems we had to solve when developing our devices was how to test them. Our solution was to develop a proprietary model eye (See Box 4: Model Testing) to assess device performance in terms of resolution and field of view. We now have two versions of this model eye. The first has field rings and a calibration guide (a US Air Force 1951 resolution target), and is designed to test resolving power and performance of ophthalmic equipment – both ours, and that of the competition. The second version is available with a range of printed retinas and serves as a training aid. During its development, we had to invent a way to print onto a hemisphere at 10 times normal resolution, which was a little awkward!

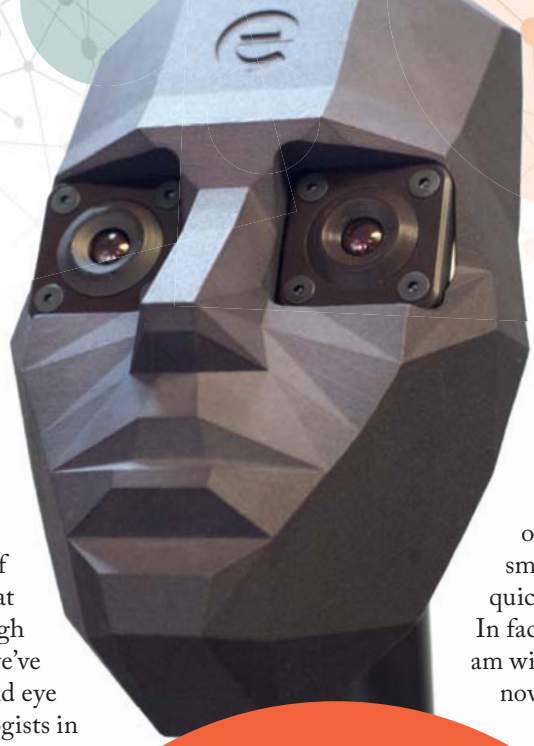
"Some of the comparative work we see from zoo vets – looking at retinas of Sumatran tigers and Bengal eagle owls – is just fascinating."

We have also combined our model eyes with our model head for a training and

Box 3: The epiCam V

- Video capabilities and 5 megapixel camera
- Non-contact imaging
- Low power illuminant that can be adjusted to suit the reflectivity of the tapetum
- 45 degree field of view with reflex-free images

The epiCam V in use



demonstration system – something we've found to be a massive hit wherever we take it. Increasingly, we get requests for customized models: for example, eyes with various pathologies or bespoke field targets at the back of the eye. One of our clients requested placement of camera sensors at the position of the macula to exactly simulate what the macula would perceive through the optics of the human eye. And we've even launched a dog model head and eye for training veterinary ophthalmologists in the use of epiCam V.

Digesting feedback

Throughout our journey so far, customer feedback has been essential in letting us know we're on the right track in terms of meeting global clinical needs; for example, revisions to the first generation of epiCam devices were heavily influenced by feedback from Zia Carrim, an ophthalmologist based in Mauritius. The epiCam made a great difference to his clinic, where he sees some very serious cases, but he could still point out areas where we could tweak the device.

Similarly, when I was in India in 2013, I had a very useful meeting with Professor Azad at the All India Medical Institute. He was only going to give me five minutes, but when he realized I was interested in what he actually needed, rather than just trying to sell him something, he gave me two hours! Such market research is incredibly valuable – I learnt about his workload, the kind of diseases they see, how they treat them, and what their needs are now and in the future. In the same way, we get fantastic input from the veterinary community, which helps us improve the epiCam V.

With any suggestions we get from users immediately going into improving the device, we've managed to make the devices better and better over the last five years. It helps being a small company, because we can react very quickly to accelerate product development. In fact – and this may upset the engineers – I am willing to say that I think the epiCams are now design-complete.

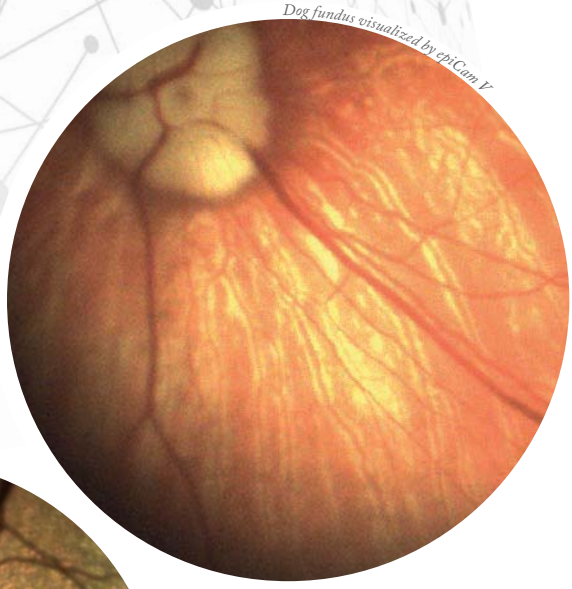
"Customer feedback has been essential in letting us know we're on the right track in terms of meeting global clinical needs."

Global position

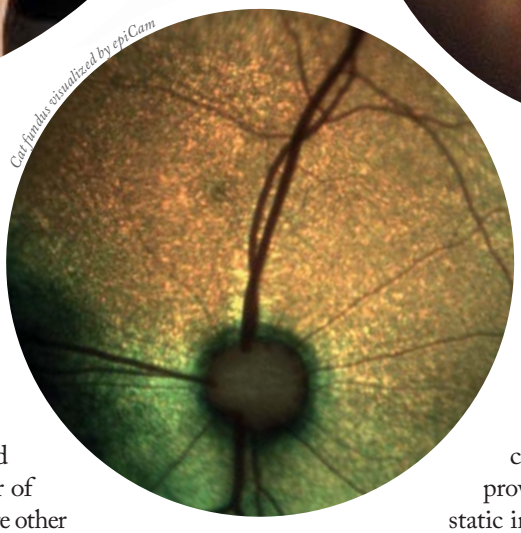
Our credo is to 'do good' while remaining commercially sustainable. Few companies achieve that – especially in the medical device space. But our model is different – and that's how we can supply low-priced devices to doctors and charities operating in resource-poor locations. The underserved communities will remain our true focus, but I do believe our cameras could be used in the developed world too. Though it's true that the UK has gold standard DR screening systems, it's also true that if the NHS relies entirely on hugely expensive desktop systems, then the number will remain limited. Wouldn't it be better if every GP had access to a simple, low-cost device, so that they could routinely screen every one of their at-risk patients; for example, anyone over 70? However, for that to happen, we'd need to generate political support – and that's perhaps a bigger mountain to climb than those we've already conquered!

Epipole model eye mounted in head

Bengal Eagle Owl being imaged by epiCam V



Dog fundus visualized by epiCam V



Cat fundus visualized by epiCam

Doing good and doing well

The opportunity to apply my knowledge to the field of ophthalmology has become a very important part of my life. I believe Epipole is doing something very valuable – the number of undiagnosed diabetics is far too high, and without improved diagnostics we will see a huge number of people developing DR. Of course, there are other pressing clinical needs in ophthalmology, and we intend to address those, too. In fact, we are going after all the other important eye diseases, one by one, starting with AMD and glaucoma. At the same time, we hope to develop our model eye system into a range of training aids – for retinal laser surgery technique instruction. And we are now prototyping a low-cost version of the model eye, which we hope will extend the opportunity to trainee ophthalmologists and optometrists.

When we started Epipole, we set ourselves three key targets: i) to make a device that would have a significant clinical impact in the real world; ii) to provide video output rather than relying on static images; and iii) to visualize the retina at high resolution and with a wide field of view. These challenges involved setting and overcoming extremely high engineering hurdles, and I am very proud of our achievement. At the same time, we've also built a company that does good, while being commercially sustainable. It's a fine line to walk!

Early epiCam in use in Indonesia

Box 4: Model Testing

- Corneal shell equivalent to human cornea
- Crystalline lens analogous to lens of human eye
- Axial length identical to that of human eye
- Water-filled; refractive index extremely close to that of vitreous humor
- Customizable to a range of needs: printed retina, different pathologies, sensors at macula
- Fits in model head for convenience and familiarization
- Manufactured by sophisticated 3D-printing – tolerance at the micron scale
- Precise model of human eye for testing or demonstrating any fundus camera or similar device, or for training in the use of such devices
- Users: academia, industry, hospitals

Epipole model eye

The Epipole team

Model dog head for training in veterinary ophthalmology

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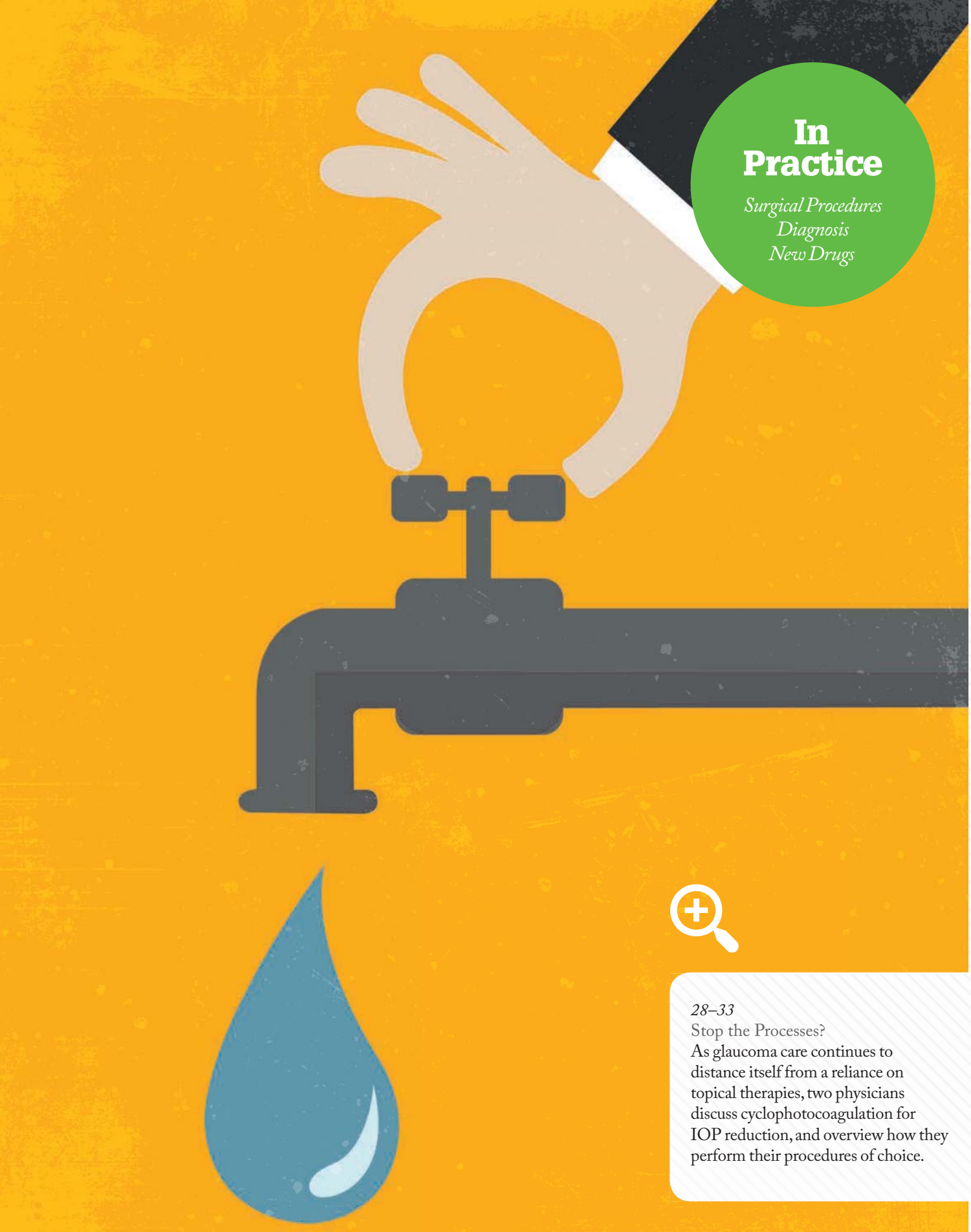
Bringing intelligent journalism and a sense of community to all ophthalmologists



In Practice

Surgical Procedures
Diagnosis
New Drugs

Stop the Processes?

