JUNE 2017 # 10

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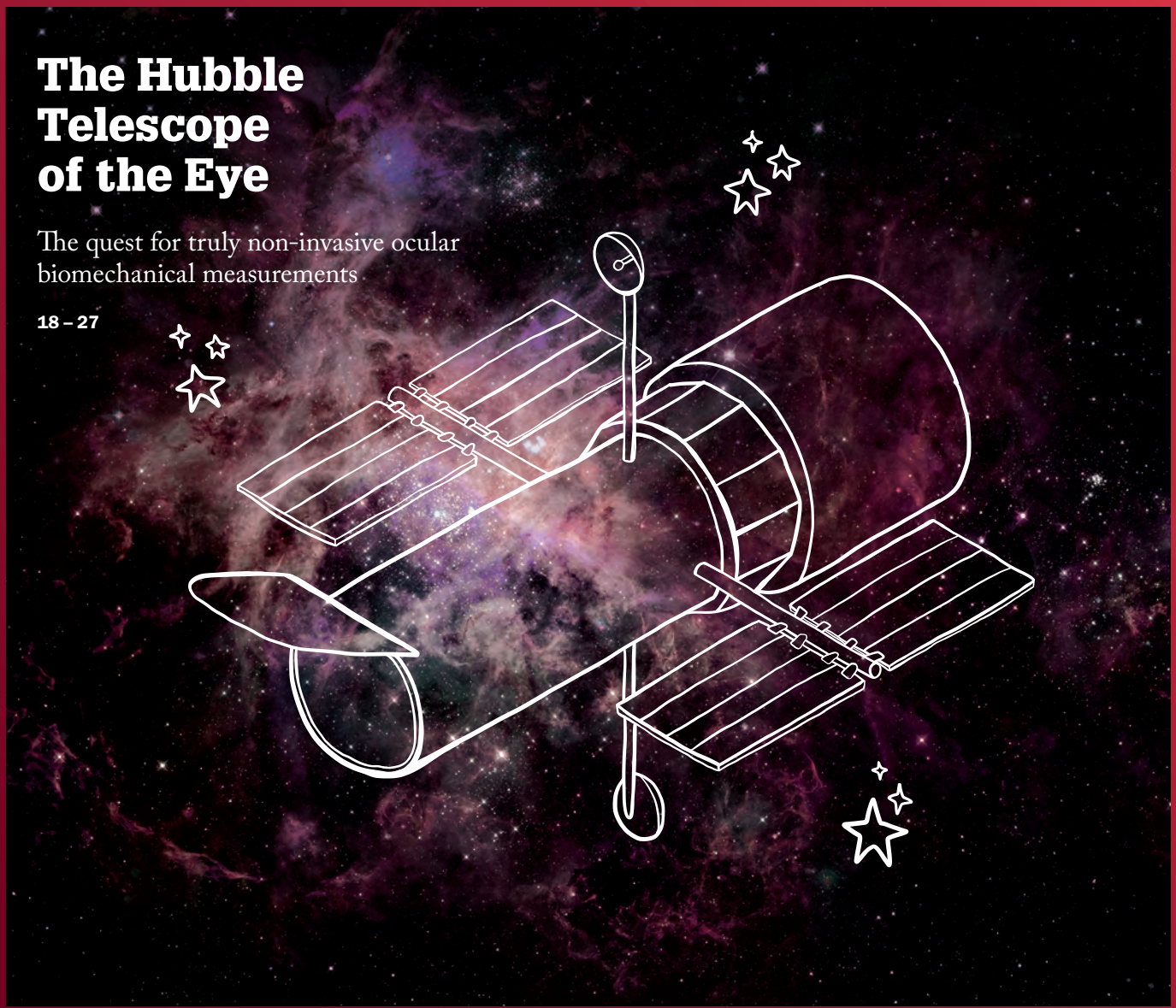

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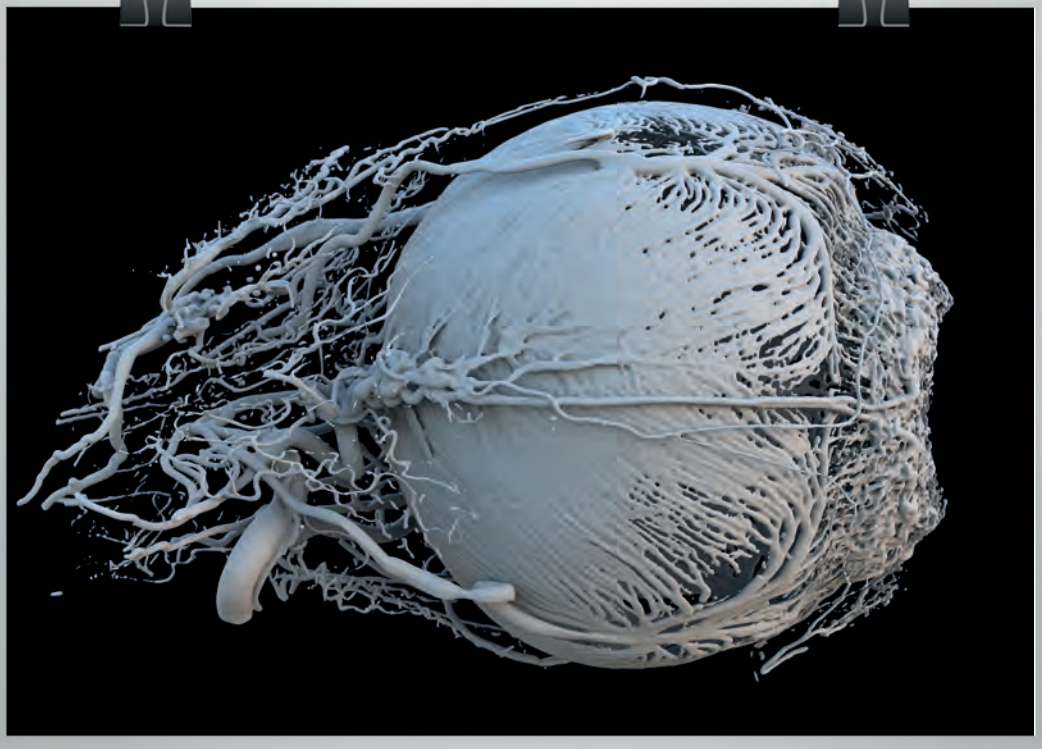

In a Micropig's Eye

This Wellcome Image Award winner depicts a 3D model of a healthy mini-pig eye. A contrast agent, µAngiofil, was injected into the microcirculation of the eye to allow visualization of the tiny vessels – the images were then transferred to a 3D model and printed. "The image displays the incredible vascular network of a healthy minipig's eye," says Peter Maloca, one of the creators of the image. "Our findings should contribute to better understanding of how the circulation is important in diseases like diabetic retinopathy or in ocular tumors. And as an image, it's amazing to look at just how wonderful an architect nature is," he adds.

Image courtesy of Peter Maloca, University of Basel, Switzerland, and Moorfields Eye Hospital, London; Christian Schwaller, Ruslan Hlushchuk, and Sébastien Barré

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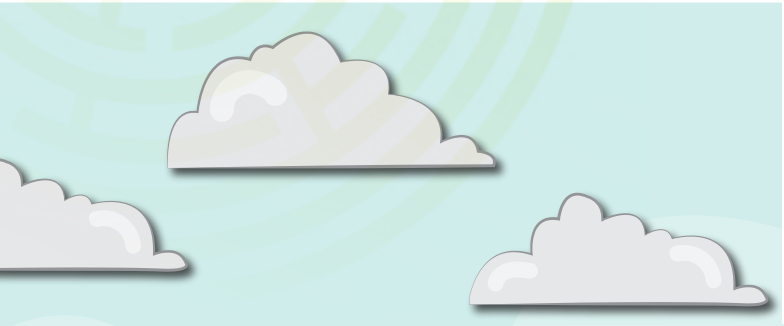

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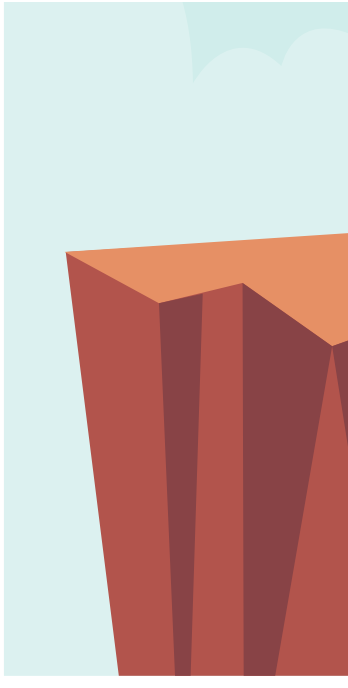

On The Cover

Julian Stevens described in vivo non-invasive ocular biometry as being "The Hubble Telescope of the Eye", inspiring this month's art theme.

Upfront

In My View

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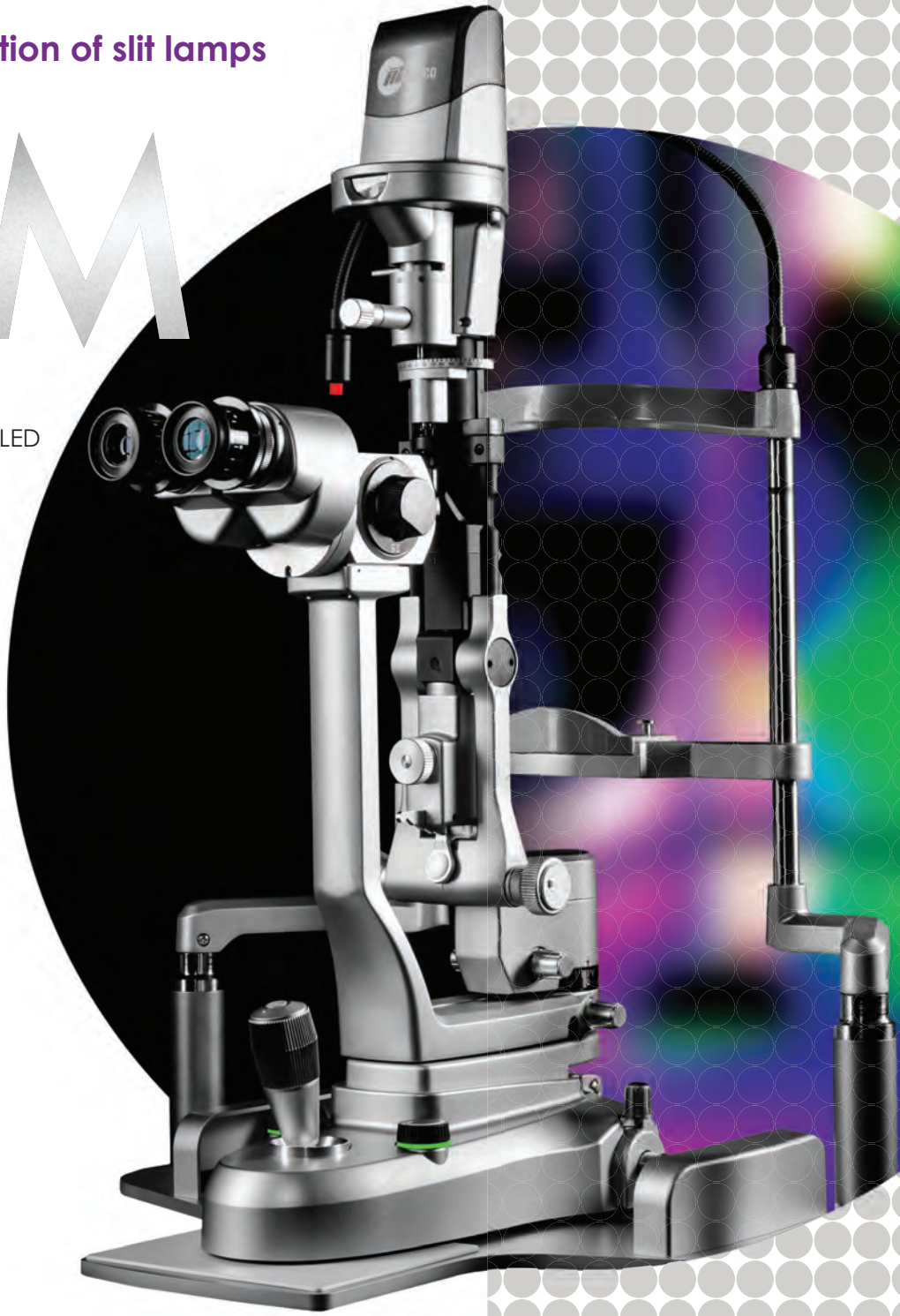

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The Ophthalmology Innovation Summit is for me the highlight of both the ASCRS and AAO Meetings. This meeting is packed with useful information for the ophthalmologist, industry executive and investor that is simply not available in any other venue. I consider OIS to be a cannot miss meeting.

★★★★★

Richard Lindstrom, MD

I love OIS, nothing else comes close in presenting the total picture of Ophthalmology with all of it's Business, Financing and Strategy.