Reducing IOP by targeting the ciliary body; two physicians present two different approaches

In the quest to move away from topical management of glaucoma – and the associated issues, including non-compliance – the field has seen a shift towards surgical management, with a boom in minimally invasive technologies transforming glaucoma care. One such option is cyclophotocoagulation – a procedure which targets the ciliary body epithelium to modulate aqueous production and lower IOP. Here, two surgeons share their preferred cyclophotocoagulation approaches, and talk through how – and why – they perform them.

ECP Explained

Top tips for endoscopic cyclophotocoagulation – an ab interno approach

By Brian Francis

At a Glance

- *Many surgical approaches focus on reducing IOP by improving outflow*
- *Cyclophotocoagulation reduces inflow – and thus IOP – by decreasing aqueous production*
- *Endoscopic cyclophotocoagulation (ECP) directly targets the ciliary processes for treatment via an ab interno approach*
- *Gain top tips from my own experiences, and learn how ECP has benefited my patients.*

Glaucoma is epidemic worldwide – and the number of people affected is set to increase to 79.6 million by 2020 – 74 percent of which will have open angle glaucoma (OAG) (1). Although a multifactorial disease, the primary treatment approach is IOP reduction to prevent further damage to the optic nerve. First-line therapy with topical hypotensive medications is effective when used according to direction; however, these can be limited by poor compliance or insufficient efficacy. It's why multiple surgical IOP-lowering treatment options are also available and in development, each of which targets different outflow and filtration pathways (see Surgical management of IOP). Of these, treatments that target aqueous production are gaining in popularity.

It was first discovered in 1905 that severing the ciliary body could decrease IOP (2). In the 1960s, transscleral ultrasound radiation was used to achieve the necessary destruction (3). Since then, multiple methods of cyclodestruction have been popularized, including cyclophotocoagulation through a transpupillary route, or a contact or non-contact transscleral route (4). Transscleral cyclophotocoagulation (TSCP) – in which ciliary processes are targeted from an external approach with a Nd:YAG or diode laser – has been through several iterations since it was first introduced in the 1970s. In 1992, Martin Uram introduced the use of an intraocular endoscope paired with a diode laser to achieve cyclophotocoagulation using an ab interno approach (5). Endoscopic cyclophotocoagulation (ECP) applies 810 nm wavelength light directly onto the ciliary processes, with positioning visualized by the surgeon through the endoscope. Here, I overview my top tips for performing ECP, and share some case studies of its use.

ECP: Top Tips

Anterior segment approach

- The key to this approach is to treat as many ciliary processes as possible. Even with a 360 degree treatment, the posterior aspect of the processes can be missed. For a significant effect it is advisable to treat 360 degrees, including in between each process. Many surgeons do not treat the intervening space between each process, but as the ciliary epithelium completely encompasses each process – including between the peaks and valleys – it is advisable.
- Titrate the power to achieve a good effect with whitening and shrinking of each process, taking care not to over-treat and cause them to 'pop'. Laser power can be adjusted manually and length of delivery controlled by the foot pedal. Proximity of the probe to the process being treated is important as being too close can result in delivering too much energy – I have found that it is ideal to have six to 10 processes within view.
- Thoroughly inflate the ciliary sulcus with a heavy viscoelastic until the iris nearly touches the cornea. Healon GV (Johnson&Johnson Vision) is my choice, because there is no bubble formation, the higher molecular weight maintains the space, and I find it easier to remove than others. Pushing the iris forward and the lens back will give you the space in which to work.
- A 2.2 mm limbal clear corneal incision works well. Too large an incision may cause the loss of viscoelastic, resulting in poor inflation. When complete, ensure the removal of all the viscoelastic. I have found that some form of irrigation and aspiration is typically needed to avoid pressure spikes. Flushing with BSS and trying to 'burp' it out may not be sufficient.
- For the anterior approach, I prefer the patient to be pseudophakic. It is possible to treat a phakic eye, but it is much more difficult. If the patient is aphakic and vitrectomized, do not try to inflate the sulcus with viscoelastic – use an anterior chamber maintainer, which will preserve the integrity of the globe while the surgery is performed.

Pars plana approach

- Execute a pars plana incision, generally with a 20 or 19 G MVR blade or a 2.2 mm keratome. Perform the procedure through a standard three port vitrectomy or a two port vitrectomy with an anterior chamber maintainer. Place the vitrector in one port and the endoscope in the other. View with the endoscope and perform a limited vitrectomy. Then perform the ECP procedure. Once accomplished, switch hands and perform a vitrectomy and ECP with the other hand from the opposite side. I find this technique works quite well even for anterior segment surgeons.
- For the pars plana approach, it is advisable to avoid 360 degree treatments – a greater portion of the ciliary epithelium is treated due to improved access to the entire length of the ciliary processes. This is especially true with ECP Plus (see below), which includes not only the pars plana approach but treatment of all of the ciliary processes along with approximately 1–2 mm of pars plana. This treatment may result in acute IOP reductions and should be used with care to avoid hypotony.

General top tips

- To facilitate treatment of the ciliary processes via the anterior or posterior approach, scleral depression may be used. This maneuver splays out the processes, allowing for more complete treatment of the processes and the areas in between. If ECP becomes challenging due to significant anterior segment pathology, such as posterior synechiae, consider the pars plana approach.
- Anterior and posterior synechiae can typically be severed to facilitate access to the ciliary sulcus. In some cases, residual lens material or posterior iris synechiae are discovered. Removal is possible if necessary, however, these can sometimes be circumvented by manipulation of the probe. This will require an adjustment of the power as the probe tip will generally be in close proximity to the ciliary processes. As previously stated, if these are severe consider a pars plana approach.
- The most common complication of ECP is inflammation, and this needs to be managed thoroughly. Treatments can include intracameral

dexamethasone (600–1,000 µg), subconjunctival dexamethasone, and IV or topical steroids. Oral prednisone can also be administered postoperatively. I find it best to treat aggressively at first, and then taper relatively quickly to avoid extended treatment. As steroid response can occasionally mask IOP lowering, taper the steroid once inflammation is controlled and reevaluate the IOP if the desired IOP has not been reached.

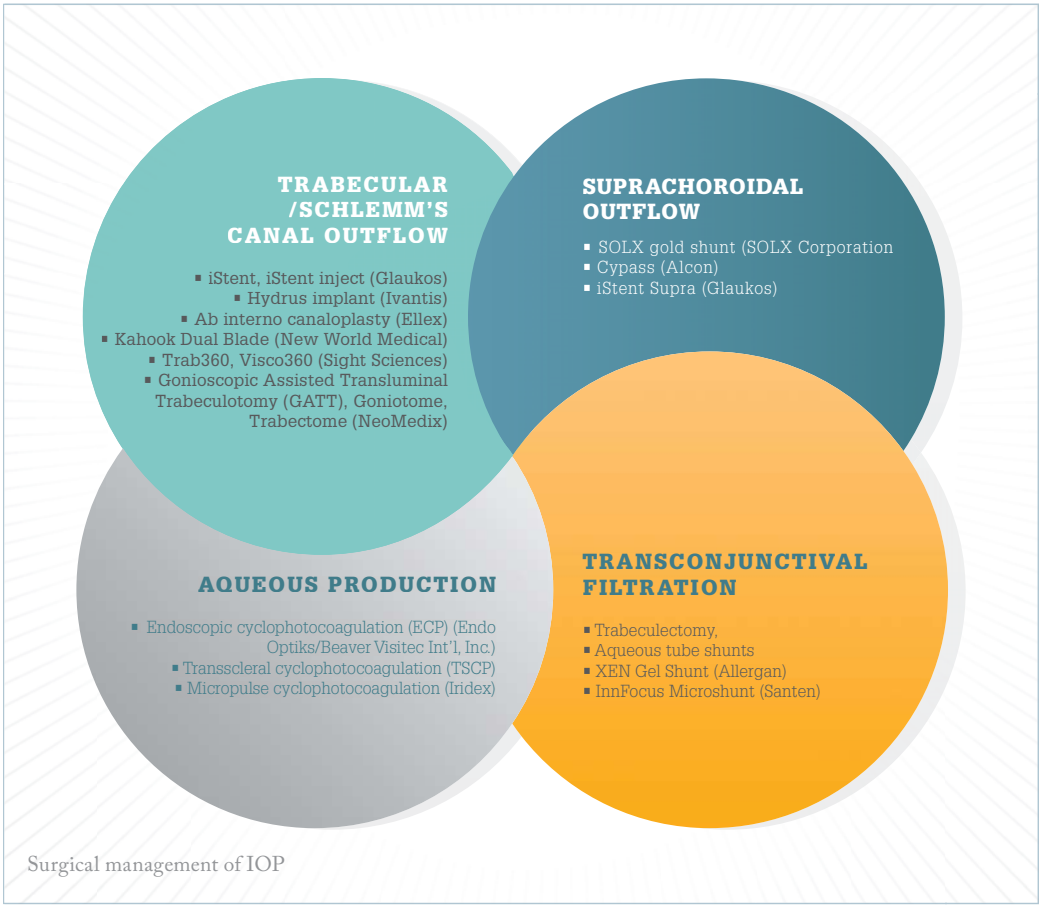
ECP: case by case

Many other surgical options are only available to patients with OAG, but ECP can be used in a wide spectrum of glaucoma patients – either OAG or chronic angle-closure – as well as at any disease stage. For patients with refractory glaucoma who have failed other procedures, the ECP Plus procedure (ECP via a pars plana approach combined with vitrectomy and pars plana laser treatment) has been shown to be effective (6). ECP can also be effectively combined with any other outflow surgery, and because techniques can be readily learned by anterior segment surgeons, it can be used in combination with cataract surgery.

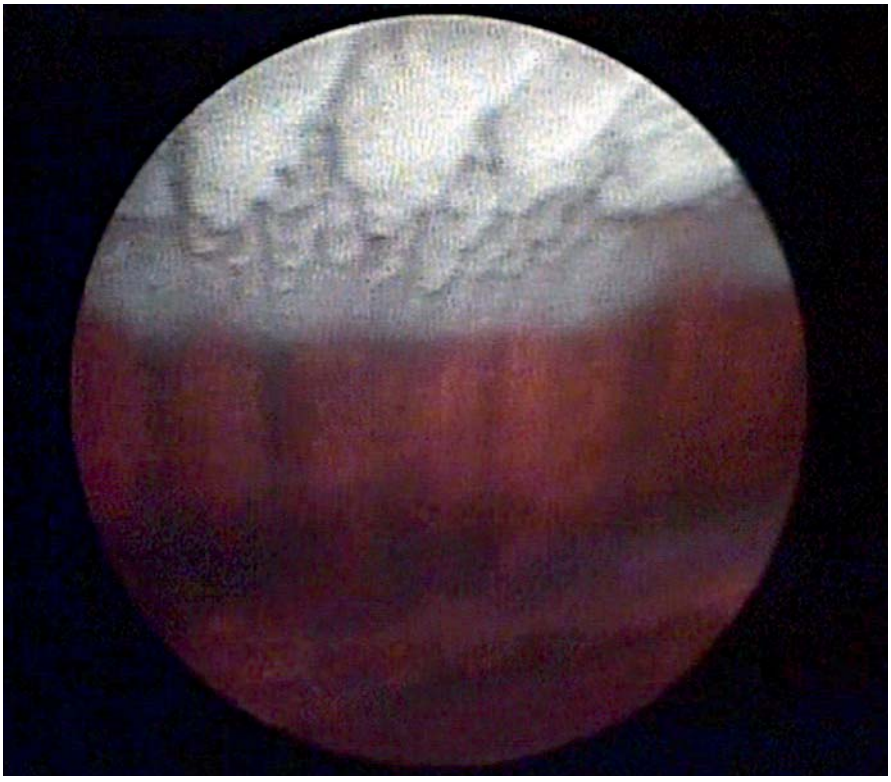
The flexibility of ECP in the glaucoma treatment paradigm is illustrated in the following three cases.

Case 1

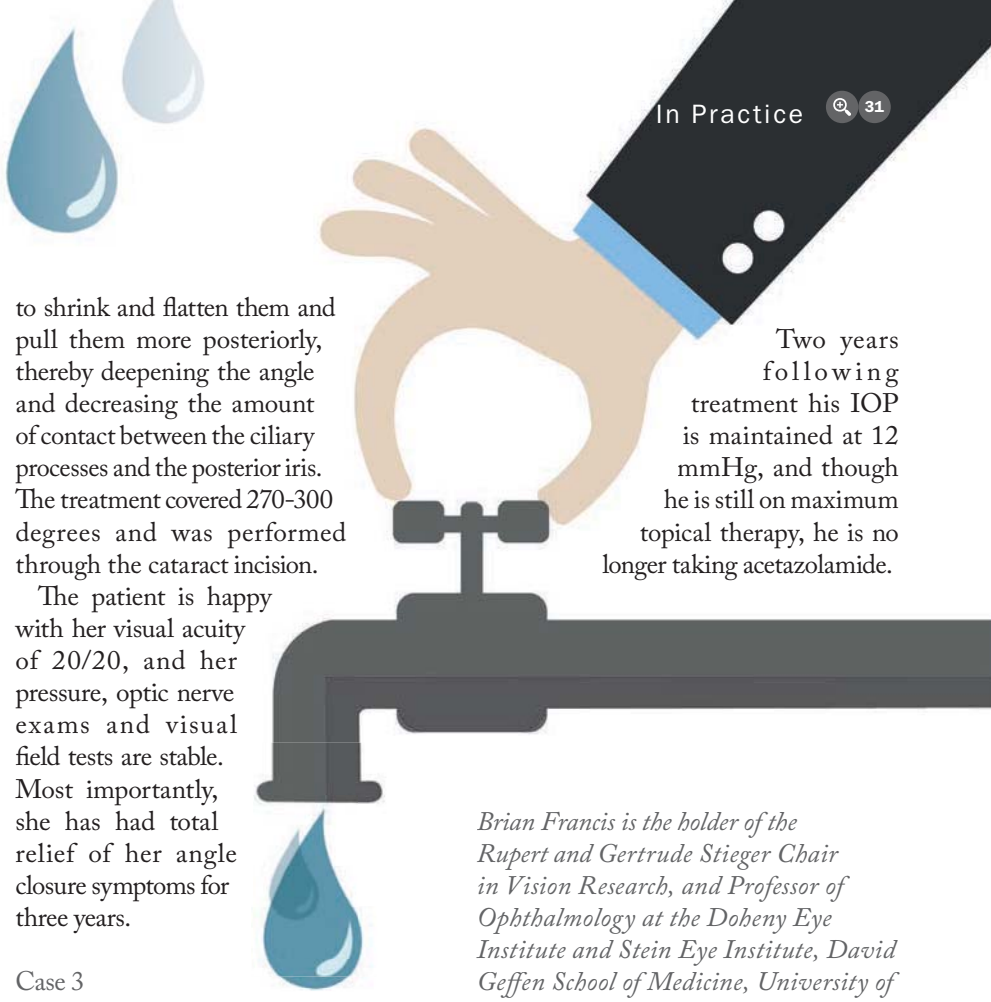
A 68-year old Asian female with a history of mixed mechanism glaucoma and chronic angle closure presented with moderate glaucoma damage. Her cup-to-disc ratio was 0.75, and her pressures were controlled at 16 –18 mmHg with two medications (latanoprost at night and timolol in the morning). Her visual field tests were stable with a mean deviation of approximately -6.0 dB. The patient manifested visually significant cataracts (best corrected visual acuity, 20/60). After discussion with the patient, we decided to combine cataract surgery with ECP; because of the patient's



Surgical management of IOP



ECP plus: Ciliary epithelium is photocoagulated on the ciliary processes as well as a row along the pars plana at the base of the processes.



angle closure, we determined that reducing aqueous production was a better option than angle-based outflow procedures. Following combined cataract surgery with ECP, she initially maintained her glaucoma medications. We then tapered off her medication, and her IOP now sits between 15–17 mmHg without any medications. Her visual field tests are stable and her visual acuity has improved to 20/20.

Case 2

A 32-year old Caucasian female presented with symptoms of intermittent angle closure, including headaches, eye pain, and visual phenomenon – particularly at night time. Gonioscopy and anterior segment OCT revealed that she had appositional angle closure in three to four quadrants. The patient was also hyperopic with a +2.25 D correction. The first treatment, a laser iridotomy, was successful at creating a patent opening, but the patient was still experiencing symptoms of intermittent angle closure. Repeat gonioscopy verified that the angles were still quite narrow, and the patient had a plateau-type approach, some phacomorphic component, and that the peripheral iris was also very anteriorly displaced.

Ultrasound biomicroscopy (UBM) verified the very narrow angles and also revealed some anterior lens vault. Very prominent, anteriorly rotated ciliary processes were pushing the peripheral iris anteriorly. Pilocarpine treatment was tried, but the patient had severe side effects including decreased vision. Repeat laser iridoplasty was an option as it was somewhat effective previously, but the patient considered this to be a "band-aid" measure that would not last, so we discussed incisional surgery. Even though her vision was 20/25 with a clear lens, we opted for lens extraction combined with endoscopic cycloplasty (ECPL) to improve her anatomical abnormality. The ciliary processes were treated with laser to shrink and flatten them and pull them more posteriorly, thereby deepening the angle and decreasing the amount of contact between the ciliary processes and the posterior iris. The treatment covered 270-300 degrees and was performed through the cataract incision.

The patient is happy with her visual acuity of 20/20, and her pressure, optic nerve exams and visual field tests are stable. Most importantly, she has had total relief of her angle closure symptoms for three years.

Case 3

This final case is a 72-year old Latino male with advanced primary open angle glaucoma (POAG). His cup-to-disc ratio was 0.90 in one eye and 0.95 in the other, with IOP at 16 –18 mmHg. Both eyes had previous trabeculectomies and Baerveldt aqueous tube shunt implants. Both of these surgeries failed to adequately control IOP, and the patient was receiving maximum topical medication to maintain his target pressure of below 15 mmHg. The patient was lost to follow-up for one year and when he returned, he was also taking oral acetazolamide 500 mg twice daily because the drops alone were not controlling his IOP. He was uncomfortable taking the acetazolamide and experiencing side effects, including tingling, fatigue and gastrointestinal symptoms, prompting him to return to me for a new option.

At this point, his central vision was still 20/25 but he had severe visual field constriction. Talking through the options, we decided to perform ECP on each eye at separate sessions. Each received 360 degrees of ECP from an anterior approach.

Two years following treatment his IOP is maintained at 12 mmHg, and though he is still on maximum topical therapy, he is no longer taking acetazolamide.

Brian Francis is the holder of the Rupert and Gertrude Stieger Chair in Vision Research, and Professor of Ophthalmology at the Doheny Eye Institute and Stein Eye Institute, David Geffen School of Medicine, University of California Los Angeles. Francis reports that he is a consultant for Endo Optiks/ Beaver-Visitec, Inc.

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Reassessing TSCP's Role

Transscleral cyclophotocoagulation as an in-office approach to glaucoma management – and an earlier option in the treatment paradigm


The TSCP procedure.

By David Gossage

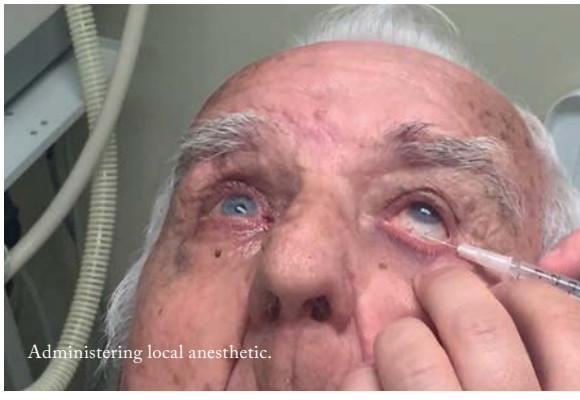
Traditionally, cycloablation procedures to lower IOP have been reserved for patients at – or near – the limit of maximum tolerated medical or surgical therapy, or for patients with refractory glaucoma. One such procedure is transscleral cyclophotocoagulation (TSCP). Performed in the office or in the OR using an 810 nm laser and a transscleral laser delivery probe, TSCP involves ciliary body destruction by targeting the ciliary epithelium to reduce aqueous humor production and therefore lower IOP.

Though effective, cyclophotocoagulation treatments can have some limitations and associated risks. One important limitation of traditional cyclophotocoagulation is the requirement for anesthesia. The treatment endpoint is ablation of the ciliary body in the superior and inferior regions, often marked by an audible 'popping' sound. As this is painful for the patient during treatment, anesthetic is required in the form of retrobulbar block, heavy sedation or general anesthesia in the OR. Although retrobulbar block is feasible, it comes with its own risks and potential complications, including retrobulbar hemorrhage, ocular perforation (especially in patients with high myopia or staphyloma), diplopia, retinal artery and vein occlusion, risk of perforating the nerve sheath or optic nerve damage. The TSCP procedure itself has also been associated with complications, such as hypotony, hyphema, vision loss, and inflammation that can lead to pain or discomfort after treatment.

As such, clinical decisions surrounding cyclophotocoagulation – and other cyclodestructive procedures – often balance safety and efficacy with quality of life, meaning that many physicians are not prepared to damage the ciliary body unless the prospect for disease progression and visual field loss are substantial.

However, I believe that the role of TSCP for glaucoma management can be reassessed. With new techniques and technologies available it should no longer be considered only a 'last resort' treatment, but rather used earlier in the disease process and in patients who have good vision.

MicroPulse technology – a treatment delivery mode in the Cycloe G6 laser console from Iridex – separates a continuous wave laser beam into segments, delivering targeted pulses of energy to the ciliary epithelium to modulate aqueous production. There is also some evidence that shows that segmented laser energy delivery augments the aqueous outflow pathway by constricting and expanding ciliary muscles (1). As the laser is applied with a duty cycle of 31.3 percent, energy is only delivered for around a third of the treatment application. Between pulses of energy, the tissue can cool, preventing a build-up of thermal energy and thermal spread. The reduction in overall energy also means that there is less pain and discomfort for the patient, which raises the potential to perform TSCP as an in-office procedure, using only local anesthesia – an approach we use for many of our patients.

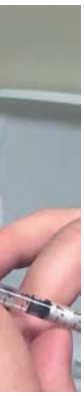

Administering local anesthetic.

At a Glance

- *Transscleral cyclophotocoagulation (TSCP) destroys the ciliary processes, and lowers IOP by reducing aqueous humor production*
- *Although an effective procedure, TSCP is often considered a 'last resort' because of the discomfort of the procedure, the need for anesthesia or deep sedation, as well associated risks and complications*
- *As newer technologies become available, the role of TSCP should be reassessed such that it can be considered earlier in the treatment paradigm*
- *Using a segmented laser, TSCP can be used as an in-office procedure under local anesthesia.*

In-office TSCP

In our clinic, we introduce MicroPulse TSCP to patients who are currently receiving IOP-lowering therapies. We find it a nice adjunct to most existing treatment



approaches, and most of the cases I have performed are in individuals who have previously received laser trabeculoplasty. Previous argon laser trabeculoplasty (ALT) is not a contraindication, even though it yields destruction of the trabecular meshwork.

Local anesthesia

We begin the procedure by using a cotton tip to apply topical anesthesia to both the superior and inferior conjunctiva. We then inject local anesthetic (0.5 cc of 2 percent lidocaine with epinephrine) subconjunctivally to numb the globe, and allow it to diffuse for about 10 minutes. After the patient is comfortable, we set the laser at 2,000 mW of power with a 31.3 percent duty cycle.