★★★★★

Stephen Slade, MD

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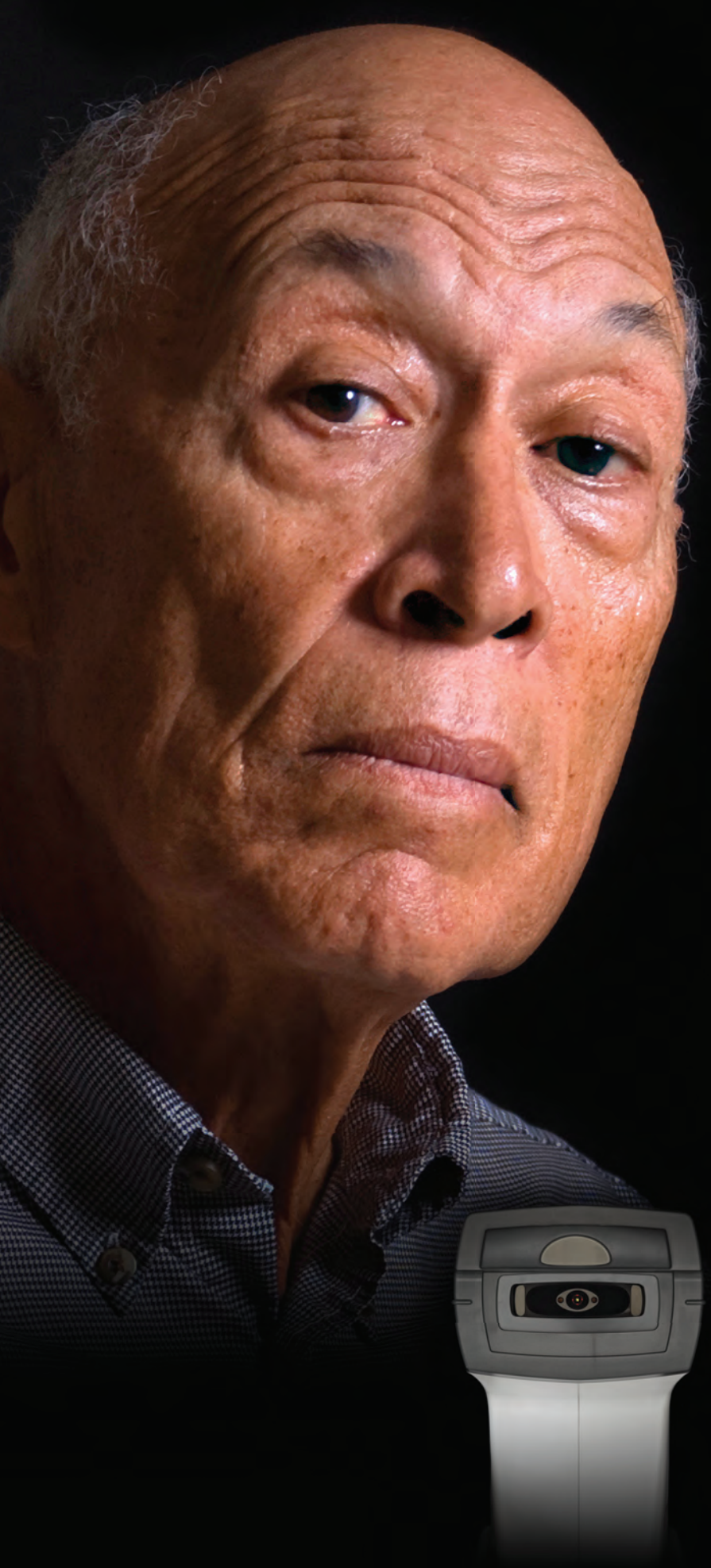

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The Big News Is Big Data

Might the next Nobel Prize in Physiology or Medicine go to a coder, rather than a researcher or doctor?

In May, I attended the annual meetings of both ARVO and the Royal College of Ophthalmologists. And what was the big news at both? Big Data.

As ever, many of the best conversations I've had on these topics have been in hotel bars next to the congress venues... So what did I learn?

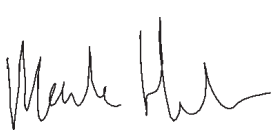
Electronic medical records (EMRs) are the future. Well-designed ones with lots of data are powerful – and will soon offer real-time information on the safety and efficacy of interventions in your institute and beyond. Of course, most of you dislike filling in the forms, clicking drop-down menus and radio buttons, spending more time typing than talking to patients. Fortunately, all of you people happily using Siri, Cortana and Google Now are making speech-to-text tech pretty awesome. Within 5–10 years, your EMRs could be filled in by the computer listening to the conversation with your patients, with any diagnostic scans being added in automatically. A quick check by the doc and it's done.

The automated algorithmic analysis of retinal image work is now well-known, and it is going to represent some amazingly helpful decision support and assist with the accurate triage of patients – separating the 'worried well' from those truly needing attention from ophthalmologists. Pearse Keane worries about the High Street: optometrists are all now adopting OCT. The amount of image data needing quality analysis will soon explode. It has to be dealt with somehow – and I think we have the answer.

And AI approaches can do even more. I watched Cambridge University's Peter Thomas present his group's work on automated eye tracking, pupil and face analysis tech. It was so smart that it could map every muscle visible in the face and track each one's every movement, so patients undergoing a short eye test need only be filmed to diagnose and assess any number of gaze, pupillary or facial nerve disorders.

What's most interesting to me is this: a future Nobel prize in Physiology or Medicine could go to an artificial neural network researcher, whose contribution was entirely in silico – someone who has never seen the inside of a medical school, let alone interacted with a patient. And might that person and their team have done more than Lister, Fleming or even Hippocrates to transform medicine?

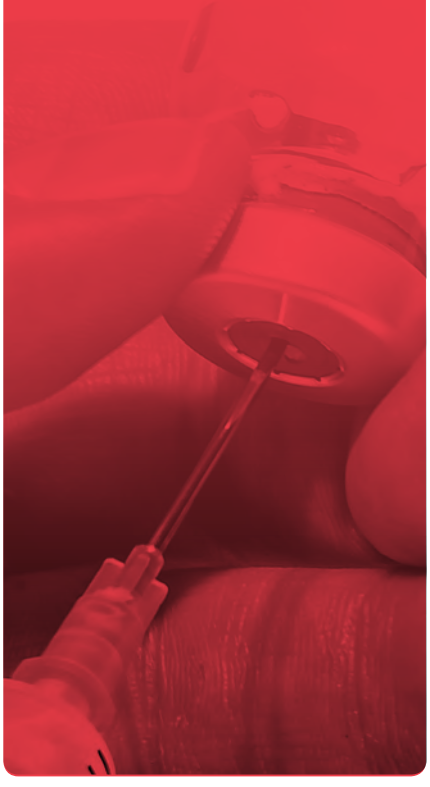
Mark Hillen
Editor

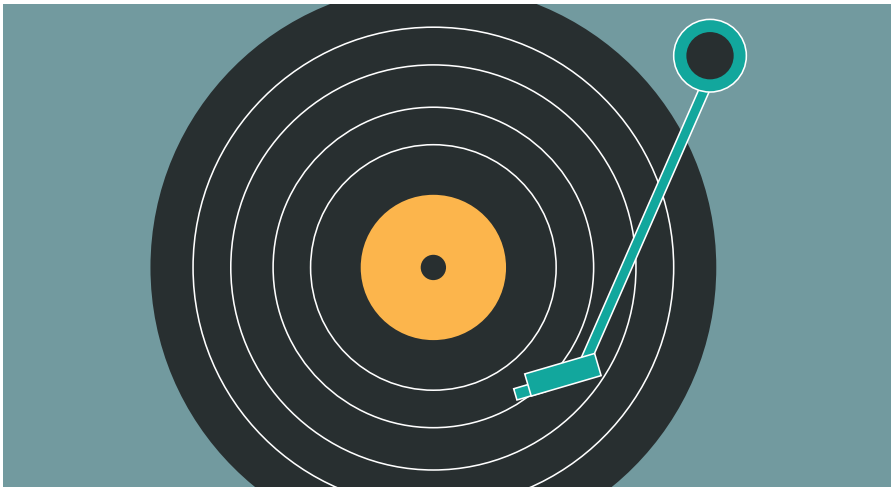


Upfront

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

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





Dropping the Needle

Topical anti-VEGF therapy may offer AMD patients an alternative to injections

"We hope to be able to provide a new method of treating patients with age-related macular degeneration (AMD)," says Felicity de Cogan of the University of Birmingham, UK, and lead author on a recently published paper describing topical delivery of anti-VEGF antibodies to the posterior segment (1). And it looks like they may have found one – with the help of cell-penetrating peptides (CPPs).

Originally, de Cogan was researching the use of CPPs in microbiology, but through collaborations with neuroscientists at her institute (Lisa Hill and Ann Logan) and clinicians from Queens University, Belfast, UK (Mei Chen and Heping Xu), the potential of CPPs to deliver drugs into the eye became evident. "Anti-VEGF therapies are well-established treatments for AMD but there has been little research on their topical delivery," says de Cogan. "The CPP formulation brings together the well-established field of CPPs and the unmet clinical need for improved delivery methods for patients with AMD."

CPPs (also known as protein transduction domains) act as chaperones, facilitating the cellular uptake of complexed proteins, but according to the authors, "The internalization mechanism has not been fully elucidated." In their study, the team exploited simple charge-based interactions to formulate anti-VEGF drug complexes decorated by the CPPs. After confirming that the peptides were nontoxic to cultured ocular cells, they topically applied complexes of CPPs and anti-VEGF drugs (bevacizumab or ranibizumab) to rat and pig eyes. Through OCT imaging and enzyme-linked immunosorbent assay analysis of ocular tissues, they demonstrated that CPPs were able to enter the anterior chamber (Figure 1) and reach the posterior segment.

"We were surprised at how quickly CPPs could enter the eye after drop application; they can be seen in high quantities in only six minutes," says de Cogan, adding that a key finding was the fact that CPPs could carry a large therapeutic protein such as anti-VEGF through to the back of the eye.

The team also compared anti-VEGFs delivered by CPPs with intravitreal injection in a mouse model of choroidal neovascularization (CNV), and found them equally efficacious at reducing lesion size (both $p<0.001$ versus negative controls of

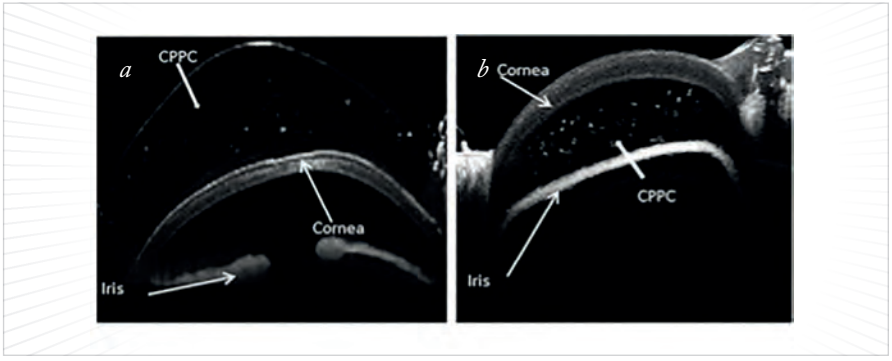


Figure 1. OCT images of fluorescent CPP in an eyedrop on the corneal surface the time of application (a) and within the anterior chamber by 6 minutes (b). (1). CPPC, CPP complex.

CPP-only, anti-VEGF-only and PBS eye drops). "The anti-VEGF therapeutic had the same outcome on disease progression whether it was delivered topically by CPPs or intravitreal injection," says de Cogan. The topically-delivered anti-VEGFs were found to reach physiologically-relevant concentrations and clearance from the retina after 24 hours suggested the need for a daily dosing regimen.

According to de Cogan, CPPs are highly effective antimicrobial agents, potentially negating the need for preservatives in eyedrop formulations. But what about the issue of poor patient adherence to eyedrop regimens? "The regime won't work for everyone and some patients may find a monthly injection preferable. The key to this technology is that it gives patients a choice and provides an alternative that might have reduced side effects," says de Cogan. The team hope to begin clinical trials within a year of raising funding. *RS*

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Business in Brief

Collaborations, acquisitions and a potential case of misleading information…

- Sightlife Surgical have teamed up with Shigeru Kinoshita to bring a new corneal therapy to market. The treatment, which involves the injection of cultured human donor endothelial cells into the anterior chamber, has shown promising results in over 30 patients in Japan.
- Aerie Pharmaceuticals has reported that their IOP-lowering combination therapy (netarsudil ophthalmic solution 0.02% [Rhopressa] and latanoprost; Roclatan) has met the primary efficacy endpoint in their Phase III trial (Mercury 2). Over the 90-day study period, the once-daily eyedrop showed statistically significant superiority over both latanoprost and Rhopressa monotherapies for lowering IOP in patients with glaucoma and baseline IOP 20–36 mmHg.
- ClearSight's parent company, Sharklet Technologies, announced that it has been acquired by Peaceful Union, a China-based equity medical device firm.
- In December 2016, Lensar announced it had filed a Chapter 11 bankruptcy petition. Now, they've announced that they will become a wholly-owned subsidiary of PDL BioPharma, in an order that has been court-approved.
- STAAR Surgical has announced that their EVO+ Visian implantable contact lens (ICL) has received a CE mark. Containing an aspheric extended depth of focus (EDOF) optic, the ICL is indicated for the correction or reduction of hyperopia and myopia between +3 D and -18 D.
- The District Court of Hamburg has issued a preliminary injunction in favor of VSY Biotechnology BV against Carl Zeiss Meditec AG (CZM) because of what VSY describe as a "misleading press release" published by Zeiss (1), which stated that "VSY Biotechnology BV and its exclusive distribution partner Fritz Ruck Ophthalmologische Systeme GmbH were convicted by the court to recall all their trifocal lenses on the market and destroy all such lenses in their possession."
- Representatives from VSY told The Ophthalmologist: (i) this is a ruling by the German Court of First Instance; (ii) VSY have the right to appeal the judgment in the Higher District Court and if necessary, the Federal Supreme Court in Germany – a process that may take several years; (iii) this ruling would only apply in Germany; and (iv) VSY has asked the European Patent Office to invalidate CZM's Patent EP 2 377 493 B1, claiming that this trifocality patent lacks novelty.

Reference

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No More Playing Pirate?

Amblyopes might soon be able to ditch the patch for virtual reality therapy

Imagine receiving vision treatment just by watching your favorite television shows. Well, patients with amblyopia could soon be doing just that – with a virtual reality (VR) headset designed to rebalance visual input to both eyes.

The idea is the brainchild of Dean Travers, a former professional skier who became interested in amblyopia after suffering post-concussion vision loss in one eye (20/20 to 20/80). Commenting on the mainstay treatment of patching he said, "Being a pirate isn't cool for very long" (1), so he endeavored to develop something better, teaming up with fellow Harvard University students (Alex Wendland and Scott Xiao) to form start-up company Luminopia. "We were shocked that patching was still one of the best options to treat the condition, so we started looking into the research and came up with the idea of applying VR," says Xiao, co-founder and Chief Scientific Officer.

David Hunter of Boston Children's Hospital, Massachusetts, USA, is acting as Clinical Advisor to the team. "Nobody likes telling children they have to wear an eye patch all day, and for good reason; patches are uncomfortable, and for kids with amblyopia, they actually cover up the eye that has better vision making it harder to read and even play," says Hunter. Similarly, he explains that although eyedrops are another option for treatment, they aren't popular either because of the side effects of pupil dilation and "foggy" vision.