The treatment

Laser is applied in 10-second passes along the entire inferior or superior region of the eye, for a total of 90 seconds of treatment time per hemisphere. The 3 and 9 o'clock positions should be avoided because of the long ciliary nerves. Unlike previous versions of cyclophotocoagulation, there is no visible – or audible – tissue destruction to use as a treatment endpoint. Instead, treatment duration is decided at the surgical planning phase. For example, a treatment time of longer or shorter than 90 seconds may be used depending on the extent of IOP-lowering needed, and treatment duration can be titrated specifically to patients. Use of a lid speculum throughout the procedure is discretionary; some patients find it uncomfortable, and it is possible to simply hold the lids open while applying the laser.

Post-procedure

After the procedure, we ask patients to apply a topical corticosteroid QID for one week. We typically see the patient back in the office at one week, one month, and three months post-procedure, depending on how their IOP is responding. As far as outcomes, we usually aim for patients to reach a target IOP rather than attempting a percent or numerical reduction in IOP; however, in our experience, 35 percent to 40 percent reduction in IOP can be expected.

Our experience

We have found several advantages to performing in-office TSCP under local anesthesia. It is more time efficient than performing a retrobulbar block, or administering heavy sedation or general anesthesia – whilst also avoiding associated risks. There is no 'downtime' waiting for the OR staff to turn a room around or waiting for patients to be prepped for surgery. And that allows the treating physician to manage their time more appropriately. There is also less cost to the patient and insurance company because OR/ambulatory surgery center and anesthesia fees can be avoided. Moreover, as deep sedation or general anesthesia are not needed, we can verbally communicate with the patient during the procedure; not only do patients feel more comfortable as we apply the laser, but they can also inform treating staff if there is any pain or discomfort. So far, no patients have asked us to stop the procedure because of pain or discomfort.

The procedure is non-invasive, and easily repeatable if necessary. In summary, as new technologies become available, it is time to consider the potential of TSCP as an in-office approach to treating glaucoma – and not just for patients who have a poor prognosis or refractory disease.

David Gossage is a comprehensive ophthalmologist at Gossage Eye Institute and Optical, Hillsdale, MI, USA. Gossage reports that he receives compensation from Iridex for scientific lectures.

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Research advances
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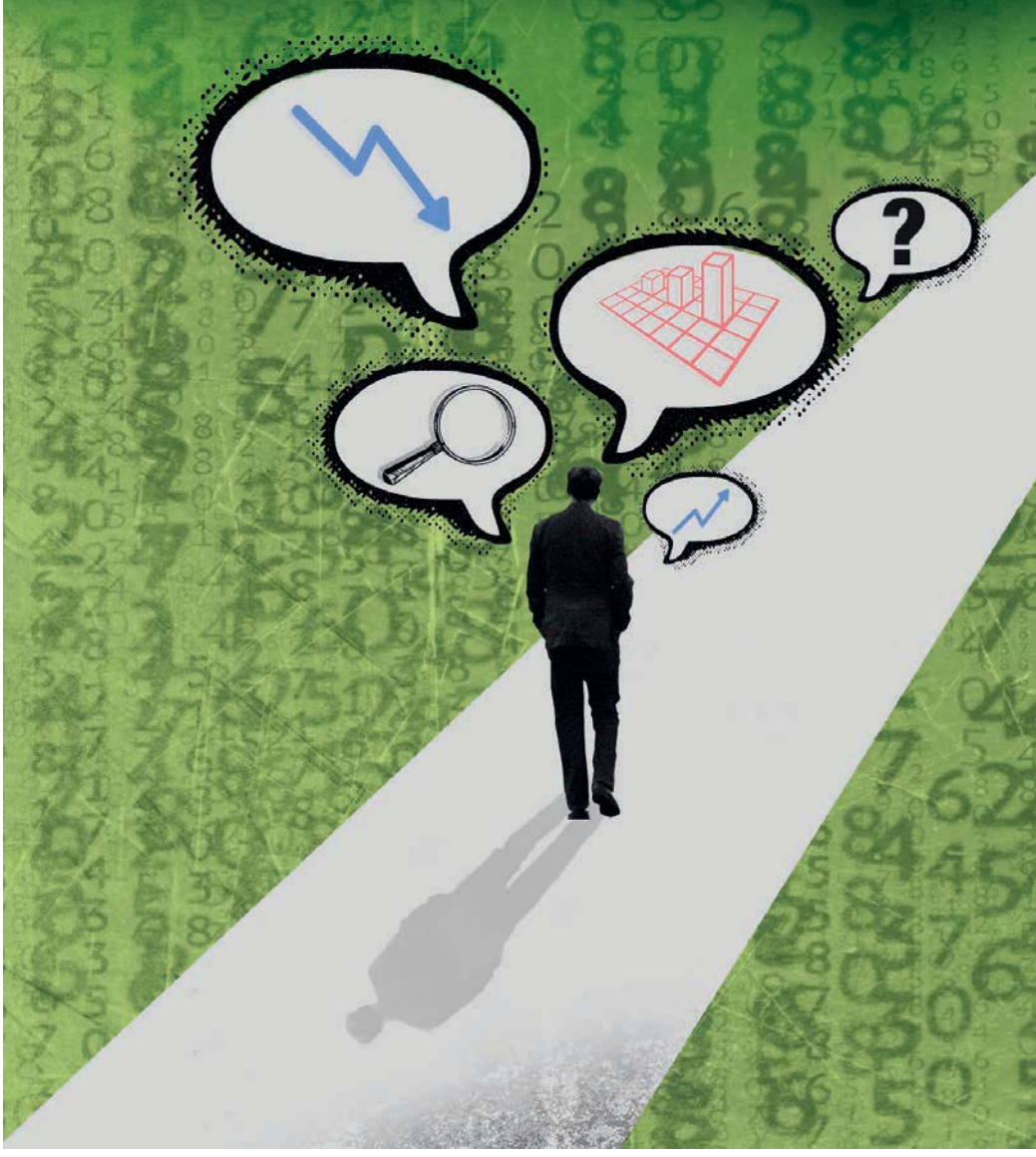
Surprising Associations, Surprisingly Available

Clinical records harboring useful data are there for the taking – we just need to access and analyze them

By Anthony Khawaja



With clinical care comes patient-specific records of medication history and disease outcomes. Today, these data are better captured and curated, and more widely available than ever before – which is exciting because such information from routine clinical care can readily provide important and unexpected insights into drug effects or disease biology. Our recent investigation (1) into potential associations between glaucoma risk and systemic medications is testament to this. Our idea was to assess every medication class for its potential contribution to the probability of developing serious glaucoma. But with hundreds of drug classes to independently analyze, we needed a very large number of patient records to get statistically meaningful results.

At a Glance

- *Expert interrogation of large medical records databases may yield important insights into drug effects and disease biology*
- *From a medical insurance claims dataset, 423 drug classes (1,763 drugs) were assessed for an association with glaucoma risk (6,130 test records, 30,650 controls)*
- *Unexpected findings included a 26 percent higher risk of POAG associated with calcium channel blocker prescriptions, and a 30 percent lower risk associated with SSRI prescriptions*
- *Much can be learned from clinical databases, and findings from these studies can open the door to research novel disease pathways.*

Big ideas need big data

Luckily, my collaborators had access to (and were familiar with) the Truven Market Scan Data Set (2) - a database comprising US insurance claims from nearly 200 million patients. These records were generated through routine clinical care, and so are not as rigorous as trial data; nevertheless, they include key facts, such as which patients had glaucoma and of what type, what procedures they underwent and what medications they had been prescribed. It was exactly what we needed.

"Routine clinical care can readily provide important and unexpected insights into drug effects or disease biology."

We developed a methodology (Box 1) to interrogate the Truven dataset and analyze potential associations between systemic drug use and development of primary open angle glaucoma (POAG). In brief, we matched two populations of patients – those with POAG who had received a glaucoma procedure, and patients who had undergone cataract surgery but had not been diagnosed with any form of glaucoma. We then compared prescription drug use in the preceding five years. And it was exciting! With such a large patient group, we could test all 423 drug classes yet maintain statistical validity. I felt sure that we would discover something new. And we did.

Box 1: Methodology Outline

- Analyzed US insurance claims database containing medical records for >170 million patients
- Test population: patients with POAG who had received a glaucoma procedure
- excluded: patients with other forms of glaucoma
- Control population: patients who had undergone cataract surgery without a glaucoma diagnosis
  - excluded: patients with glaucoma or undergoing non-routine cataract surgery
- Alternative control population: patients with any visit to an ophthalmologist
- A total of 423 drug classes (1,763 drugs) were assessed, used in the five years preceding POAG procedure in 6,130 test patients, matched to 30,650 controls
  - alternative control population: 6,269 tests matched to 43,883 controls
- Association of drug use with POAG was analyzed by logistic regression using standard statistics packages (SAS, STATA and R)
  - Drug classes significantly associated with POAG were separately analyzed for dose-response effect on POAG risk

Surprise, surprise

One of the clearest signals we identified was an association between beta-blocker use and reduced glaucoma risk – an effect known since the 1960s and caused by the ability of systemic beta-blockers to lower IOP. We were pleased to find this, as it was rather like an internal control, proving to us that our model was working. But another observation really caught our attention; although a number of associations were evident (Table 1), two drug classes stood out in particular.

Firstly, we found a strong association between calcium channel blocker prescriptions and increased POAG risk; the scale of the increased risk (26 percent) was remarkable, and the statistical significance very high ($P=1.8\times10^{-11}$). Previous studies have hinted at a possible link between calcium channel blockers and glaucoma, but never revealed a consistent association. To find such a strong signal was therefore completely unexpected. Secondly, we found an even stronger and larger-scale association between selective serotonin reuptake inhibitors (SSRIs) and decreased POAG risk; the protective effect for SSRI users is ~30 percent as compared with non-users, and the statistical significance is even higher than for calcium channel blockers

SSRI	*Beta-blockers*	*Calcium channel blockers*
• 30 percent lower risk • Odds ratio (95% CI), 0.70 (0.61–0.82) • $P=1.04\times10^{-15}$	• 23 percent lower risk • Odds ratio (95% CI), 0.77 (0.72–0.83) • $P=2.71\times10^{-14}$	• 26 percent higher risk • Odds ratio (95% CI), 1.26 (1.18–1.35) • $P=1.78\times10^{-11}$

Table 1. Top three drug classes significantly associated with POAG risk

($P=1\times10^{-15}$ and $P=6\times10^{-24}$ in analyses based on the alternative control population). We also found a marked dose-response effect: longer SSRI use was associated with a progressively lower risk of having a glaucoma procedure.

As we only have observational data at this stage, we cannot be certain of a causative relationship between drug use and altered POAG risk. In theory, the increased risk associated with calcium channel blockers could instead be caused by the high blood pressure – the symptom the drugs are prescribed to treat, rather than the drugs themselves. However, this seems unlikely, as our analysis indicates that ACE inhibitors – the commonest antihypertensive class in the study – showed no significant association with glaucoma risk. Similarly, we found no association between POAG risk and anti-depressive classes unrelated to SSRIs

(such as tricyclics). A separate statistical analysis revealed no association between depression diagnosis and POAG risk. Therefore, it is possible that the protective association observed with SSRIs is a function of drugs that interfere with serotonin reuptake. Another theoretical possibility is prescribing patterns: for example, physicians may be less likely to prescribe SSRIs for POAG patients. But our finding of a clear correlation between increasing SSRI use and progressively lower risk of POAG counteracts any role played by prescribing patterns. At this stage, the associations between particular drug classes and POAG seem to be genuine.

What's going on?

Right now, we're not sure what our findings mean – but we know they merit further investigation into potential mechanisms driving disease. The SSRI association could be mediated through serotonin pathways in ocular tissues, but this is currently a poorly understood field. Serotonin receptors are expressed in retinal ganglion cells (3) – but also in the iris and ciliary body. Some have suggested that serotonin pathways affect pupil diameter, which then contributes to glaucoma risk. And there is also some evidence that serotonin receptors may directly affect IOP (4). Getting to the bottom of serotonin's role in ocular biology will be a fascinating journey.