How does the VR system work? "The software designed by the team at Luminopia works by dynamically rebalancing video input through a VR headset," explains Iason Mantagos, also of Boston Children's Hospital, who is leading an ongoing clinical trial evaluating the headset for binocular stimulation treatment of amblyopia. In the trial, patients wear a 3D headset and watch videos on a smartphone for one hour per day. Split into two four week segments, patients enrolled in the eight week trial were randomized to a 'full' treatment group who received the VR therapy from the beginning, or a control group who watched regular videos for the first four weeks before crossing over to the treatment for the remainder of the trial.

Next, the team plans to conduct further validation studies and wants to improve the device before potentially launching the platform in Canada and the US in the next few years. Says Hunter, "The idea that we might soon be able to tell kids that they don't need a patch or eyedrops, but will 'have' to watch their favorite TV show or movie for an hour every day while wearing VR goggles is great news for doctors and parents alike." And the kids can still play pirates – if they want. *RS*

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Mind the Gap

In patients with glaucoma or thin corneas, don't trust GAT-corrected IOP values – instead look to the difference between DCT and GAT

IOP measurements from Goldmann applanation tonometry (GAT) assessments aren't all that accurate; central corneal thickness (CCT) can impact pressure readings, with IOP_{GAT} being underestimated on thin corneas and overestimated on thick ones (1). But although several GAT correction formulas exist, how accurate are they? And how might those inaccuracies impact glaucoma care?

A Zurich-based team of researchers decided to investigate (2). "Over years working with dynamic contour tonometry (DCT) we realized that the well-known relationship between CCT and over- and underestimation of IOP_{GAT} is not valid in all cases. The question came up of what results correction formulas provide as they calculate mainly with CCT parameters," says corresponding author Christoph Kniestedt of Talacker Eye Center, Zurich, Switzerland. In their prospective, cross-sectional clinical trial, they measured IOP in 112 patients with glaucoma using Pascal DCT and GAT. Comparing IOP_{DCT} with conventional (uncorrected) IOP_{GAT} (IOP_{DCT}-IOP_{GAT}), they found a mean discordance of 3.3 mm Hg ($p<0.001$). Comparing IOP_{GAT} that had been corrected by five separate formulas, the discordance between DCT and GAT ranged between 2.7 to 5.4 mmHg (all $p<0.001$).

The group also identified a positive correlation between discordant IOP values and glaucoma severity ($r_s=0.33$, $p<0.001$). "We have shown that glaucoma is in a more advanced stage when the difference between IOP_{DCT} and IOP_{GAT} increases," says Kniestedt. CCT was found to be negatively associated with discordant values ($r_s=-0.22$, $p<0.02$). Concluding that GAT values are significantly discordant with DCT measurements in eyes with thin corneas and advanced glaucoma, the authors advised: "[…] to not place reliance on GAT readings, and abandon any correction formula" (2).

Commenting on the results, Kniestedt says, "The question is whether we really need to know the accurate IOP, or if it is sufficient to be aware of an additional risk factor such as $IOP_{GAT-DCT}$ difference. I would say that the second is sufficient; if we had a device to measure the real IOP – and if the measurement was significantly different from the 'gold standard' GAT – then we would need to re-write our textbooks and guidelines." Kniestedt explains that a patient who has an IOP of 18 mmHg and an $IOP_{DCT-GAT}$ difference of 5 mmHg might have a higher glaucoma risk than a patient who has a GAT value of 20 mmHg but an $IOP_{DCT-GAT}$ difference of 1 mmHg. "If we know the DCT-GAT difference and, as such, the additional risk factor in any individual patient, then we can use the old GAT value perfectly well." *RS*

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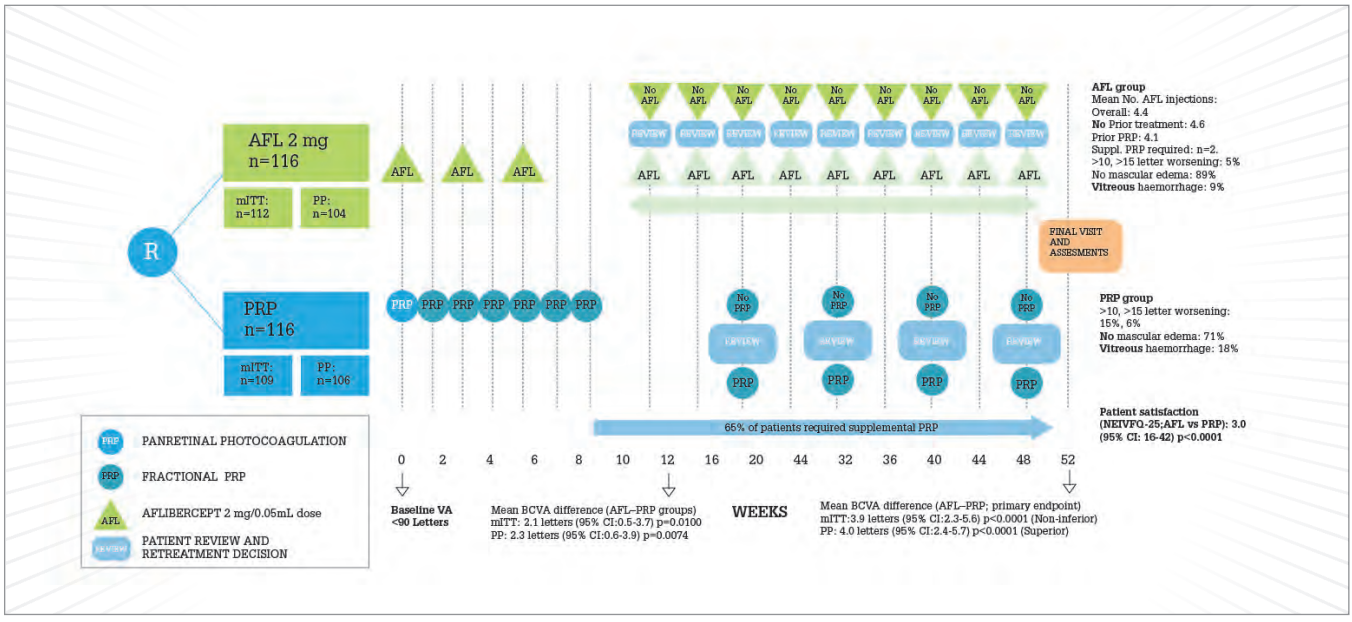

Figure 1. CLARITY study design and key efficacy and safety outcomes. AFL, aflibercept; BCVA, best-corrected visual acuity; CI, confidence interval; mITT, modified intent-to-treat; PP, per-protocol, PRP, panretinal photocoagulation; R, randomization.

CLARITY Achieved

Can an anti-VEGF agent outdo PRP for the treatment of PDR?

For nearly 40 years, the standard treatment for proliferative diabetic retinopathy (PDR) has been panretinal photocoagulation (PRP). It works (partly through reducing VEGF), but at a cost: it risks permanent visual field loss, DME exacerbation – and even with timely PRP treatment, 1 in 20 eyes still go on to develop severe vision loss. As retinal neovascularization is a central component of PDR, might the mighty anti-VEGF agents that have been so successful in treating other retinal neovascular disease supplant the venerable PRP?

In 2015, the DRCR.net published the results of Protocol S (1), which compared the outcomes of patients with high-risk PDR (with and without macular edema) treated with PRP or ranibizumab 0.5 mg. After two years of follow-up, the conclusion was that "treatment with ranibizumab resulted in visual acuity that was noninferior to […] PRP" and that "ranibizumab may be a reasonable treatment alternative, at least through 2 years."

But what about aflibercept? CLARITY (2) was a multicenter Phase IIb non-inferiority trial that compared aflibercept 2 mg with PRP over a one-year period. The study design and key results are illustrated in Figure 1, but the essence is this: patients with PDR, treated with aflibercept, displayed superior visual acuity after one year compared with those treated with PRP. The study's chief investigator, Sobha Sivaprasad, says: "This study is the first to show superior visual outcomes with an anti-VEGF agent, when compared to PRP, in proliferative diabetic retinopathy without baseline macular edema. These are significant findings for an eye condition that has been treated with PRP as standard-of-care for the past 40 years to demonstrate that aflibercept could potentially be adopted as an alternative treatment option, in the first year, in compliant PDR patients in the future." She also notes further avenues for investigation: "The three initial doses may represent over-treatment, and spreading a few doses evenly across the year may offer a cost-effective alternative to PRP." *MH*

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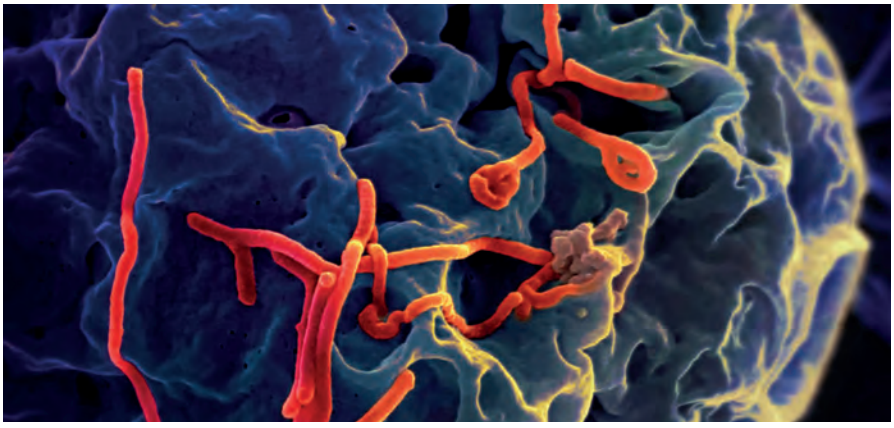
Survival Scar

Characteristic retinal lesions provide clues on how Ebola virus enters the eye



What and why?

Case-control prospective study examining whether any specific retinal signs can be attributed to past Ebola virus disease in survivors and whether the virus persists in the aqueous humor (1).

Who?

Eighty-two Ebola virus disease survivors with post-Ebola syndrome who had previously reported ocular symptoms, and 105 unaffected and asymptomatic controls.

How?

Ocular examinations, including widefield retina imaging (scanning laser ophthalmoscopy) and OCT analysis; paracentesis of the anterior chamber was performed on two patients with white cataract.

Findings?

A novel retinal lesion was identified in 14.6 percent of Ebola virus disease survivors; the scarring followed the pattern of optic nerve axons (Figure 1).

The aqueous humor sampled from two Ebola virus survivors with white cataract was negative for viral RNA.

Upshot?

According to corresponding author Paul Steptoe (2), "The distribution of these retinal scars or lesions provides the first observational evidence that the virus enters the eye via the optic nerve to reach the retina in a similar way to West Nile Virus. Luckily, they appear to spare the central part of the eye so vision is preserved." He added, "Our study also provides preliminary evidence that in survivors with cataracts, aqueous fluid does not contain Ebola virus, therefore enabling access to surgery." *RS*

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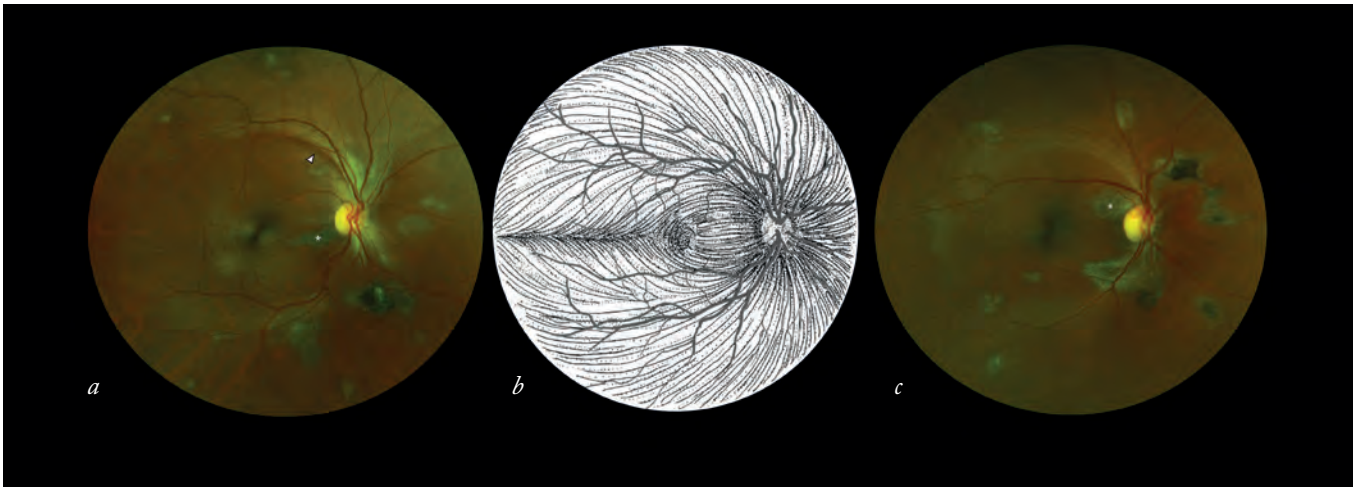

Figure 1. Composite SLO retinal images showing peripapillary or peripheral lesions, observed following the anatomic distribution of the ganglion cell axon (retinal nerve fiber layer). a. Example 1, right eye. b. Illustration of the ganglion cell axon anatomic distribution. Courtesy of W.L.M. Alward. c. Example 2, right eye. Credit: University of Liverpool.

In My View

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

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

Contact the team at edit@theophthalmologist.com

Congenital Glaucoma: Are We Operating Prematurely?

The instinct is to act early to save vision – but at what cost?

By Nader Bayoumi, Assistant Professor of Ophthalmology at Alexandria Faculty of Medicine, Alexandria University, Egypt

Glaucoma in children is a disaster waiting to happen. If undetected for too long or inadequately treated, the inevitable fate is blindness. In children, treatment is almost always surgical and there are many options, including angle surgery, filtration surgery (or a combination of the two), drainage device placement and cyclodestructive procedures. But inadequate treatment – just like no treatment – results in a relentless progression towards total vision loss. The visual deterioration is multifactorial and can be attributed to corneal pathology (progressive enlargement, edema and scarring), refractive error (myopic shift) and most importantly, optic nerve cupping attributed initially to posterior laminar bowing (which is reversible) and later neuronal damage (which is irreversible). Fortunately, timely successful surgery results can reverse many of these changes. The consensus is that the best chance is the first chance, and that each subsequent procedure has progressively lower success rates. Hence, maximizing the chance of a successful initial procedure is of utmost importance.

Most of us were taught that we should operate on pediatric glaucoma cases as early as possible – which means some procedures are performed on children only a few days old. But operating on very young children presents issues. Glaucoma diagnosis is not always clear at such an early age because it is very difficult to accurately measure IOP given the very narrow palpebral fissures present in very young children. Opening such small eyes almost invariably applies pressure to the globe, resulting in artefactually and artificially high IOP measurements. Additionally, cloudy corneas in such young patients are not always related to elevated IOP; many clear spontaneously with time. Further, a hasty decision to operate without waiting to perform further examinations does not allow us to establish whether the disease is progressive in nature. And then there are other issues related to the operative procedure itself; first, it's technically difficult (through a very narrow palpebral fissure) and second, filtration surgery has a very high chance of failure because of the aggressive healing response in infants – the tendency to fibrose is inversely proportional to age.

But... How long could and should you postpone surgery for glaucoma in young infants? In my practice, we recommend two months. This is tempered by the clinical scenario: two months would not cause much optic cupping – or any deterioration that cannot be reversed if the subsequent surgery was successful, plus corneal edema would not result in any permanent scarring over this short period. Waiting also gives time for the palpebral fissure to grow, making IOP measurement more accurate (as well as diagnosis and evaluation) and surgery far easier to perform. And if the cornea is cloudy from a cause other than elevated IOP, there is time for spontaneous clearing to occur. The final advantage of waiting is that the healing response gets less aggressive with time, improving

chances of filtration surgery success. So the surgeon's dilemma is this: perform a hasty, technically difficult operation with an extremely low chance of success, with a potentially doubtful diagnosis… or wait for a 60-day delay that brings with it a solid diagnosis, makes the procedure technically easier to perform and has a higher success rate, plus the eventual reversal of almost all possible pathological changes induced by the disease. I strongly believe that the second option is the right one, and that's why, in my practice, the minimum age for operation on children with glaucoma is currently two months.

Expectations and Exit Strategies

In younger patients, focus on the corneal plane for correction of presbyopia

By Günther Grabner, Chairman Emeritus, University Eye Clinic Salzburg, Paracelsus Medical University, Salzburg, Austria

No technique for correcting presbyopia is perfect – a compromise always has to be made. But I believe that solutions of the corneal plane are the best for younger patients; there are many benefits and a few approaches you can take. If you have a good laser available, it can be put to good use in the cornea – presbyLASIK is well-established, and studies with long-term follow-up are available (1, 2). Newer techniques have also emerged; for example, laser blended vision, which has seen good success rates (3). PresbyLASIK can simultaneously correct sphere and astigmatism, is mostly reversible, and gives the option of extraocular correction – if the patient is not happy, you can always try a contact lens to avoid further laser treatment. Other approaches do exist (thermal keratoplasty and conductive keratoplasty, for example), but, because they are not widespread and have to some extent disappeared from the market because of large amounts of regression, I will not cover them here.

Similarly, decentered ablations in presbyLASIK are no longer used. Central and peripheral presbyLASIK has been published on extensively; if you want to get into the details, Ioannis Pallikaris has done an excellent survey of these techniques (4). Central presbyLASIK is good for near vision, but doesn't perform well with distance vision and is a little difficult to correct. Peripheral presbyLASIK is good for distance vision and has good safety, but provides limited near vision. Patient satisfaction is generally high, but some patients can lose up to two lines of near visual acuity. Spectacle independence is better in hyperopes than in myopes, and patient selection and management are crucial. However, it's important to remember that laser correction is a static modification of a dynamic process – so as I said before, it's always a compromise. Moreover, there are few long-term studies on the effect of epithelium remodeling over time and the progression of presbyopia.

Another option that I believe holds great promise are corneal inlays; indeed, the cornea is the best place to put a piece of plastic in the eye to treat presbyopia. Inlays have two primary advantages: they are tissue sparing and removable. But there are also the challenges of ensuring that the optics are effective and that the results are stable and predictable. A few options are now available, including intracorneal microlens systems, such as the Raindrop, Icolens and Flexivue – and the small aperture depth of focus Kamra inlay, which has been approved in the US and implanted in over 3,000 cases in the last year (and more than 22,000 cases since studies of it began) (5). All of these implants are highly biocompatible, and are almost fully reversible; if the patient is not happy, take them out early, and the cornea essentially reverts back to normal.

My advice in these cases? Manage patient expectations, always have an exit strategy and remove corneal implants early if the patient isn't happy. For younger patients without cataract who don't want to risk intraocular problems, corneal techniques can offer better safety and are reversible – if you take out the inlay, it's gone. There's no risk of endophthalmitis, capsular rupture, refractive surprises as with IOLs, vitreous loss, retinal detachment or secondary cataract, which means you lessen your chances of an unhappy patient with side effects that are difficult to treat. This is why, in my view, the cornea is the way to go!

The author reports no conflicts of interest relevant to the content of this article.

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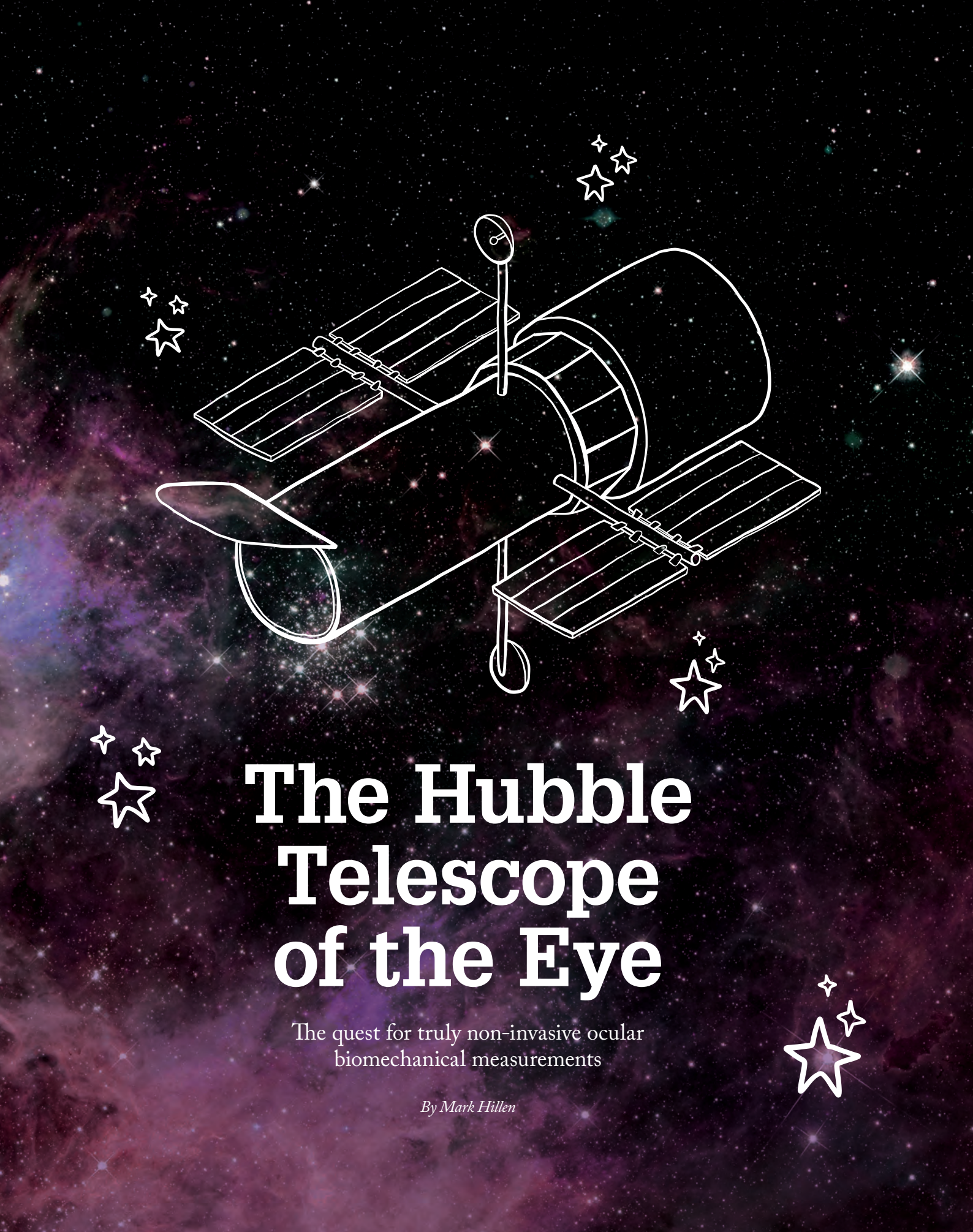


The Hubble Telescope of the Eye

The quest for truly non-invasive ocular biomechanical measurements

By Mark Hillen

When it comes to rheology – the branch of physics that deals with the deformation and flow of matter, especially the non-Newtonian flow of liquids and the plastic flow of solids – the eye is one hell of a playground. Some structures are somewhat rigid (like the sclera) and others barely at all (the aqueous humor). It's a pressurized system, drainage issues can cause huge problems, there's a multitude of muscles that can change not only the direction of the eye at any given moment but also the shape of the tissues inside it. Aging progressively stiffens the principal component of the eye's focusing system: the lens, and this is all before we get to refractive surgery like astigmatic keratotomy, PRK, LASIK, and SMILE weakening the cornea, let alone any disease states.

The cornea is an exquisite example of a close structure-function relationship. It is mechanically strong – strong enough to cope with a wide range of intraocular pressures that can be present in the eye (not just ocular hypertension or glaucoma, but intraocular surgical procedures like cataract surgery, too) and still maintain its geometry. In all of these situations (unless a pathology is present), it is also able to remain transparent throughout life, which is important as the cornea provides about two-thirds of the refractive power of the eye. So the cornea has two main functions: protect the eye and refract light. But even a small change to the structure of cornea can make a big difference to one – or both. The classic example is keratoconus: cone development and progression can rapidly lead to huge dioptric changes in patients' refraction (and if untreated, ultimately rupture). Further, small arcuate incisions or the laser ablation of relatively small amounts of tissue can both lead to big changes in how the cornea refracts incoming light.

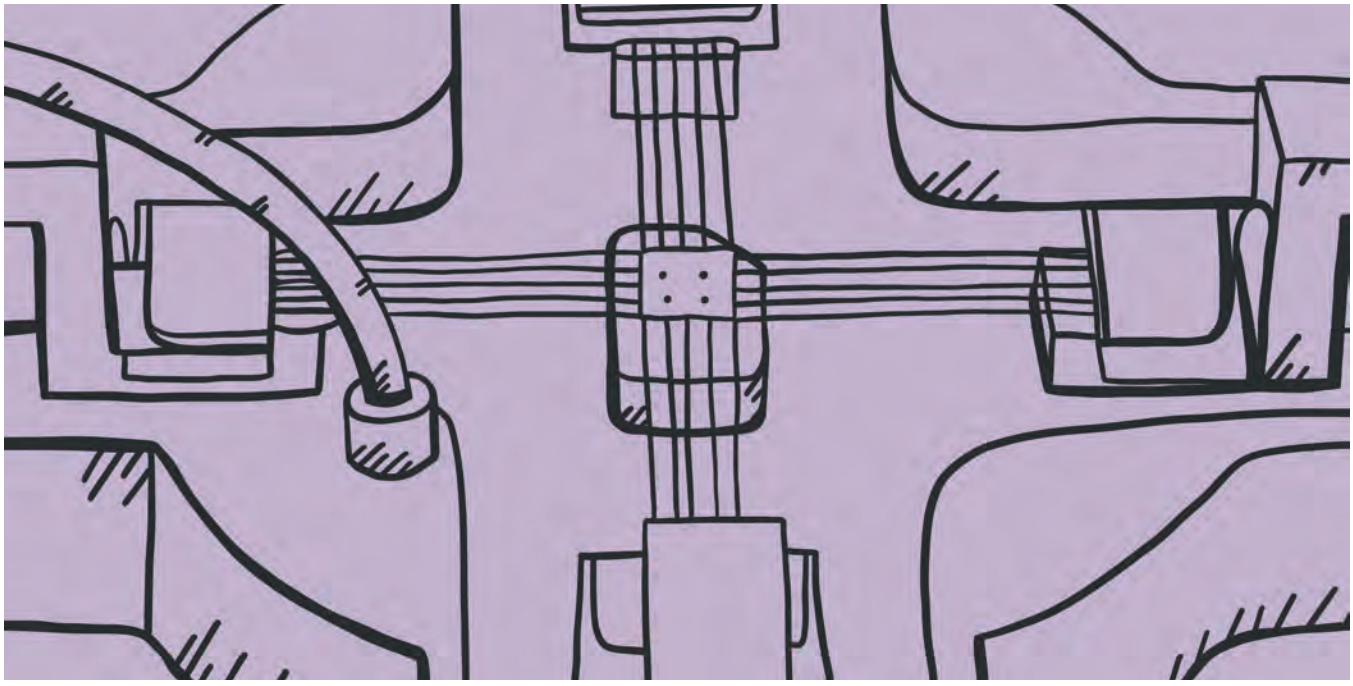
"We've known for many years that the topography of a cornea clearly influences its behavior – and many devices have been developed that measure this and track these changes over time," says University College London's John Marshall. "It's allowed us to make assumptions regarding the state of the cornea, and make diagnostic decisions based on them. It is useful information, but it can't quantify biomechanical properties like corneal stiffness."

Today's corneal biomechanical assessments

Peng Shao and Amira Eltony of Harvard Medical School and the Wellman Center for Photomedicine explain traditional limitations. "What we do know about corneal biomechanics has mostly come from ex vivo cornea experiments. Strip extensometry (where the cornea is cut into strips and subjected to uni-axial or bi-axial loads) or pressure inflation experiments have given the vision science community some great insights," notes Shao. Eltony explained that "You have to bear in mind that these are all destructive tests. They compromise the structural integrity of the cornea where the collagen fibers have been cut, and are limited to the experimental setting." John Marshall adds that the loading method bears little relationship to physiological loading and that, in the eye, the cornea is curved, which leads to "non-uniform stress distributions." Given the importance of the cornea to vision, there's no hope of obtaining biopsy tissue here. A cornea stripped from its pressurized, tensioned native environment can only reveal so much information...