The mechanisms driving the calcium channel blocker association also require some unraveling given that both low blood pressure and hypertension diagnosis are associated with increased glaucoma risk (5). There is evidence that the higher risk of glaucoma with lower blood pressure is only seen in patients receiving antihypertensive treatment (6); it is possible that the increased risk is not due to low blood pressure per se, but due to other effects on the optic nerve by specific antihypertensives such as calcium channel blockers. The relationship certainly needs investigating because hypertension is a common comorbidity in glaucoma, and so many patients are taking calcium channel blockers – in fact, Japanese physicians sometimes prescribe these drugs to protect against glaucoma...

What next?

Although clinical practice shouldn't change because of our findings, we do think our data reveal important information and interesting hypotheses to explore. One of our imminent next steps is to repeat our work using another dataset, such as the UK BioBank. If the associations still hold in an independent data set, it warrants further work; we must establish the biological basis of the effect – for example, by investigating whether these drugs can modulate glaucoma risk in animal models.

Our findings could also guide fundamental research into disease mechanisms; for example, the role of serotonin pathways in glaucoma etiology. POAG is complex and multifactorial; certainly, IOP is not the whole story, as high IOP patients don't always get glaucoma, and low IOP patients sometimes do. As we still don't understand much of the biology that underlies this disease, we need new hypotheses. And datasets, such as the one we investigated, could suggest specific avenues to explore.

Currently, we are investigating the relative risk associated with different calcium channel blockers. We are also examining associations between systemic medications and relevant ocular features, such as cup-to-disc ratios. More generally, there is still so much to do with datasets like Truven. I think we are 'missing a trick' because nobody has investigated associations between systemic medications and macular degeneration or diabetic retinopathy. Given that patients with these conditions are older and more likely to be receiving systemic medications, we really need to understand how different drugs might affect disease progression and response to medication, or even to surgery. Database 'mining' can really help this kind of investigation, and can generate novel and surprising discoveries. It's also a very cost-effective approach: interrogating existing records doesn't incur the costs associated with getting informed consent from – and running tests on – each of several hundred new patients. The data is already available. We just need to take more advantage of the new insights available to us.

Anthony Khawaja is a Consultant Ophthalmologist at NIHR Biomedical Research Centre Moorfields Eye Hospital and UCL Institute of Ophthalmology, London, UK.

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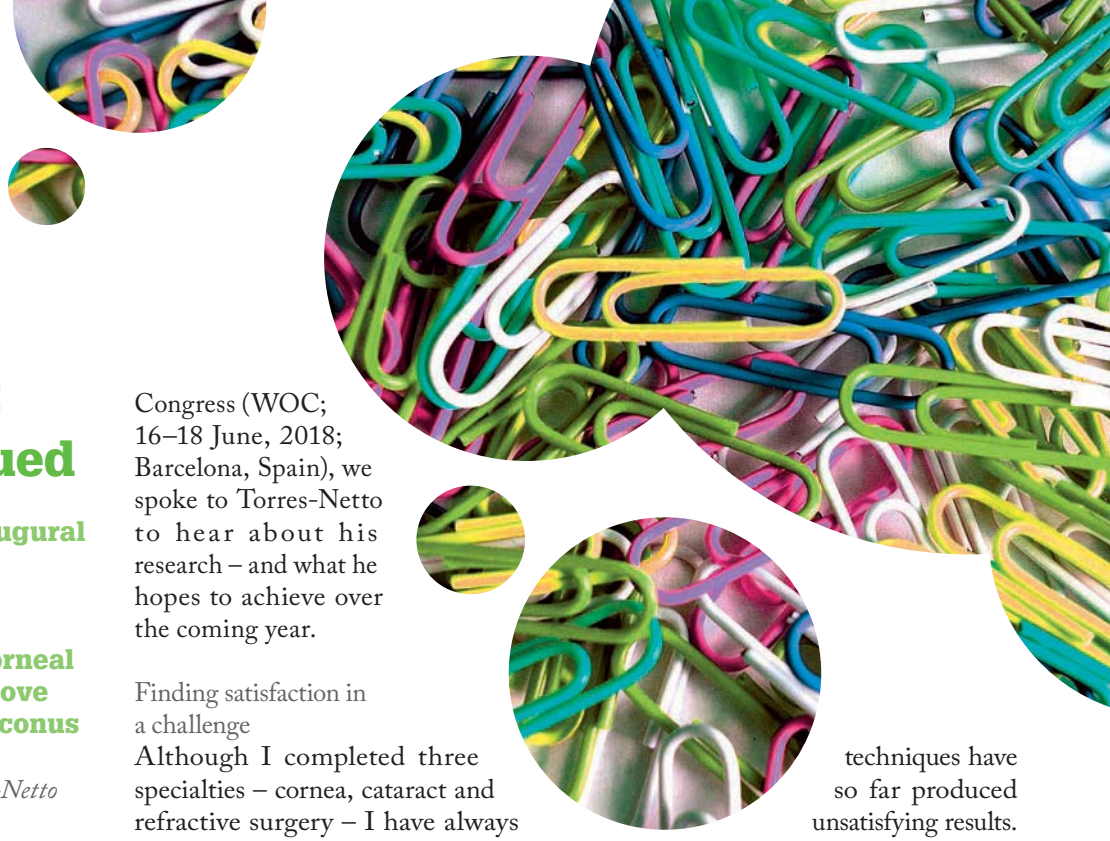


Corneal Crosslinking: To Be Continued

The recipient of the inaugural ICO-Allergan Advanced Research Fellowship discusses how he will continue research on corneal biomechanics and improve the treatment of keratoconus

With Emilio de Almeida Torres-Netto

2018 marked the inaugural ICO-Allergan Advanced Research Fellowship – an award specifically designed to help young ophthalmologists continue their research (see Box - The ICO-Allergan Advanced Research Fellowship). The recipient? Emilio de Almeida Torres-Netto, a cornea, cataract and refractive surgery specialist currently at the University of Zurich, Switzerland. Hot on the heels of officially receiving his award at the World Ophthalmology Congress (WOC; 16–18 June, 2018; Barcelona, Spain), we spoke to Torres-Netto to hear about his research – and what he hopes to achieve over the coming year.

At a Glance

- *The ICO-Allergan Advanced Research Fellowship was launched in 2017 to support young ophthalmologists in continuing their research*
- *Emilio de Almeida Torres-Netto, of the University of Zurich, Switzerland, is the inaugural recipient of the Fellowship*
- *Torres-Netto discusses his research into corneal biomechanics and keratoconus, and describes how he will continue his research in the coming year*
- *Nominations are now open for the 2019 ICO-Allergan Advanced Research Fellowship.*

Finding satisfaction in a challenge

Although I completed three specialties – cornea, cataract and refractive surgery – I have always had a particular interest in keratoconus. Perhaps because it is a challenging disease to treat, and its prognosis has changed a great deal over the years. Previously, the only treatment available was penetrating keratoplasty, which dealt mostly with the most advanced cases. And although new modalities of treatments have been developed, including the global standard of corneal crosslinking with UV-A light and riboflavin, there is still room for further development. The new perspectives that are being pursued, and the possibility to research and further develop in this field, have inspired my interest in keratoconus. It is amazing to receive the ICO-Allergan Advanced Research Fellowship to help further my research in keratoconus and corneal crosslinking (CXL) with Farhad Hafezi at the University of Zurich, Switzerland (see Box – Next Steps in Keratoconus Research).

Improving crosslinking

Treating progressive forms of keratoconus is one of our key areas of interest, and we are deeply involved in investigating how to make the crosslinking procedure more effective. As part of our work, we have been looking into how to improve the effectiveness of epi-on CXL assisted with iontophoresis (epi-on I-CXL). Epi-on techniques have so far produced unsatisfying results. Our group demonstrated that crosslinking doesn't occur in the absence of oxygen (1), hence it is likely that stromal oxygen concentration might be too low when the epithelium is intact. Recently, we presented findings that proved we could significantly increase the biomechanical effect of epi-on I-CXL ex vivo when using a low irradiance (1.5 mW/cm^2) and long irradiation time (60 minutes) – double the time of the Dresden protocol – indicating that oxygen diffusion may remain as a limiting factor (2). Although this epi-on I-CXL procedure is still less effective than epi-off CXL, our modified method might improve efficiency of the procedure and help establish this method as an alternative CXL treatment option; for instance, in special cases or low-compliance patients. Moreover, our preliminary laboratory studies have also shown that temperature might be an important factor for oxygen diffusion in the CXL procedures, and we are hoping to investigate if cooling the tissue using chilled BSS could increase oxygen diffusion deeper into the corneal stroma.

It's a mechanical thing

Improvement of current excimer and femtosecond laser technology is also part of our ongoing studies. In 2017, we showed

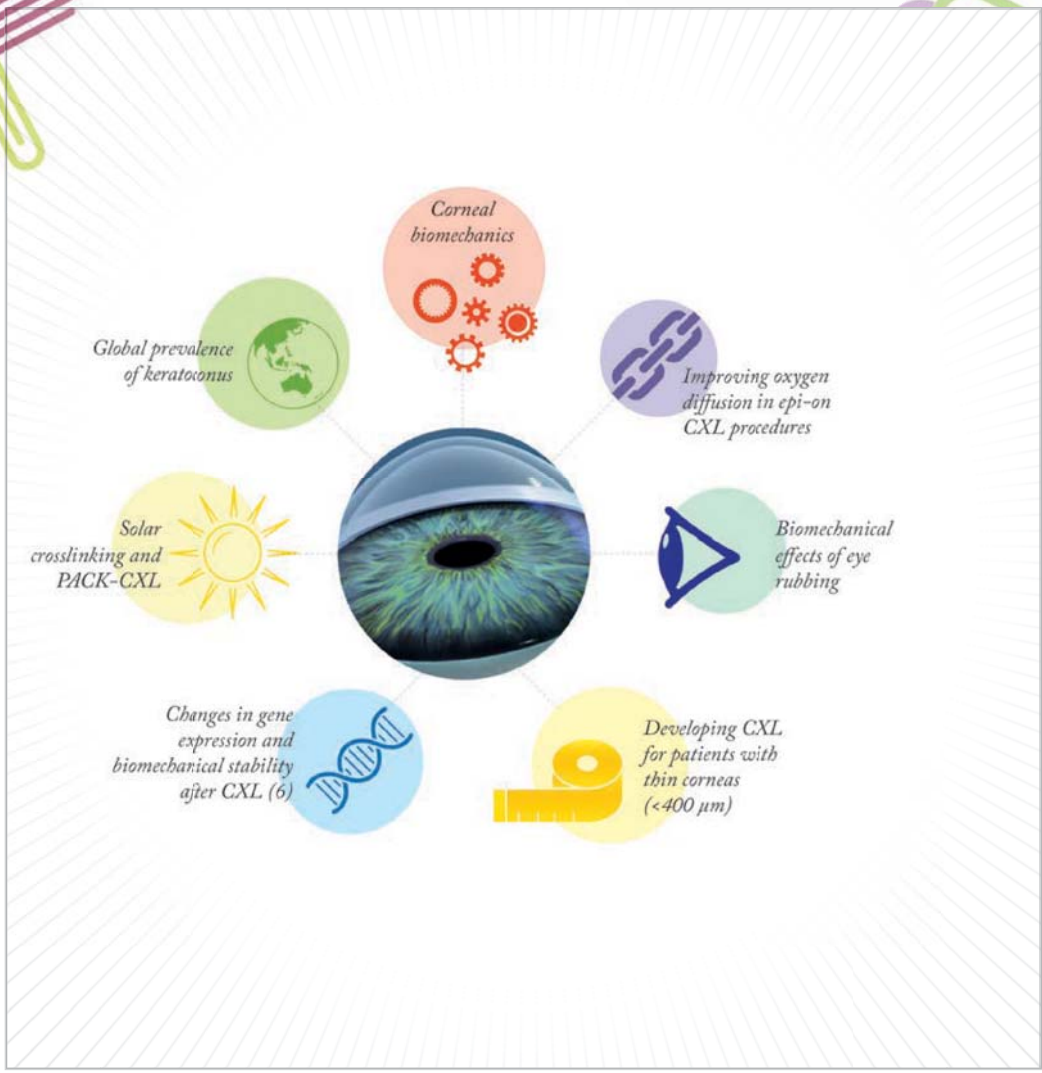
Box – The ICO-Allergan Advanced Research Fellowship

What?
The $50,000 Fellowship supports the continuation of innovative research that advances scientific understanding and clinical management of ophthalmic diseases worldwide.