Unlike corneal topography, for in vivo, nondestructive assessments of corneal biomechanics, Marshall notes that "you currently need dynamic measurements to quantify biomechanical properties at any given time, like tracking the change of shape of the cornea in response to a measured load" – just like those provided by Reichert's Ocular Response Analyser (ORA) and Oculus' Corvis Dynamic Scheimpflug Tonometer (ST). Both use a puff of air to deflect the cornea. ORA uses an infrared beam and both use very high-speed cameras to track how the cornea responds to this deflection, capturing the ripples out to the periphery. Appropriate processing of the ORA infrared waveforms that return can give you some useful parameters – corneal hysteresis (CH; the ability of the cornea to absorb and dissipate the energy from the air puff – in other words, the rate-dependent viscoelastic response), corneal resistance factor (CRF; the total visco-elastic response of the cornea) and "corneal compensated" IOP (IOP_{CC}). This last one is important – IOP measurements using the trusty old Goldman tonometer have long been known to be affected by corneal thickness and stiffness – and topical prostaglandin therapies are known to soften the cornea, so it's valuable to be able to measure IOP without the influence of these confounding factors. With the Corvis ST, the depth of air puff-induced deformation can be measured and, once IOP has been taken into account, should be primarily related to corneal biomechanical properties. But again, there are limitations with these methods. The data are only gathered from the center of the cornea and under pressures that aren't physiological in terms of either magnitude or direction. Further, CH, CRF, and other deformation parameters have been shown to be influenced by other factors, such as differences in central corneal thickness and IOP (1).

Julian Stevens, Consultant Ophthalmologist at London's Moorfields Eye Hospital puts it this way, "With these techniques, we're essentially bouncing the cornea like a trampoline. The reality is, measuring IOP is important, but actually, once you know how stiff the sclera and cornea are, then it becomes a much more interesting number than just



A classic corneal biomechanical assessment: strip extensometry.

the headline IOP on its own, and the individual importance of the IOP can be much better understood."

There are a number of other approaches, such as Placido disk imaging or optical coherence elastography, which can be used to measure corneal shape changes after corneal indentation by interventions like a puff of air or a concave lens. But as Eltony explains, "They all share the same problem: these are at best an overall corneal biomechanical measurement. They can't detect localized stiffening or weakening in the cornea." If you want a stiffness map (and if you're dealing with a patient with prior refractive surgery or a corneal ectatic disorder, you really do), these classic mechanical approaches won't give you the right information. But two other non-contact approaches look like they can: Brillouin spectroscopy and laser interferometry.

The next generation

Brillouin spectroscopy

Brillouin spectroscopy is a quantum mechanical process that isn't directly comparable to the classic mechanical assessments described above. This approach does not involve any dynamic or shape-changing processes, but probes biomechanical properties of (quantum) mechanical fluctuations on an atomic level (or by its wave analogy). Probing is instead performed non-invasively by a dynamic process: the analysis of photon-phonon interactions.

"What's really held Brillouin spectroscopy back for years has been signal detection."

To go any further in this story, we need to understand what a phonon is. Quantum mechanics textbooks would describe a phonon as "the elementary vibrational motion in which a lattice of atoms or molecules uniformly oscillate at a single frequency." It's perhaps more helpful to view phonons as a description of the collective excitation of molecules or atoms in condensed matter. In tissues, phonons are present due to the thermodynamic fluctuations of the molecules and atoms that constitute those tissues, and phonons can be also created by light. These spontaneous mechanical fluctuations in the tissue can also be probed by light: photons from the light source enter, interact with these acoustic phonons and scatter the light in a characteristic manner. Brillouin spectroscopy (Figure 1) is the measurement of spectral changes in how

light is scattered by an object – and it reveals information on the phonon's properties, and therefore (and crucially), the viscoelastic properties of the medium. In other words, for each point a scanning confocal laser beam hits, the instrument detects the spectral shift between the outgoing light and the light that returns. This should be directly correlated with the modulus of elasticity at that point, meaning you can map in all three dimensions and generate a stiffness map.

The only problem? Other phenomena scatter the light too, and the frequency shifts involved with the Brillouin scattering are in the gigahertz range and have a very faint signal strength.

What's really held Brillouin spectroscopy back for years has been signal detection. When it comes to assessing the biomechanics of an inanimate object, detectors like Fabry–Pérot interferometers or angle-dispersive etalons did the job – as the object is inanimate, it can be imaged for as long as is needed. But for biomedical imaging, these approaches aren't good enough – they were either too slow, or their signal-to-noise ratio was too low to be useful. A breakthrough came in 2007 at Harvard University and Massachusetts General Hospital when Giuliano Scarcelli and Seok-Hyun (Andy) Yun managed to combine Brillouin spectroscopy and confocal microscopy with a virtually imaged phase array (VIPA) detector that enabled very high throughput and efficient spectral separation. The speed and signal-to-noise ratios were high enough, and multiple frequencies could be detected at the same time, speeding the acquisition time (2). Achievement unlocked.

However, the gap between demonstrating proof-of-concept and actually having a product that clinicians can use can be huge. OCT took seventeen years from concept to clinic – and in the case of the Harvard team, a far speedier nine years to develop the technology to a stage where it was fast and sensitive enough for clinical use. The Brillouin confocal microscope is now called the Brillouin Optical Scanner System (BOSS), and is being commercialized by Intelon Optics; a prototype is now being used clinically.

Laser interferometry

The other approach is laser interferometry. It uses the principle that if you can view the displacement of an object in response to a known load, you can determine several useful properties of the material – including stiffness (3,4). Here, displacement is measured by holography – or its digital form, electronic speckle pattern interferometry (ESPI) – and it can be used to create 3D phase-related displacement fields for mapping. John Marshall explains, "A monochromatic coherent laser is split into two: one wavefront illuminates the object, the other acts as a reference beam. Both are combined in an imaging device. The resulting image is a pattern of speckles

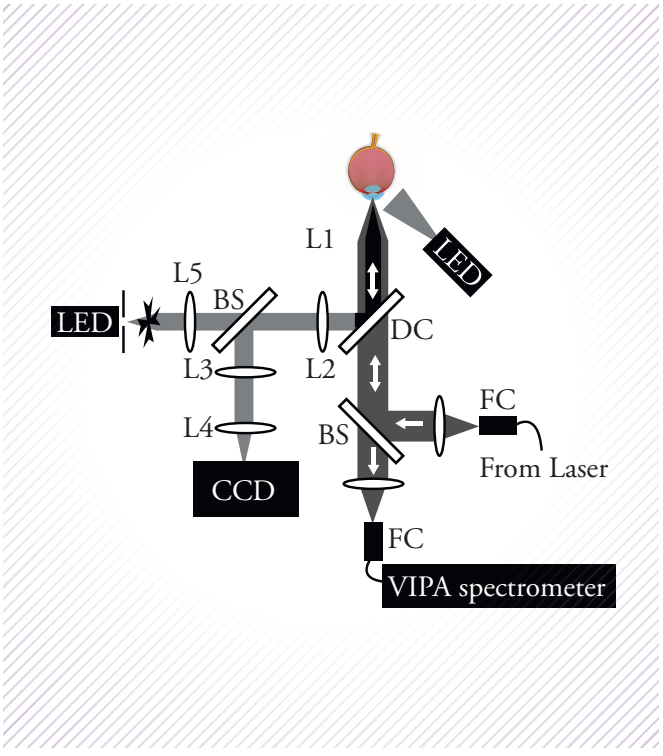


Figure 1. The Brillouin confocal in vivo microscope in schematic form.

that encodes information on the wavelength displacement of returning light. In principle, performing laser interferometry is pretty simple: take a reference measurement and take another measurement after applying a load, then subtract the speckle patterns" (Figure 2). A similar technique, electronic speckle pattern shearing interferometry (ESPSI) can also be used to measure the surface strains of a sample after a mechanical load (3,4); rather than using a reference beam, the object is used as its own reference. The wavefront that returns from the object is transformed from the original wavefront and interferes with it. "Shearing interferometry is performed by splitting the wavefront into two parts – one part is transformed by the object in a specific way, and the wavefront is recombined to give a specific speckle interference pattern – and as before, two measurements are made, before and after displacement, followed by a subtraction of both patterns," says Marshall. "This gives you is the rate of displacement, i.e. strain – or information on which areas of a structure are weaker and which are stronger." ESPI and ESPSI are widely used in engineering for applications like the detection of cracks in aircraft wings, or vibration and strain monitoring – but could also of considerable utility in understanding the biomechanics of the eye. The development of an in vivo device is currently ongoing.

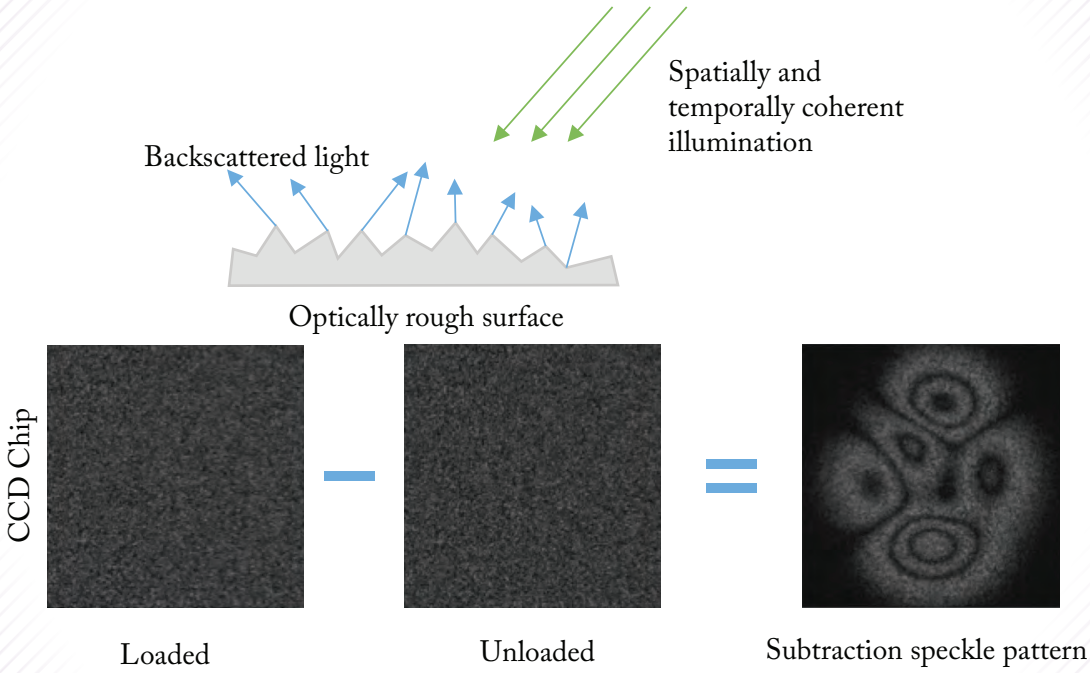


Figure 2. Principles of non-contact, non-destructive full field laser interferometry (3). Spatially and temporally coherent light illuminates the tissue of interest. Light is backscattered from an optically rough surface and is detected by a charge-coupled device (CCD) as a depth-resolved speckle pattern. An initial reference measurement is taken, followed by a measurement after loading. A subtraction speckle pattern is generated, showing the effect of the loading.

What's the potential?

Corneal ectasia screening and corneal collagen cross-linking

Let's start with refractive surgery and with "do no harm." LASIK-induced ectasia is the stuff of nightmares – that's why there is a whole spectrum of diagnostic procedures to help avoid causing it, from genetic tests to corneal topography. But forme fruste keratoconus (or any other subclinical weakening of the cornea) is incredibly challenging to detect with corneal topography; it's suspected or identified based on very subtle changes. But it's the weakening of corneal collagen fibers that results in the changes in corneal topography (5,6) – and if Brillouin microscopy or the laser interferometry approach can detect the weakening at an earlier stage than other methods, many patients who would have otherwise undergone laser refractive surgery and gone on to develop ectasia would be spared the ordeal.

There's also a more obvious application: optimizing corneal collagen cross-linking (CXL) and monitoring post-CXL corneas for any signs of ectasia progression (7). Before performing CXL, knowledge of the strongest and weakest regions of the cornea (Figure 3) is particularly valuable when it comes to optimizing beam profiles and scanning patterns. But it's the knowledge of how effective the procedure has been in strengthening a patient's cornea that will feed into the optimization of not only how the light is delivered, but also which riboflavin solution works best under certain circumstances. Stevens notes, "We need to get a lot smarter with CXL to ensure that each eye that's cross-linked is properly cross-linked and we need a measurement of strength to reference the individual cornea against the population distribution." Next generation corneal biomechanical assessments should help with that.

Brillouin microscopy has already been used to measure the differences in corneal elasticity before and after CXL – and to assess novel CXL techniques (Figure 4) (8,9). The corneal flattening effects of CXL are also being investigated for the treatment of low myopia – and it's clear how knowledge

> "This could mean that you could plan a strategy that would correct for a large proportion of SIA, well in advance of scrubbing up for surgery."

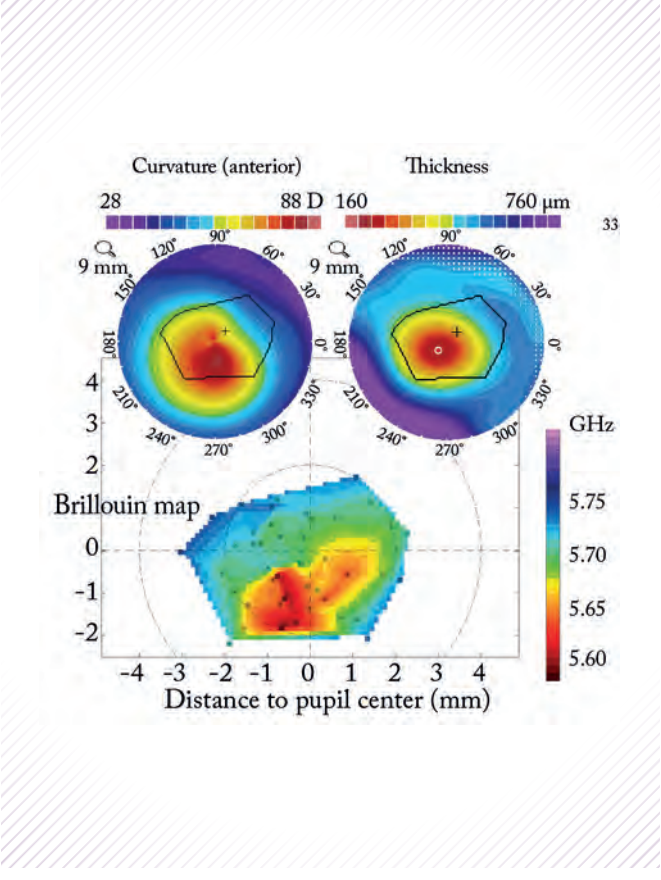


Figure 3. Brillouin elasticity map (as represented by the mean anterior Brillouin shift) of a 40-year old with advanced keratoconus (9). Image courtesy of Andy Yun.

gained through the use of corneal Brillouin microscopy or laser interferometry might help optimize the procedure.

Laser refractive surgery

Every cornea has its own unique biomechanical properties and, when it comes to incisions or ablations, each cornea reacts in a slightly different way – not only to the procedure, but also in recovery. A better understanding of each patient's individual corneal biomechanics before and after refractive surgery should help further optimize current finite element models of the cornea and how it reacts to surgery – ultimately leading to more accurate outcome predictions. Such knowledge could also predict the amount of surgically induced astigmatism (SIA) that is caused during any procedure that involves corneal incisions (like cataract surgery). It also means you could plan a strategy that would correct for a large proportion of SIA, well in advance of scrubbing up for surgery.

"The astigmatism nomograms for astigmatism correction in cataract surgery take into account SIA," says Stevens. "If you go to a nomogram calculator website like my own (Figure 5), the first thing you have to put in is your own SIA. So with my standard incisions, I get an overall 0.3 DC against-the-wound shift. So with a temporal incision, in those patients who do not undergo astigmatic correction, the overall effect is a 0.3 DC push vertically – so I steepen the vertical meridian by 0.3 DC. That's my standard across my overall population. But in reality, each eye is different. I have some eyes which have 1.0 DC of shift. Others have zero shift at all. Some of that's topographic noise, some of that's any other number of factors, including epithelium, tear film changes and many other factors. But if we had knowledge of the individual cornea's biomechanics, we'd be able to get about a 50 percent improvement in astigmatic treatment outcomes using intrastromal femtosecond laser arcs."

Glaucoma and ocular hypertension

A better understanding of the biomechanics of the eye has other applications too – like characterizing the stiffness of the trabecular meshwork (TM). One of the hallmarks of primary glaucoma is the accumulation of glycosaminoglycans in the extracellular matrix and a thickening of TM beams (10). This results in a loss of trabecular spaces and, combined with chronic inflammatory changes, appears to alter the biomechanics of the TM; it becomes stiffer, changes outflow and can influence the onset and progression of glaucoma (11,12). If you're able to measure TM stiffness, it not only helps screen for potential problems, it also opens up a potential new pharmacological

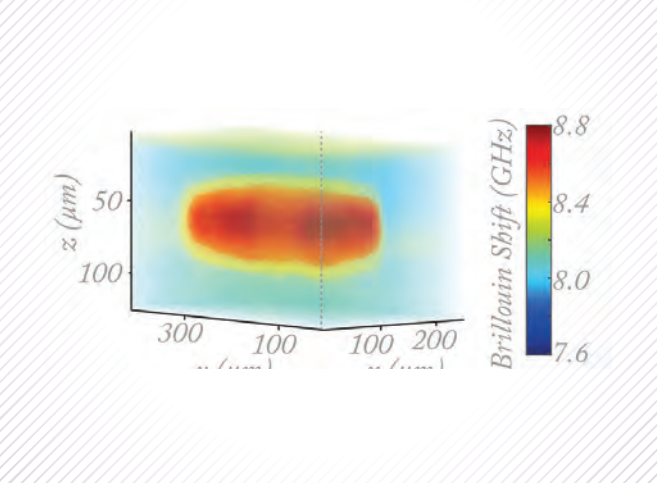


Figure 4. Reconstructed 3D view of a cross-linked cornea imaged by Brillouin microscopy (2). The region in red is the cross-linked region and corresponds to a higher Brillouin shift (due to a higher stiffness) than the surrounding area.

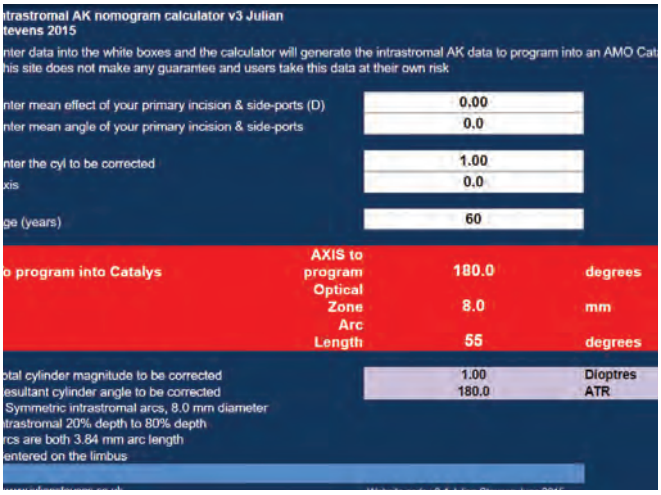


Figure 5. An example of an intrastromal astigmatic keratotomy nomogram calculator for use during femtosecond laser-assisted cataract surgery – the first being the surgeon's own surgically-induced astigmatism.

approach for glaucoma therapy – as well as a measurable endpoint to test any such therapy's efficacy (12).

And there's another application in glaucoma: scleral biomechanics. A number of biomechanical models have suggested that the sclera transmits IOP-induced mechanical strain to the optic nerve head (13), and experiments in ex-vivo human eyes have confirmed that the greatest scleral strain is in the peripapillary region (14). A number of mouse studies have suggested that eyes that are stiffer at baseline (and therefore more resistant to elongation) are less likely to experience one of the defining features of glaucoma: retinal ganglion cell (RGC) loss (15,16). Could peripapillary scleral collagen cross-linking (SXL) help protect eyes with elevated IOP from RGC loss and optic nerve damage? Performing SXL is easier said than done – the sclera can be difficult to access, care needs to be taken to avoid damaging extraocular muscles, and issues that pertain to uniform light delivery need to be resolved – but all of these aspects look like they can be overcome (17). It's also likely that the exact positioning and amount of SXL needs to be individualized, which is where techniques like Brillouin microscopy or laser interferometry might come in. Stevens notes that "If SXL can be successfully performed, then there's another potential application: arresting scleral elongation to control myopia and prevention."

The aging lens

Presbyopia can also be considered a biomechanical problem. It's widely accepted that the natural crystalline lens gradually loses elasticity as people age, with a subsequent decrease in accommodation range – but the specifics (changes in lens stiffness with age and how much it compromises accommodation) remain unknown. Although the lens can be imaged (and its ability to accommodate) in vivo with ultrasound biomicroscopy, OCT, or even magnetic resonance imaging, not one of those methods reveals anything about lens stiffness. Brillouin microscopy has already been used to show that, in mice, the lens nucleus is considerably stiffer than the cortex, and saw a "marked age-related stiffening" (18). In vivo Brillouin sagittal stiffness profiles have already been characterized in humans – from young adults to those

"Biomechanically-guided SXL could prove to be an effective treatment for glaucoma or for the prevention of pathologic myopia."

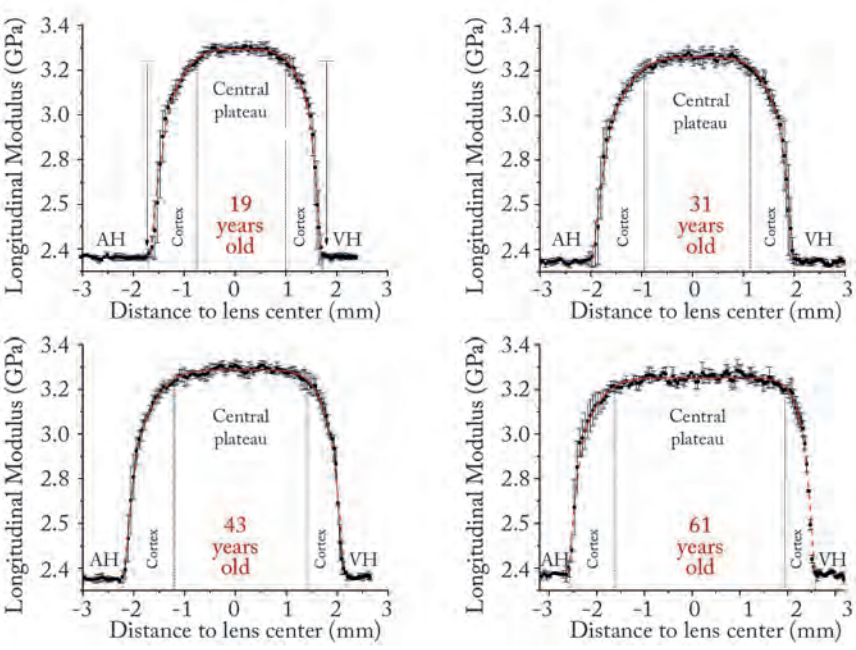


Figure 6. Lens biomechanics change as people age. In vivo Brillouin sagittal stiffness profiles (from aqueous humor [AH], through the lens to the vitreous humor [VH]). The central plateau is defined as the top 98 percent value in longitudinal modulus. The points and error bars represent the mean and standard deviation of successive scans taken along the sagittal axis. Adapted from (17).

in their seventh decade (Figure 6) (19).

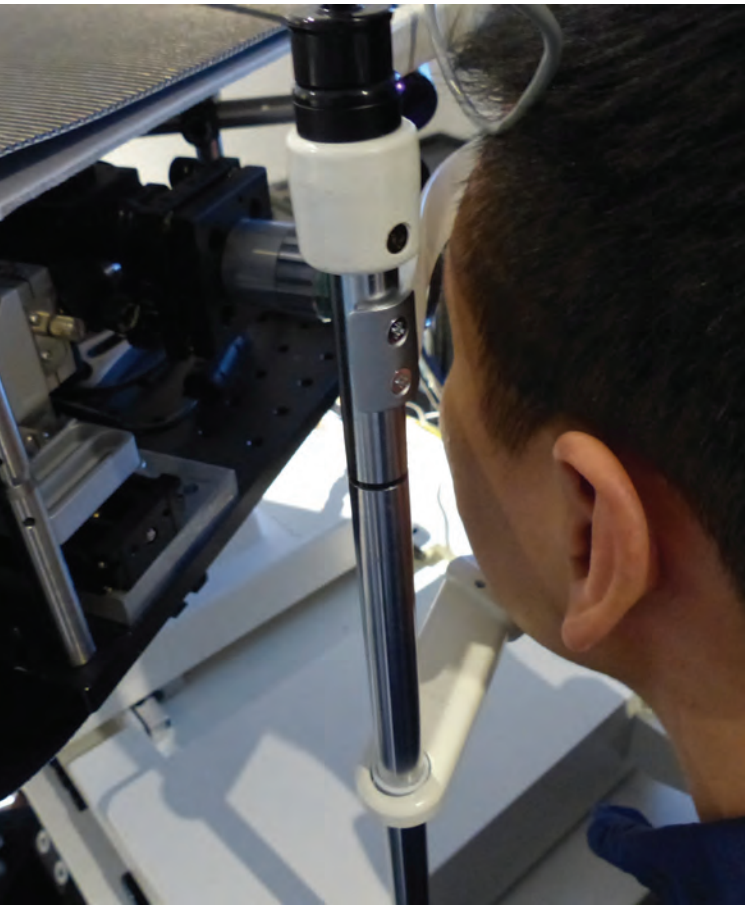
With lens-softening eyedrop treatments for presbyopia on the horizon – be it lanosterol or Novartis' EV06 compound under clinical evaluation – the role of any technology that can non-invasively assess their impact is not hard to imagine. However, Stevens notes, "The aging lens probably has some other degradations in terms of fibrillation of lens crystalline bundles and fibers, and just general disorganization and damage. So crystalline lens softening will have limits in restoring lens shape change and will not reorganize disordered crystalline lens fibers. But these techniques are the way of measuring lens stiffness in vivo and will be essential to understanding future presbyopia treatments."

Following in Hubble's footsteps

A better understanding of in vivo ocular biomechanics has the potential to offer better screening of patients for ocular disease, meaning earlier identification and more timely intervention. It could also mean that refractive surgery can become more personalized, predictable – and with better patient outcomes. And biomechanically-guided SXL could prove to be an effective treatment for glaucoma or for the prevention of pathologic myopia.

Right now, instruments like in vivo interferometers and BOSS are still a number of years away from being commercially available. But if they can be brought into the clinic, imagine the potential benefits it could bring to a whole spectrum of patients faced with a whole spectrum of diseases.

Julian Stevens views such technology as "the Hubble space telescope of ophthalmology – you can actually assess ocular biomechanics directly" and believes that it will rapidly change the way ophthalmologists and optometrists think about the cornea. "The scanner on its own provides data – data that will improve in quality over the next 5–10 years. But that data will be integrated into finite element models of the cornea. And very soon, we will have a whole lot of data alongside back-end intelligence to help interpret the scans you perform. It exactly like cardiologists' ECG scans, which come with very sophisticated deep learning AI analysis. Soon, we'll have



the same for the biomechanics of the eye. We're going to get new insights and improve what we do. It's as simple as that."

John Marshall reports no commercial interests in the technology and products mentioned in this article. Julian Stevens reports that he is a consultant to Intelon Optics, STAAR Surgical AG, Abbott, VistaOptical, Oculentis AG and Revision Optics. Peng Shao and Amira Eltony are Harvard Medical School research fellows under the supervision of Andy Yun, Scientific Founder and board member of Intelon Optics.

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Julian Stevens considers the impact of next-generation ocular biomechanics assessments in the clinic

Will we see intraoperative assessments of corneal biomechanics?

Intraoperative assessments will be extremely exacting from a technical point of view compared with what we're doing now. As soon as you place a drop of topical anesthetic on the cornea, the hydration changes; as soon as you take the epithelium off or make a LASIK flap or create a SMILE lenticule, or even if you fire the femtosecond laser into the cornea, you're going to change not just the hydration, but a whole ton of other parameters.

Once you start putting femtosecond laser pulses in, you have an amazing array of bubbles (except for Ziemer systems or the megahertz femtosecond lasers of the future) but even then, there is still a lot of light scatter coming back, and that will change the parameters. Intraoperative measurements will be highly complex. But if there's a need, there will be clever people who will find a solution. It's probably a "would like" rather than a "must have" right now – there are lower hanging fruits we can grab to get a better outcome.

How will next-generation corneal biomechanics assessments change femtosecond laser-assisted cataract surgery?