Who?
Young ophthalmologists (below the age of 40), who have at least 12 months research training.

When?
Applications are now open for the 2019 fellowship, and the winner will be notified at ARVO 2019 annual meeting in Vancouver, Canada.

How?
Application instructions and more information can be found at: http://bit.ly/ICO-All.



Next Steps in Keratoconus Research

how modulating excimer laser parameters could potentially decrease corneal inflammation (3). We are still working on modulating excimer laser parameters to try and diminish inflammation, as this could be useful in complex cases and have a central role in the haze formation pathway. Biomechanical impacts on the cornea are another area of interest in my research. In terms of keratoconus, we are hoping to investigate how eye rubbing might affect the biomechanical properties of the cornea. Although the keratoconus community agrees that eye rubbing is a major risk factor for progressing keratoconus, it has not yet been proven how the mechanics of eye rubbing directly affects biomechanical properties of the cornea. We have just developed a machine that can simulate eye rubbing and we are looking forward to the answers we can get from this project.

Looking to the sky

UV light from the sun is often used in lower income regions to clean and sterilize water. As UV light is an integral part of the crosslinking procedure, we wondered if we could harness UV light from solar energy to perform 'natural' crosslinking. This could have a huge impact in regions and countries with lower incomes. We're not yet sure exactly how to crosslink corneas using the sun, but we are currently working on a procedure involving oral riboflavin that does not require epithelial debridement. Developing a feasible, and most importantly effective, epi-on procedure would be fantastic – and we are hopeful!

Furthermore, as resistance to antibiotics is a global problem that we will have to face in the coming decades, we are also working on enhancing photoactivated chromophore for infectious keratitis (PACK)-CXL to treat corneal infections. Such a treatment would be highly beneficial for low income regions and could benefit many patients, and we are currently working on multicenter clinical and laboratory studies to make this treatment a reality.

Challenging dogma

The prevalence of keratoconus is commonly cited to be 0.05 percent (4), suggesting it to be a rare disease. Looking deeper into this statistic, it became clear that it arose from a 48-year study, from 1935 through 1982, based on limited technology: light retinoscopy and keratometry mires were used to examine patients. As we can detect and diagnose keratoconus with a greater accuracy than before, we must question if this number really is up to date. Recently published papers from different geographical regions suggest not. To test, we performed a pilot study in Saudi Arabia. Although some publications have already identified a higher prevalence of keratoconus in the Middle East, we identified a prevalence of 4.8 percent using Scheimpflug imaging – almost 100 times higher than the commonly cited 0.05 percent prevalence (5). It's a huge difference and, because of this, establishing the global prevalence of keratoconus is one of our major projects at the moment, and we're currently collecting data in several countries to establish the real prevalence of keratoconus based on modern diagnostic instruments.

Moving on and up

Although these are the main projects that I'm working on (and those that the Fellowship will help support), we have much more going on! For example, our group also recently showed how genetic transcription occurs in response to CXL (6). It is an exciting time to be working in the field of keratoconus and corneal biomechanics, both clinically and in research, under the leadership of Farhad Hafezi. As keratoconus and corneal ectatic diseases are one of the most frequent causes of severe visual impairment in the young, we hope that this project will help strengthen our understanding of keratoconus and corneal biomechanics, and improve CXL technology to perform more effective and safer treatments.

Emilio de Almeida Torres-Netto is currently completing a PhD and Research Fellowship at the Federal University of São Paulo, Brazil, in association with the University of Zurich, Switzerland.

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On a Different Path

Two veterans of ophthalmic pathology describe what drew them to a less common, but clearly crucial, specialism

A Vision for Pathology: Sarah Coupland

Director of the North West Cancer Research (NWCR) Centre, Liverpool; Professor and George Holt Chair of Pathology at the University of Liverpool and Honorary Consultant Histopathologist at Royal Liverpool and Broadgreen University Hospitals NHS Trust, UK; and former Vice-President of ARVO.

Specialism: Ocular oncology
Key inspiration: "I have always had a fascination about human biology and physiology, and understanding the mechanisms behind them. Pathology is essentially the understanding of what alterations occur in these processes to initiate disease, and enables a methodological and scientific approach to better diagnose and treat the conditions."
Notable memories: "Recently receiving the International Council of Ophthalmology (ICO) Ophthalmic Pathology award at the World Ophthalmology Congress (WOC) in Barcelona, Spain. This award is only given out every four years, and it is a huge honor to receive it."

What inspired you to enter ophthalmic pathology?

My father was a medical oncologist and my mother a nurse, so I grew up with "medical speak" over the dinner table – it almost became second nature to me. I always wanted to study medicine, and after graduating from Medicine in Sydney, I moved to Berlin, and began a PhD in ophthalmology – I was interested in specializing in this field because of its fine surgery. My PhD examined the immune mechanisms involved in corneal rejection and how these could be influenced by various immunosuppressive drugs. I performed corneal transplantations in rats, followed by histological and immunohistological examination of their eyes. And that's how I rediscovered my enthusiasm for the morphological understanding of disease mechanisms, and how they could be modified by treatment.

At a Glance

- *Ophthalmic pathology might be one of the less common ophthalmic specialisms, but it is no less crucial*
- *Here, two leaders in the field share their career journeys and overview their day-to-day work*
- *Sarah Coupland shares what inspired her to enter the field of ophthalmic pathology, and provides an insight into her work on ocular oncology*
- *Hans Grossniklaus discusses balancing his pathology and research roles with being an ocular oncologist, and shares what is exciting in the field right now.*

After completing my PhD, I did a three-month elective with William Lee in Glasgow – a period during which I finally made the decision to specialize in histopathology. I then spent seven years training in general pathology with Harald Stein at the Charité Benjamin Franklin, Berlin – at that time a referral center for lymphomas, head and neck surgery and ophthalmic tumors – and emerged with a number of pathology subspecialties under my belt.

What is unique about ophthalmic pathology?

As an ophthalmic pathologist concentrating on ocular oncology, I interact closely with clinical teams. Ophthalmological diagnoses are very reliant on morphology and images. The beauty of the eye – and the surrounding structures – allows both the ophthalmologist and the pathologist to literally see many disease processes 'in situ' in the patient, which can allow for easier interpretation of the samples. That being said, many cases are difficult because the samples are tiny! For example, intraocular biopsies of the choroid or vitreous can be very demanding; one is expected to squeeze out as much information as possible on morphology, immunophenotype and genotype. Ocular tumors are rare, but this does not mean that they are any less malignant (or less fatal) than the more common cancers. The majority of our work focuses on uveal melanoma – the

most common primary intraocular tumor in adults – and we have a very good collaboration with the clinical team. Unfortunately, approximately 50 percent of these patients develop metastases to the liver, which at present are not curable. We offer a molecular prognostic service that helps classify uveal melanomas into those that have a good or poor prognosis based on chromosomal abnormalities and mutations in the tumor cells. That prognostic patient curve is used by the clinical team, as well as the clinical psychologists, to discuss the prognosis of the patient and the risks of developing metastases. Patients with tumors that show an intermediate to a high risk of developing metastases to the liver are then stratified by the clinicians and the medical oncologists for more intense liver surveillance. The algorithms for our prognosticator are built on data from over 2,000 patients and we're constantly refining the tool as we obtain more data; we're currently in the process of validating the third version via a multicenter collaborative study.

My favorite aspect of ophthalmic pathology work is making a difficult diagnosis in a timely manner to improve a patient's outcome. The typical scenario would be a vitreous biopsy for suspected vitreoretinal lymphoma. These are notorious for the fragility of the tumor cells and the relatively high rate of non-diagnostic samples. By working closely with the vitreoretinal surgeons, we have been able to make recommendations with respect to how the sample is taken, transported and processed in the lab to improve the diagnostic yield. Vitreoretinal lymphomas are high-grade tumors and so diagnostic delays must be avoided to improve the patient's chance at survival.

What are you currently working on?

My main area of research is trying to understand uveal melanoma and improve the therapy of metastatic melanomas, with the ultimate aim of improving outcomes for patients – which at the moment are pretty abysmal. As I mentioned above, around half of uveal melanomas metastasize into the liver. As they locate to the space of Disse, an immune privileged site, there often isn't an inflammatory response until the metastatic tumors are quite large and have really taken 'root' in the liver. Moreover, these tumor cells manipulate hepatic stellate cells to induce fibrosis – almost like they are creating their own fortifications. We're currently investigating the interactions between uveal melanoma cells and hepatic stellate cells to understand the fibrotic process (1). We have also shown that cultured uveal melanoma cells can synthesize their own lattice-like extracellular matrix upon which they can grow (2). As this peri-tumoral and intra-tumoral fibrosis might hinder the access of drugs and inflammatory cells to the tumor cells, it is important that we understand the tumor microenvironment to develop effective strategies that actually allow therapies to reach the target cells.

We're also currently collaborating with 12 other groups on a project called UM Cure 2020, which is using genomics, proteomics and metabolomics technologies to analyze human uveal melanoma metastases to try and better understand the characteristics of the tumor cells and determine if we can use any new targeted therapies. There are also two pharmaceutical companies involved in the project who are looking for druggable targets. UM Cure 2020 is being led by Institut Curie in Paris, France, but as we are a major component as are coordinating the virtual biobank across the consortium and the histological examinations of a variety of specimens. In Liverpool we have created a unique oncology biobank with primary tissues and associated bloods from patients, allowing us to take part in projects such as UM Cure 2020 and The Cancer Genome Atlas (TCGA) (3).

If you could change one aspect of your field, what would it be?

Sarah Coupland receiving the ICO Ophthalmic Pathology Award 2018 (WOC; June 16–19, 2018; Barcelona, Spain). Left, Hugh Taylor (Immediate Past President of the ICO) and right, Rafael Barraquer (WOC 2018 President).

I was taught that the pillars in the understanding of medicine are the "three Ps": pathology, physiology and pharmacology. If we are to make progress in the understanding of the pathogenesis, prevention and treatment of disease, we have to invest in these cornerstones of scientific medicine. Academic pathology is one of the most fragile subspecialties in medicine at present, pathologists have to come out of the shadows, and have to increase awareness of its importance and create initiatives to make it attractive and prevent its complete disappearance.

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Putting Pathology in Practice: Hans Grossniklaus

Interim Vice Chair, Emory Eye Center; F. Phinizy Calhoun Jr. Professor of Ophthalmology; Director, L.F. Montgomery Pathology Laboratory; Director, Section of Ocular Oncology and Pathology; Emory Eye Center, Atlanta, GA, USA.

Specialism: Ocular oncology and pathology

Key inspiration: "My interest in ophthalmology was inspired by Torrence Makley and William Havener at Ohio State University. While a medical student, I read many articles by W. Richard Green at the Wilmer Eye Institute, and was impressed by his knowledge and productivity. As an ophthalmology resident, I attended the Armed Forces Institute of Pathology (AFIP) course on Ophthalmic Pathology, and was inspired by Lorenz Zimmerman, Dick Green, Ramon Font, Jerry Shields and others to pursue a career in ophthalmic pathology and oncology."

Notable memories: "Whilst there have been many notable experiences, I remember a case in which we were able to decipher a rare condition that had baffled the experts as X-linked lymphoproliferative disease. It was very rewarding to find a long sought after answer."