The evolution of the femtosecond laser for cataract surgery has been a gentle one. The slow introduction is because FS lasers are more precise – and the surgeons who using them love them – but it has been hard to find better refractive outcomes. Perioperative astigmatic treatment is one key area where there is a huge improvement using the femtosecond laser compared with manual surgery. An intrastromal FS laser application is about twice as accurate as manual surgery. So if you use one, there's an instant improvement in outcomes – no matter how good you are as a surgeon – and the laser is more repeatable than any manual surgery.

But even with the intrastromal application of femtosecond lasers, there's still a lot of noise in terms of variation in both delivery and outcome. Alex Day, my fellow at Moorfields Eye Hospital, and I looked at this and found that about half the variation in outcome could be ascribed to biomechanics using corneal hysteresis assessments. I can't wait to get my hands on a BOSS scanner and some proper Brillouin scatter measurements so that I can feed that data into the nomogram, and create a smart nomogram for the individual eye, as opposed to the generic one that we have right now.

The world is moving towards mass customization, and we need to follow with our surgery. We've modeled and, with some biomechanical feedback, we believe that we can improve astigmatic outcomes by an immediate 50 percent. That's huge. And that's why I'm very excited about this.

How soon until this technology reaches the clinic?

There are a number of physical, environmental and measurement hurdles to overcome, but overcome they will be! The development of the technology will depend on very smart people working around these issues and devising solutions. But like all new technologies, the speed of adoption depends on funding – the more funding, the faster the technology will come into clinical use.

> "The world is moving to mass customization, and we need to do that as well with our surgery."

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In Practice

Surgical Procedures
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Unique Cataract Challenges Versus Postoperative Success

Performing cataract surgery in patients with herpetic disease is not straightforward, so it's crucial to plan ahead and to choose your timing (and the IOL) carefully – but remember that a successful outcome is not out of reach

By Kenneth Beckman

Cornea specialists encounter many patients with herpetic disease – and these patients can pose unique problems when it comes to performing cataract surgery. However, with the right planning and management, you can achieve the best outcome for the patient. I like to break my own management into three stages: preoperative, intraoperative and postoperative considerations.

At a Glance

- *Cataract surgery in patients with herpetic disease can pose unique challenges but, with the right planning, you can achieve great results*
- *Before surgery, you need to identify a "quiet window", get your readings, and decide upon the appropriate surgical approach. It's also important to pick the right IOL*
- *During surgery, be sure to protect the surface of the eye, beware of floppy irides, and consider using Trypan blue for better visualization in cloudy corneas*
- *When it comes to follow-up, medication management is key; be aware of the medications your patient was on before surgery, and plan accordingly*

Before

For epithelial disease, my preference is that patients have been quiet and stable for six months at a minimum. However, for chronic uveitis this may be difficult to achieve – so there may be only small windows of quiescence (and limited opportunity to proceed). In fact, many of these patients are being co-managed with retina/uveitis specialists; if the view of the fundus is limited by the cataract, I often need to proceed whenever a quiet window occurs in these patients, breaking my own six month rule.

The first step is to make sure you have a stable surface – just as we do with any cataract patient, particularly ones who have surface disease and dry eye. You need to optimize the tear film and ensure that the surface is as good as it can be – some of these patients may also benefit from a punctal plug.

Do I have confidence in my IOL calculations?

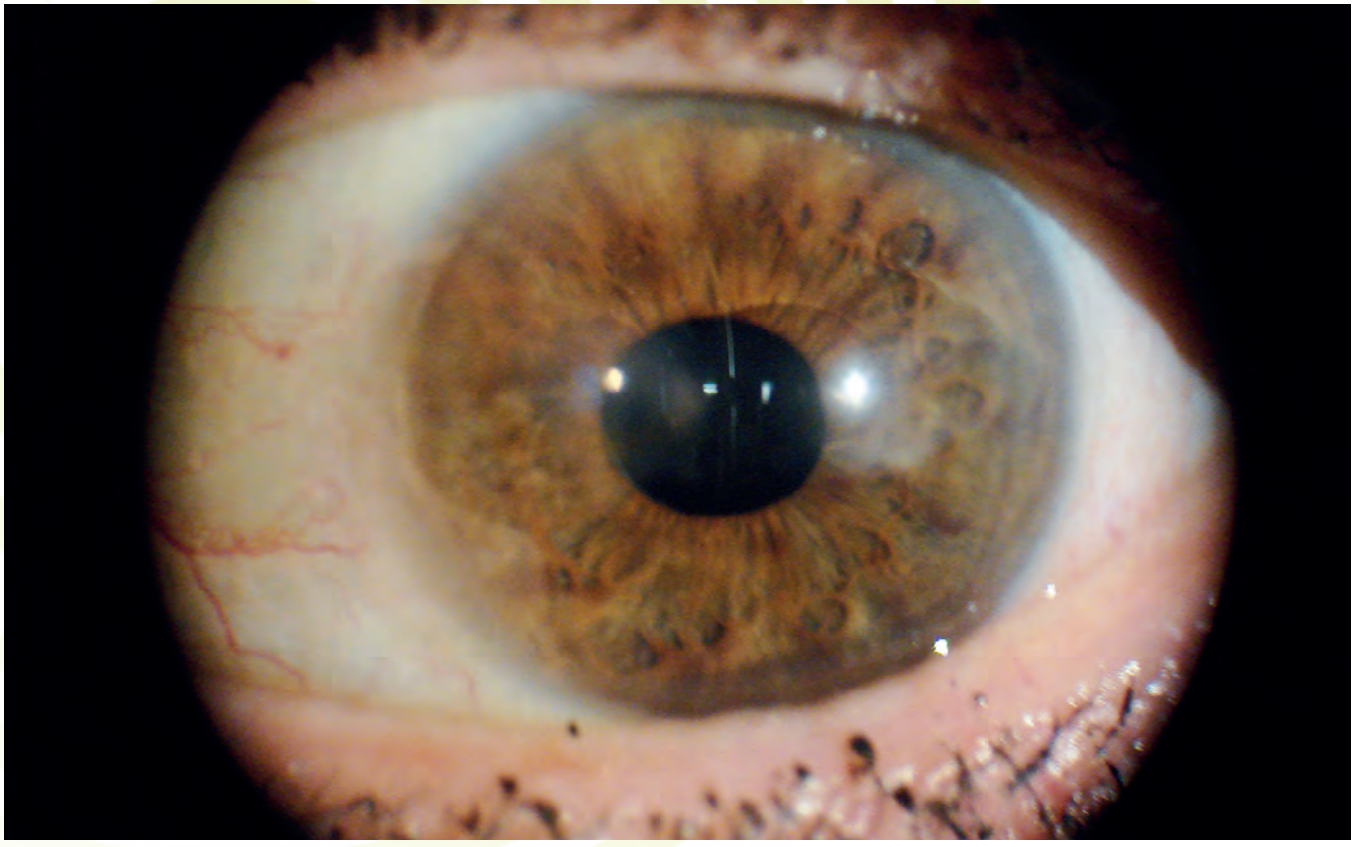
Many of these patients will have corneal scarring, which can cause a number of further problems, such as inaccurate keratometry (K) readings, which in turn leads to inaccurate IOL calculations. Corneal scarring can also lead to postoperative aberrations and visual disturbances, even if you choose the correct lens. The solution is to firstly get the cornea cleaned up as best you can, being sure to manage the tear film. Next, get multiple sets of K readings (including manual ones). I look at corneal topography, IOL Master readings, and manual K readings. If these all look consistent, I'm usually comfortable to proceed. But what can be done if you can't get good readings? It may help to compare with the other eye – or older records, if you have any prior to the onset of corneal disease. Occasionally, an amniotic graft membrane may be needed to improve the surface enough to obtain accurate measurements.

> *"With the right planning and management, you can achieve the best outcome for the patient."*

Is a corneal transplant required?

If the corneal scarring is sufficiently bad, a corneal transplant may be the next step – a tough call for many surgeons. My approach is to ask the question, "Can I see through the cornea well enough to take out the cataract?" If the answer is "Yes", I'll remove the cataract and see how much of a problem the cornea poses postoperatively. In these cases, you'll often be surprised and find that the patient sees much better than you expected. In some cases, you'll be able to introduce a scleral contact lens after surgery and optimize a patient's vision, avoiding the need for a cornea transplant.

If the cornea is so cloudy that cataract surgery would be made difficult, then I'll often do the transplant first. But this leads to another dilemma: do you perform the transplant on its own, or do you do the transplant and the cataract at the same time? If there's a significant cataract, you want to get it



A postoperative cataract surgery patient with a HSV scar on the central cornea. Credit: Kenneth Beckman.

done at the same time, using the "open sky" technique, which involves removing the cataract after the cornea has been removed from the eye. If you do the cornea alone in these cases, it may take months, or even over a year, before the cornea stabilizes enough to allow you to reenter the eye and remove the cataract.

Occasionally, I perform the procedures in the opposite order. When I know the corneal scarring is significant enough to require a transplant, but I can still see through it to get the cataract out, I might remove the cataract first in a closed eye, then perform the cornea transplant in the same setting, because I feel it poses less risk than the open sky method. However, it's uncommon to be able to see through the cornea well enough to do the cataract, and yet still demand cornea removal.

What medication is currently prescribed?

Medication is another important preoperative consideration – often, these patients are on antivirals and steroids. In these cases, I will maintain the existing medication, and may increase the level of antiviral the patient is receiving to the one I use preoperatively. My typical dose is 400 mg of acyclovir four times a day, anywhere from three to seven days preoperatively (famciclovir or valaciclovir are appropriate alternatives).

Which IOL?

I'm particularly hesitant to use multifocal lenses in a scarred cornea, and a good general rule for these patients is to use premium lenses with caution. An accommodative lens is an option, as you are likely to encounter fewer problems with aberrations – but if there is any concern over the accuracy of the IOL predictions, I'd also be hesitant to use an accommodative IOL. Though they can work well from an aberration standpoint, there is still a risk of an unhappy patient if they are a diopter or half a diopter off-target.

For the most part, I prefer a monofocal lens for these patients. When it comes to astigmatism, success can be found with arcuate incisions made using a femtosecond laser. But it's important to remember that, if a patient has a lot of astigmatism and you use a toric lens, you may not be able to use a scleral contact lens postoperatively – and that means you could run into a problem that you are unable to fully correct.

During

Once you go into surgery, it's important to protect the surface of the eye – it's going to be very vulnerable, so you need to ensure that you keep it well lubricated.

You may have issues with visibility, so I would recommend using Trypan blue. Normally, we think of using Trypan blue when we have a white cataract, but I've found that it also helps improve contrast in some patients with a cloudy cornea. Another tip is to use your surgical microscope's ability to change illumination on-the-fly, if that's an option. My microscope can change from on-axis to off-axis illumination, and I frequently play around with the settings to give me the best background illumination to visualize the capsulorhexis. With my old microscope, I sometimes used to switch the illumination off completely and instead use the vitrectomy light pipe, held from the side, to give a nice reflex illumination of the capsular bag. The lesson is: don't be afraid to play with the illumination, as doing so can help you complete the capsulotomy.

Such patients also have a tendency to suffer iris atrophy and will often present with similar characteristics to those seen with floppy iris syndrome (such as patients who have been prescribed Flomax). In these cases, use your favorite technique for floppy irises, whether that's a Malyugin Ring, iris hooks, Omidria, or something else.

After...

Postoperatively, I use my standard course of medication: an antibiotic and a non-steroidal drop. For steroids, I taper very slowly, usually starting at QID and staying there for two weeks. Then, I'll taper down weekly: three times per day for one week, then two times per day for one week, and so on.

Notably, if the patient was on a steroid before I operated, I won't go below their preoperative medication level – I'll stay there indefinitely. I believe one of the most common causes of postoperative flare-ups is caused by doctors cycling through their normal routine and forgetting that their patient was on a drop before the operation. And if the patient is being co-managed by an optometrist, who wasn't aware of their existing medications, they may also taper off the drops.

"The lesson is: don't be afraid to play with the illumination."

For the antiviral drug regimen, I usually recommend acyclovir four times a day for about three weeks. When I start tapering the steroids, I cut the acyclovir down to twice a day, until they're finished with the steroids, and then the regimen ends. But again, if they were on acyclovir preoperatively, I keep them on their previous dose.

Remember: it's important to continue to monitor these patients' herpetic disease not just during the postoperative period, but long afterwards too. Finally, if vision isn't where you want it to be, you need to continue treating their tear film. Often, I'll use a scleral contact lens to see how much more I can improve vision, and this generally works very well.

In short, herpetic disease does not have to be a barrier to good postoperative vision.

Kenneth Beckman is Director of Corneal Surgery at Comprehensive Eyecare of Central Ohio, and a clinical assistant professor of ophthalmology at Ohio State University.

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Single Incision: Multiple Advantages

The what, how and why of stab incision glaucoma surgery (SIGS)

By Soosan Jacob

Though trabeculectomy can be effective in lowering IOP, it has a high failure rate and many patients suffer complications post-operatively. One of the main problems with trabeculectomy is that, when creating the flap, you're creating a conjunctival wound that is going to heal by scarring – and scarring is one of the major reasons for failure. How do we get round these problems?

At a Glance

- *Although trabeculectomy is often effective in lowering IOP, the procedure comes with the risk of conjunctival scarring, treatment failure, and complications, such as bleb failure, oversized bleb formation, bleb dysesthesia etc.*
- *For patients with OAG, one alternative is stab incision glaucoma surgery (SIGS), which creates an intentionally compromised corneoscleral tunnel through a single stab or small incision*
- *Advantages of SIGS include less fibrosis, posteriorly-directed flow, and a larger area of available virgin conjunctiva for future surgeries*
- *Here, I offer an overview on how to perform SIGS, and explain why it could be a better primary surgery for patients with OAG and no prior conjunctival dissection.*

By making the conjunctival incision as small as possible by performing stab (or small) incision glaucoma surgery (SIGS) – a procedure I introduced for patients with open angle glaucoma (OAG) in 2013.

The basic principle of SIGS is very simple – it's a single 2.8 mm keratome incision straight through the conjunctiva and sclera into the cornea and the anterior chamber. This corneoscleral tunnel is then compromised by punching the inner corneal lip to create a controlled leak for aqueous drainage. Tunnel trabeculectomy has been described previously as successful filtration surgery (1–3), and whilst SIGS uses the same concept, the scleral tunnel is created in one step as opposed to tunnel trabeculectomy, which first creates a flap in the conjunctiva and also has a triplanar tunnel as opposed to the biplanar nature in SIGS.