As an ophthalmologist, pathologist and a researcher, you wear quite a few 'hats'…

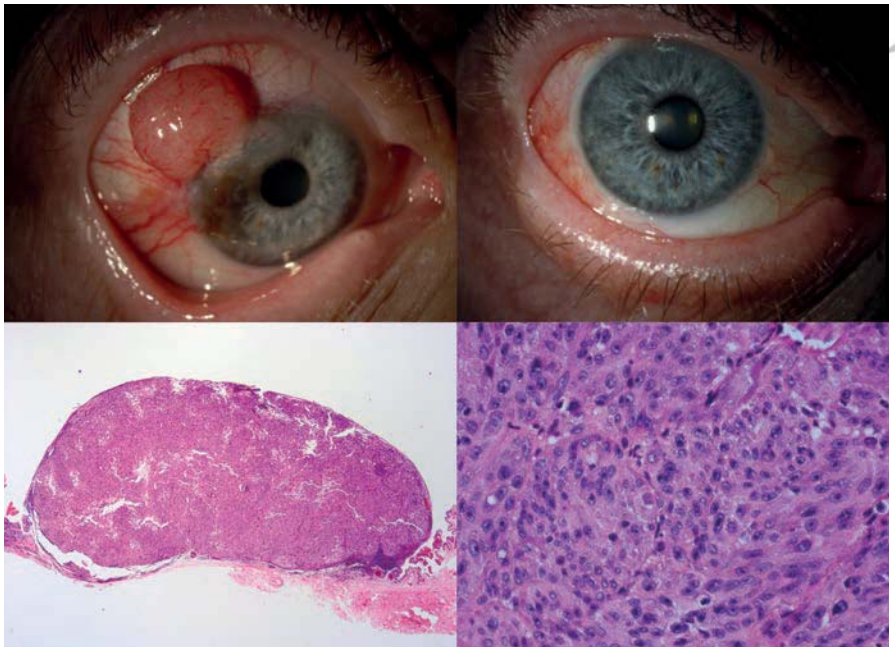
Yes – but I have combined all three so that my practice and my research are focused. My pathology practice is geared towards tumors, my clinical practice is as an ocular oncologist and my research is on ocular tumors, so it all gels. The key elements are working as a practicing ocular oncologist, ophthalmic pathologist, and ocular oncology translational scientist focused on melanoma and retinoblastoma. I am able to combine seeing patients and treating them (surgically, and/or with lasers and targeted medications) with an intimate understanding of the pathology of their disease. This, combined with research directed at improving my patients lives, are key elements to my roles.

A "typical" day would be seeing patients or doing surgery during half of the day as a practicing ocular oncologist, signing out ophthalmic pathology cases as a diagnostic ophthalmic pathologist and designing/performing/evaluating experiments as a translational experimental pathologist. During all of this, I am also teaching medical students, residents and fellows.

What is most exciting in the field, right now?

There are exciting new potential treatments for metastatic uveal melanoma. Although checkpoint inhibitors have proven to be relatively successful for skin melanoma and metastatic cutaneous melanoma, they haven't worked so well for uveal melanoma and metastatic uveal melanoma. But combination strategies may help enhance efficacy. Though I don't think we will be able to eliminate all metastatic melanoma, hopefully we can achieve tumor involution. It will be more like treating a chronic disease, which will prolong people's lives.

Our work in Ethiopia through the Emory Eye Center Global Health Initiative is is also very exciting. This project relates to access to retinoblastoma



Top: Pre- and post-op appearance of a conjunctival melanoma that I excised and performed cryotherapy around its base in my role as an ocular oncologist. We then performed a sentinel node biopsy. Bottom: Images showing hematoxylin and eosin staining of the melanoma that I signed out in my role as an ophthalmic pathologist.

care. Unlike uveal melanoma where the primary tumor can be treated but people are still dying from metastatic disease, retinoblastoma can be treated quite successfully with a very high survival rate in the US and Europe (around 97–99 percent). But in other regions of the world, like Ethiopia, there is only around a 50 percent survival rate. Our team is working to improve medical care access for children in Ethiopia, so that their retinoblastoma can be treated at an earlier stage. When I think back, it was by serendipity that the project came together. I had two visiting Ethiopian clinicians in my lab, who asked what they could work on. I said we should work on retinoblastoma and the problems in Ethiopia. Just by happenstance, Jacquelyn O'Banion came to my lab and said that she's working on retinoblastoma in Ethiopia and asked if I wanted to be involved. I said that's exactly what I'm starting to work on! And it all came together.

We recently had a symposium in Addis Ababa, which was organized by Fran Wu, and involved members of the Ethiopian government, providers (including the ophthalmologists who take care of the children with retinoblastoma), as well as medical oncologists and pathologists. From this we developed an action plan that is now being implemented, and we will follow up in a year or two to assess how far we have gone with these action items. There is a team involved in public awareness screening and referral, and we want to establish a diagnosis and pathology team, as well as treatment and follow-up team. We're currently working on raising funding for the next meeting, and anyone who might be interested in being involved is welcome to contact me.

What's the most special aspect of your field?

We are a small international community of ocular oncologists and pathologists, and we try to work together to solve problems and take care of patients – it's a true team approach. I feel fortunate and honored to take care of my patients – and to work with such wonderful and gifted ophthalmologists and pathologists.

Strong Roots and Continuing to Grow

Past, present and future research from a world-class institute

The UCL Institute of Ophthalmology (London, UK) was founded in 1948. Seventy years later, the institute continues to be a world-leader in ophthalmic research in collaboration with Moorfields Eye Hospital. How better to mark the occasion than holding a 70th anniversary symposium to celebrate the past, present and future research from the institute? On June 28, 2018, approximately 250 expert academics, researchers, clinicians, students and trainees were in attendance to revel in the institute's history and future. Here, some of the speakers present their key 'take home' messages from their talks on the day.

Matteo Carandini, Professor of Visual Neuroscience, UCL Institute of Ophthalmology:
"We can use two-photon imaging to record the activity of more than 10,000 neurons in the visual cortex of mice during behavior. This has led us to the unexpected discovery that the visual cortex carries navigational signals. We can also record the activity of retinal neurons in awake mice, by imaging their axon terminals in a region called the superior colliculus. Using this technique, we have obtained preliminary data suggesting that retinal activity can be modulated by behavior."

Pete Coffey, Professor of Visual Psychophysics, UCL Institute of Ophthalmology:
Coffey gave a talk on the clinical pathway used by the London Project to Cure Blindness for the treatment of AMD. He also presented the first two cases in which patients received a stem cell-derived therapy, and discussed the clinical outcomes of the patients two years following transplantation.

John Marshall, Frost Professor of Ophthalmology, UCL Institute of Ophthalmology:
"My lecture, 'Echoes of Egos', was an attempt to encapsulate 70 years of the institute in 15 minutes. Although the task was impossible, I wanted to demonstrate that right from its inception the institute was a major source of influence and innovation in eye science and surgery, with implications for millions worldwide. The earliest heads of departments all became major international figures who made fundamental discoveries in physiology and vision. Work at the institute also led to a revolution in cataract surgery and the creation of corneal refractive surgery. The institute has always remained at the forefront of ophthalmology, and is now a world leader in understanding genetic eye disease, gene therapy and the possibility of stem cell therapy for age-related diseases. It is not surprising that it is the number one institution for research on the eye."

Sobha Sivaprasad, Professor and Consultant Ophthalmologist, Moorfields:
"The diabetic epidemic, new imaging modalities and clinical trials on preventive options have made it necessary to re-define the classification of diabetic retinopathy. New classifications should aim to include non-clinically visible lesions. Metabolic imaging may in fact explain the missing link between hyperglycemia and neurovascular retinal complications in diabetes."

Astrid Limb, Professor of Retinal Biology and Therapeutics, UCL Institute of Ophthalmology:
"Müller glial cells regenerate the zebrafish retina after injury. Although humans harbor these cells, there is no evidence that they can regenerate the retina. As these cells can be cultured indefinitely (from cadaveric human retina and from retinal organoids formed by human embryonic stem cells) they can be used as a source of neuroprotective factors to partially restore visual function in animal models of glaucoma and retinitis pigmentosa (RP). Based on these findings, we are currently in the process of developing a cell therapy to treat late stages of glaucoma."

Chris Dainty, Professorial Research Associate, UCL Institute of Ophthalmology:
"Imaging has evolved over the last 70 years from being purely a service function to a research-driven activity. Two highlights of my presentation were paintings by Terry Tarrant, and the development of fundus autofluorescence by Alan Bird and Fred Fitzke. Our research goal now is to visualize the structure and function of every single cell in the living human retina."

FUTURE

PRESENT

PAST

Anthony Vugler, Lecturer in Retinal Neurobiology, UCL Institute of Ophthalmology:
Research from Vugler's laboratory has shown that:

- Human retinal progenitor cells show promise in slowing photoreceptor loss in a rodent model of RP.
- In mice, outer retinal degeneration is accompanied by an increased potency of melanopsin signaling, most likely due to an increased availability of chromophore from the RPE – a phenomenom that might account for the development of photophobia in RP patients.

James Bainbridge, Consultant Retinal Surgeon, Moorfields:
"In my presentation, I overviewed the first gene therapy for eye disease – Luxturna – that has been approved for use in the US, and discussed how it is being considered for use in the UK."

Alan Bird, Emeritus Professor and Consultant, UCL Institute of Ophthalmology:
"In the early days of the clinical department there was a major contribution to public health with involvement in research into trachoma and onchocerciasis (river blindness), which at the time were classified amongst the four most important blinding diseases worldwide. Work on onchocerciasis showed for the first time that optic nerve disease was a common cause of blindness, that consequent blindness was as severe in the rain forest as in the Savanna areas, and that the recommended treatment – diethylcarbamazine (DEC) – actually caused blindness. Changing treatment to invermectin has resulted in elimination of blindness due to onchocerciasis."

Year of the Woman

Sitting Down With… Bonnie An Henderson, Partner at Ophthalmic Consultants of Boston, and Clinical Professor at Tufts University School of Medicine Boston, MA, USA.

What inspired you to become a cataract and refractive surgeon?

Coming from a family of physicians, it was expected that I'd be a physician too. I'm lucky the hereditary trait of being a doctor was passed down to me. I didn't realize it when I finished my medical training, but looking back, I'm fortunate the field I selected was perfect for my skill set. My desire to become an ophthalmologist was down to my experience with David Campbell during my ophthalmology elective. He's a brilliant glaucoma specialist with an insatiable curiosity, but he's also a kind, ethical, humble person who treated his patients with compassion and his staff with respect.

Who inspires you today?

I know it sounds like a cliché – but my mom. She's the most hard working, loving, generous person that I know. She was always there when I needed something and always supportive, regardless of the situation. I can't think of a better inspiration.

You called the last 12 months the "year of the woman" – why is that?

Many of the large ophthalmic organizations were led by women; Cynthia Bradford was president of AAO, Emily Chew was president of ARVO, Cynthia Mattox was president of the AGS, Beatrice Cochener was the president-elect of ESCRS, and I served as president of ASCRS. We were able to work together to discuss issues regarding governmental regulations in the US, and we were successful in lobbying to reduce the measures and penalties to reimbursement programs, as well as blocking a proposed program by MedPACto move physicians towards Advanced Alternative Payment Models.

What's it like for women in ophthalmology?

Thankfully, ophthalmology is one of the more progressive specialties when it comes to gender roles, with many champions for equality. The number of female ophthalmologists continues to grow every year. In fact, when I graduated medical school over 20 years ago, the class was already 50/50 male/female. However, men still dominate surgical subspecialties, which reflects in the 4:1 ratio of male to female practicing ophthalmologists. The challenges that women face in ophthalmology are not unique. They are the same challenges that women face in all industries, and in all fields of medicine.

What are you doing to help?

I'm working on a conference called EnVision Summit. The inaugural event will be held in February 2019 in Puerto Rico, and will focus on empowering women to lead in their field of specialty. Unlike other medical conferences, EnVision Summit fosters a welcoming environment that is open to families. We understand the challenges of advancing in a career while juggling the needs of personal life. This organization offers unique opportunities for new and experienced physicians to discuss issues of clinical importance, develop mentoring opportunities and facilitate collaborations for research. A major theme of this summit is how to conduct clinical research, with a spotlight session led by Malvina Eydelman, the Senior Medical Advisor of the US FDA Ophthalmic Devices Division.

What was the highlight of your ASCRS presidency?

As part of a three-year collaboration with the Outpatient Ophthalmic Surgical Society (OOSS) and others, we created new specialty-specific guidelines for ophthalmic instrument cleaning and sterilization in the US. If the ASCRS hadn't stepped in, longstanding practices for processing eye instrumentation could have been cited by surveyors as deficiencies that would warrant loss of ASC licensure or coverage. These are the types of challenges that individual physicians cannot combat alone. We need a strong organization, such as the ASCRS, to represent us and voice our unified protest. Being part of something greater than one individual was a rewarding experience.

How do you think ophthalmology will change in the coming years?

Technologic advances seem to evolve more rapidly in ophthalmology than other industries. The explosion of IOLs, use of lasers, development of injectable medications for retinal diseases and the surgical innovations in glaucoma are just a handful of the incredible changes that have occurred in the past decade. Hopefully future advances will allow patients to be less dependent on eyedrops for glaucoma, less dependent on corrective spectacles, and medical therapies will decrease visual morbidity from age-related diseases and endocrine disorders. Globally, I hope that the rate of blindness from cataracts will have drastically decreased as more patients have access to affordable cataract surgery.

What's exciting you right now?

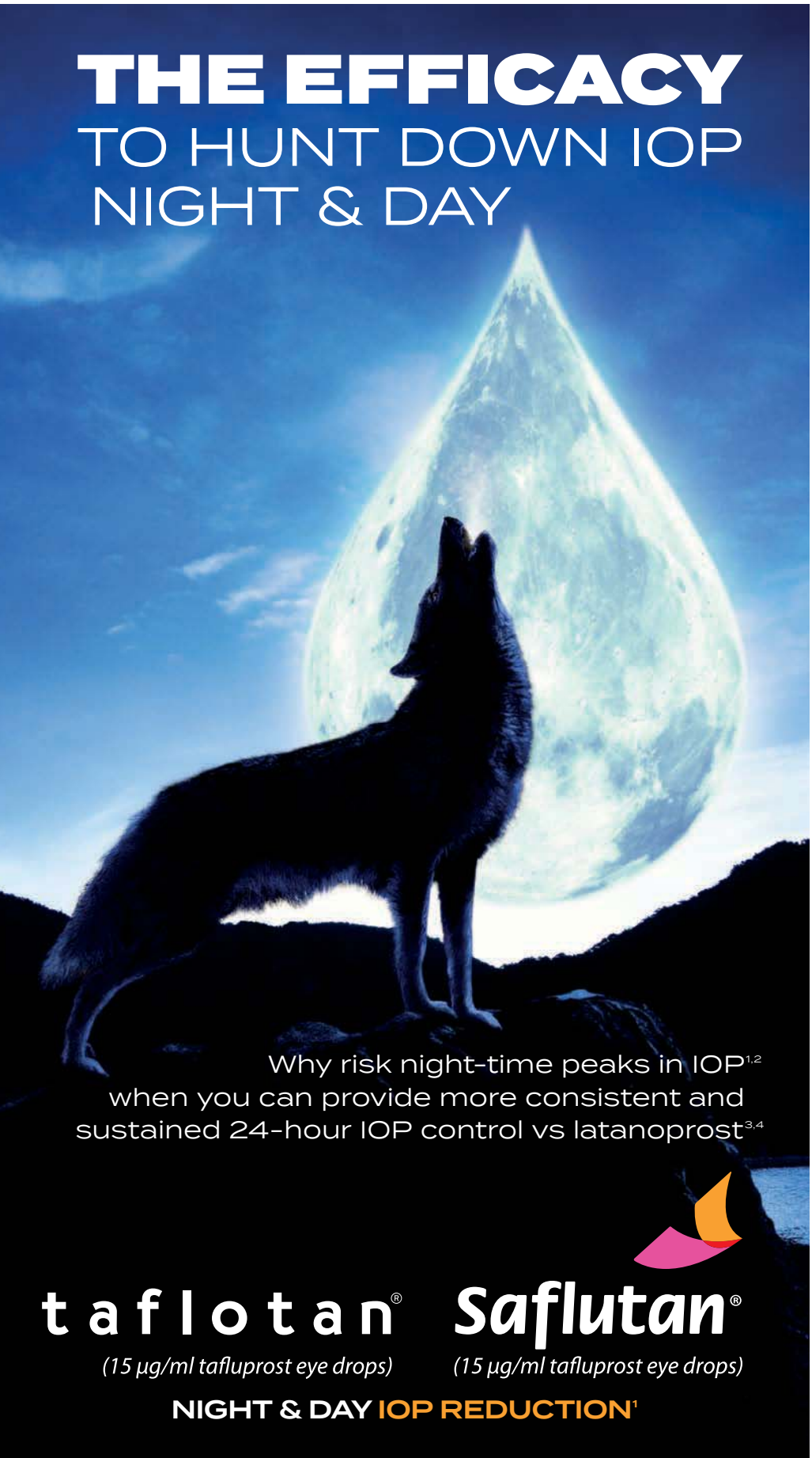
The focus on presbyopia correction. Not only because of the explosion of new IOLs, but also the new medical developments to prevent lens hardening. This field is in its infancy and will continue to grow over the next few decades.

Finally, what's your advice for future leaders?

Remember when your parents told you that you can do anything? They were right. You may never be a professional ball player, but within ophthalmology, people can achieve any goal. It's important to remember this and strive for the best. Whether that means to become the best clinician, the best educator or the best researcher, it's all possible with perseverance, hard work and creativity.

Santen

A Clear Vision For Life



Product name: SAFLUTAN® tafluprost 15 micrograms/ml eye drops, solution in single-dose container. **Composition:** Eye drops, solution, single-dose container (eye drops). A clear, colourless solution. One ml of eye drops, solution, contains 15 micrograms of tafluprost. One single-dose container (0.3 ml) of eye drops, solution, contains 4.5 micrograms of tafluprost. One drop (about 30 µl) contains about 0.45 micrograms of tafluprost. Please refer to Summary of Product Characteristics (SmPC) for a full list of excipients. **Indication:** Reduction of elevated intraocular pressure in open angle glaucoma and ocular hypertension. As monotherapy in patients who would benefit from preservative free eye drops; insufficiently responsive to first line therapy; intolerant or contra-indicated to first line therapy. As adjunctive therapy to betablockers. SAFLUTAN® is indicated in adults ≥ 18 years. **Posology and method of administration:** The recommended dose is one drop of SAFLUTAN® in the conjunctival sac of the affected eye(s) once daily in the evening. The dose should not exceed once daily as more frequent administration may lessen the IOP lowering effect. For single use only, one container is sufficient to treat both eyes. Any unused solution should be discarded immediately after use. *Use in elderly:* No dosage alteration in elderly patients is necessary. *Paediatric population:* The safety and efficacy of tafluprost in children below age 18 has not yet been established. No data are available. *Use in renal/hepatic impairment:* Tafluprost has not been studied in patients with renal/hepatic impairment and should be used with caution. *Method of administration:* To reduce the risk of darkening of the eyelid skin patients should wipe off any excess solution. As with any eye drops, nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route. If more than one topical ophthalmic medicinal product is being used, each one should be administered at least 5 minutes apart. **Contraindications:** Hypersensitivity to tafluprost or to any of the excipients. **Warnings and precautions:** Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation. Some of these changes may be permanent, and may lead to differences in appearance between the eyes when only one eye is treated. The change in iris pigmentation occurs slowly and may not be noticeable for several months. The change in eye colour has predominantly been seen in patients with mixed coloured irises, e.g. blue-brown, grey-brown, yellow-brown and green-brown. There is potential for hair growth to occur in areas where tafluprost comes repeatedly in contact with the skin surface. There is no experience with tafluprost in neovascular, angleclosure, narrow-angle or congenital glaucoma. There is only limited experience with tafluprost in aphakic patients and in pigmentary or pseudoexfoliative glaucoma. Caution is recommended when using tafluprost in aphakic patients, pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema or iritis/uveitis. There is no experience in patients with severe asthma. Such patients should therefore be treated with caution. **Interactions with other medicinal products:** No interactions are anticipated in humans, since systemic concentrations of tafluprost are extremely low following ocular dosing. Specific interaction studies with other medicinal products have not been performed with tafluprost. In clinical studies tafluprost was used concomitantly with timolol without evidence of interaction. **Fertility, pregnancy and lactation:** *Women of childbearing potential/contraception:* SAFLUTAN® must not be used in women of childbearing age/potential unless adequate contraceptive measures are in place. *Pregnancy:* There are no adequate data from the use of tafluprost in pregnant women. Tafluprost can have harmful pharmacologic effects on pregnancy and/or the fetus/newborn child. SAFLUTAN® should not be used during pregnancy unless clearly necessary (where no other treatment options are available). *Breast-Feeding:* It is unknown whether tafluprost or its metabolites are excreted in human milk. Tafluprost should not be used during breast-feeding. **Ability to drive and use machines:** Tafluprost has no influence on the ability to drive and use machines. As with any ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery. **Undesirable effects:** In clinical studies with preserved tafluprost the most frequently reported treatment related adverse event was ocular hyperaemia in approximately 13% of patients. It was mild in most cases and led to an average 0.4% discontinuation. In a 3-month, phase III study comparing the non-preserved formulation of tafluprost with the non-preserved timolol formulation, ocular hyperemia occurred in 4.1% (13/320) of patients treated with tafluprost. The following undesirable effects related to treatment were reported during clinical trials with tafluprost after a maximum follow-up of 24 months: within each frequency grouping, adverse reactions are presented in order of decreasing frequency. *Nervous system disorders:* Common (≥1/100 to <1/10): headache. *Eye disorders:* Common (≥1/100 to <1/10): eye pruritus, eye irritation, eye pain, conjunctival/ocular hyperemia, changes in eyelashes (increased length, thickness and number of lashes), dry eye, eyelash discolouration, foreign body sensation in eyes, erythema of eye lid, superficial punctate keratitis (SPK), photophobia, blurred vision, increased lacrimation, reduced visual acuity and increased iris pigmentation. Uncommon (≥1/1000 to <1/100): blepharal pigmentation, eyelid oedema, asthenopia, conjunctival oedema, eye discharge, blepharitis, anterior chamber cells, ocular discomfort, anterior chamber flare, conjunctival pigmentation, conjunctival follicles, allergic conjunctivitis and abnormal sensation in eye. Frequency not known: iritis/uveitis, deepening of the lid sulcus, macular oedema / cystoid macular oedema. Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas. *Respiratory disorders:* Frequency not known: exacerbation of asthma, dyspnea. *Skin and subcutaneous tissue disorders:* Uncommon (≥1/1,000 to <1/100): hypertrichosis of eyelid. Please also see the SmPC. *Overdose:* Treatment should be symptomatic. **Special precautions for storage:** Store in a refrigerator (2°- 8°C). After opening the foil pouch keep the singledose containers in the original pouch and do not store above 25°C. Discard opened singledose containers with any remaining solution immediately after use. **Package quantities:** 30 x 0.3 ml single-dose containers. Low density polyethylene (LDPE) single-dose containers packed in foil pouch. Each single-dose container has a fill volume of 0.3 ml and there are 10 containers in each foil pouch. **MA Holder:** Santen Oy, Niittyhaankatu 20, 33720 Tampere, Finland. **Price:** 30 x 0.3ml single-dose containers £12.20 **MA number:** PL 16058/0017. **Date of Authorisation:** 17/10/2008 **Legal Category:** POM **Date of prescribing information:** December 2017

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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).

PP-SAFLUT-EMEA-0025; Date of preparation: May 2018

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