Why perform SIGS?

There are several key advantages to performing SIGS: reduced risk of fibrosis, posteriorly-directed aqueous flow, simplicity of the procedure and post-operative management, as well as economic advantages – it's also faster to perform than trabeculectomy. I have been performing SIGS since 2013 and, in 2016, we at Dr. Agarwal's Eye Hospital and Eye Research Centre published results from a prospective interventional case series of 17 patients (4), which are summarized in Box 1 (SIGS Case Series). We are currently at a much larger series.

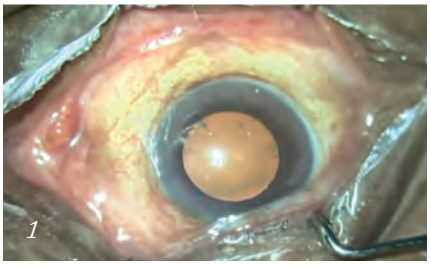
One of the main advantages of SIGS, reduced scarring, speaks for itself – decreasing the amount of conjunctival dissection means less scar formation. The small incision also preserves drainage channels in the sub-conjunctival tissue to a much larger extent than in trabeculectomy, meaning you are likely to get better subconjunctival drainage. Complications are also minimized, because there is no flap. Of course, the risk of fibrosis is not abolished, and mitomycin-C (MMC) can be given pre-operatively as a sub-conjunctival injection (0.1 ml of 0.005% or 0.01%) or intra-operatively as a MMC-soaked sponge applied to the tunnel (0.01 or 0.02% for two minutes).

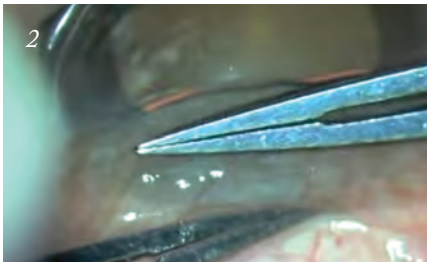
Better aqueous drainage is another main advantage of SIGS over trabeculectomy. The tri-planar flap created by trabeculectomy provides

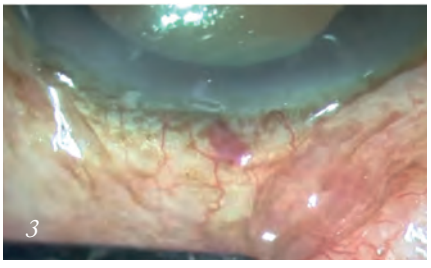
"With SIGS, there is no sideward flow because all flow is directed posteriorly, so the risk of oversized bleb formation and related complications is reduced."

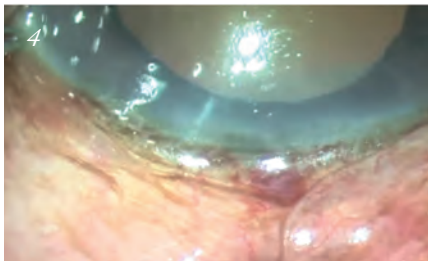
three directions of flow; both horizontal directions as well as posteriorly. But glaucoma surgeons only really want posteriorly-directed flow as horizontal flow to either side of the flap can lead to oversized and overhanging bleb formation and bleb dysesthesia. With SIGS, there is no sideward flow because all flow is directed posteriorly, so the risk of oversized bleb formation and related complications is reduced. From my experience, post-SIGS blebs are more diffuse posteriorly than those formed after trabeculectomy.

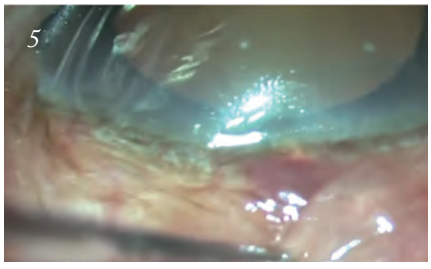
SIGS also maximizes the amount of residual virgin conjunctiva. In conventional trabeculectomy, when a large area is dissected in the first surgery, the available area of untouched conjunctiva for second surgeries becomes quite limited, increasing the risk of failure caused by fibrosed conjunctiva. SIGS leaves a large area of absolutely intact conjunctiva so it is easier to perform repeat procedures – crucial for patients with glaucoma. You can start with a small incision in the superior quadrant and, if that first surgery fails, you can then move to other quadrants.

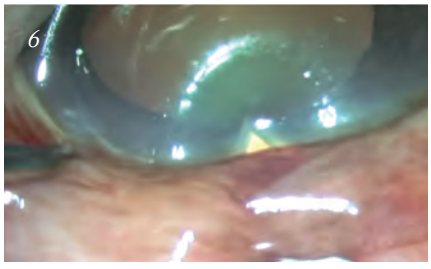


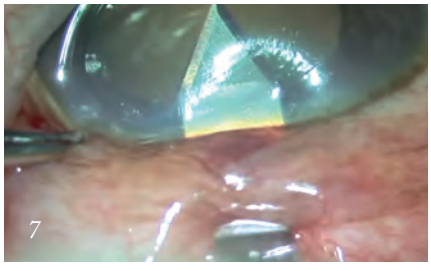






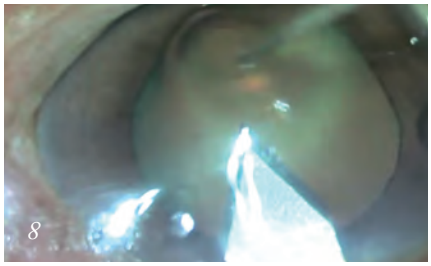






How to perform SIGS

- After peribulbular anesthesia (and optional MMC) has been applied, the first steps are to achieve a mobile conjunctiva by loosening the speculum and to push the conjunctiva downwards using a two-handed sliding technique (Images 1 and 2). A superior site is preferable as the supero-nasal fornix is short and the conjunctiva cannot be pushed as much in this location.
- *2.8 mm keratome entry*. Position the tip of a 2.8 mm bevel-up keratome 1.5 mm from the limbus and begin to tunnel forwards. The keratome should just be visible through the overlying sclera and conjunctiva (Image 3). Whilst the tunnel is being dissected, the eye position should be controlled by holding the limbus with strong one-toothed forceps (Image 4).
- *Creating the corneoscleral tunnel*. The scleral part of the tunnel should be short and shallow – the ideal length of the entry incision is 1.5 mm for the scleral component and approximately 1 mm into the cornea (Images 5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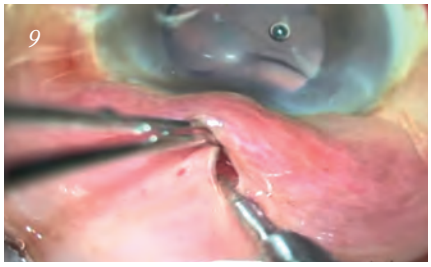
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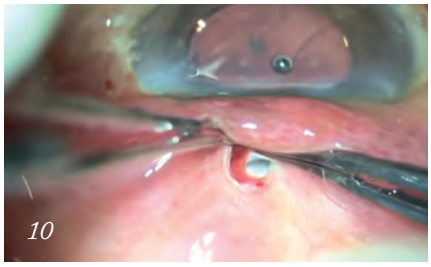
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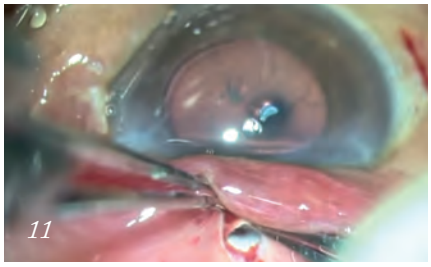
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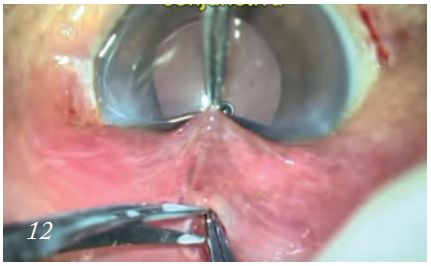
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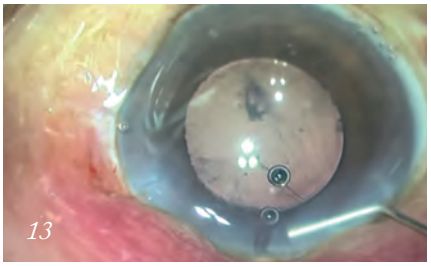
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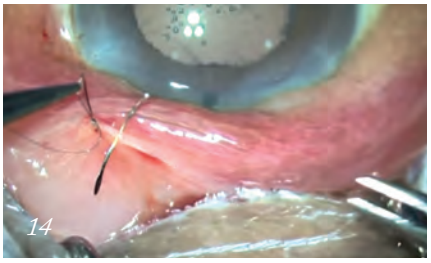
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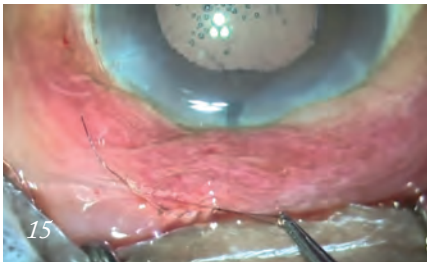
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and 6). At the limbus, the blade tip should be angled anteriorly to match the corneal curvature. The blade can then be introduced 0.5–1 mm into clear cornea before entering the anterior chamber in a horizontal plane parallel to the iris. Entry up to the shoulder of the blade should be made, avoiding both Descemet's membrane and the lens capsule (Image 7). Downwards pressure should be avoided while entering the anterior chamber.

- Remove the blade in a smooth backwards movement while holding the eye at the opposite limbus (Image 8); sideward movement of the blade can slice tunnel sides and slow withdrawal can cause the anterior chamber to shallow. Instill viscoelastic into the anterior chamber through a paracentesis or through the SIGS tunnel entry. At this point phacoemulsification and IOL implantation can be performed if the surgery is being combined with cataract removal; the SIGS tunnel will not leak as it is self-sealing because the ostium has not yet been created. Phacoemulsification should be performed with the main and side ports placed on either side of the tunnel.
- *Creating the ostium.* Slide a 1 mm Kelly Descemet's membrane punch in unretracted position and facing sideways along the tunnel and into the anterior chamber. Next, facing downwards, punch the internal lip of the corneal section and punch vertically backwards; horizontal enlargement is not required. Once the limbus is reached, the tunnel can be examined by retracting the conjunctiva; the extreme edge of the final punch should be just seen deep within the tunnel (Images 9, 10 and 11). Irrigation over the tunnel can help with easy visualization.
- *Peripheral iridectomy.* Shallow the anterior chamber. Insert angled non-toothed forceps and grasp the iris near its base just below the ostium. Retraction of the conjunctiva with non-toothed forceps by the assistant helps with visualization. Using curved Vannas scissors, cut the iris near its base (Image 12). Push the iris back into anterior chamber, ensuring that no iris is trapped in the tunnel (Image 13). As in trabeculectomy, a peripheral iridectomy is not an absolute must, however, it is preferred to be done in all cases as it avoids iris tissue blocking the ostium.
- *Checking the leak*. Wash out viscoelastic and assess leakage through the SIGS tunnel

SIGS Case Series

- A total of 17 patients underwent SIGS with pre-operative subconjunctival MMC.
- Mean reduction in IOP from pre-operative values was 38.81 ± 16.55 percent ($p<0.000$).
- Mean number of topical medications was reduced from 1.35 pre-operatively to 0.59 post-operatively ($p=0.025$).
- Post-operatively, 64.70 percent of patients achieved complete success, defined as an IOP <18 mmHg with no medications; 82.35 percent maintained an IOP <18 mmHg with two medications.
- Intra-operative complications encountered were premature entry, trapdoor hinging of internal corneal lip, conjunctival buttonhole, very small Descemet's detachment and nonbasal peripheral iridectomy (all n=1; all managed or no intervention taken).
- Six patients encountered post-operative complications of uncontrolled IOP, of which three were managed medically and three underwent repeat surgery.
- No sight-threatening complications were reported (4).

by irrigating balanced salt solution (BSS) through side-port irrigation; there should be a free flow of fluid. If it is difficult to visualize flow, hold the conjunctival cut closed while irrigating and look for bleb formation. Additional punches can be taken if the leak is inadequate. Suture the 2.8 mm conjunctival cut with a running 10-0 nylon suture and knot down with final loop – this twists the edges of the conjunctival cut making it leak proof (Images 14 and 15) – Tenon's capsule should not be included. Subconjunctival medications 0.5 ml garamycin (40 mg/ml) and 0.5 ml dexamethasone (4 mg/ml) can be given into the inferior fornix. Post-operative management is similar to trabeculectomy.

The results so far with SIGS have been very encouraging. Though the procedure isn't meant to completely replace trabeculectomies, it provides a good primary surgical option for patients who might have been considered for a trabeculectomy, bringing advantages such as minimized scarring, posteriorly-directed flow, fewer post-operative complications, as well as preserving conjunctiva for any additional future surgeries. It is also a quicker surgery to perform than trabeculectomy, which can increase efficiency in the clinic and provide economic advantages. Not every patient is suitable for the procedure, however, and exclusions include prior trabeculectomy, conjunctival scarring, angle-closure glaucoma and prior uveitis. But this isn't always cut and dry: though I personally wouldn't consider SIGS for a patient who already has conjunctival scarring (for example, from retinal detachment surgery) because they won't harness the benefits of the procedure,

"I have heard from many around the world who are performing SIGS in these complex cases and are happy!"

I have heard from many around the world who are performing SIGS in these complex cases and are happy!

As with all surgeries, there is a learning curve involved. But surgeons already performing trabeculectomies will be able to manage SIGS as well; it is also easy to convert SIGS to a conventional trabeculectomy if needed. We've had many surgeons come to us from abroad just to learn this technique, as well as many who've seen the procedure online or at conferences, and it has been great to hear how happy they are with the results of the surgery. I hope that more ophthalmologists will be encouraged to adopt the approach with their patients.

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NextGen

Research advances
Experimental treatments
Drug/device pipelines

Redefining the Eyedrop

How we're overcoming the challenges of effectively delivering topical eye medication

By Stephen Lane

Ocular surface disease (OSD) is extremely common – and though it is not always the primary complaint, it is implicated in many cases that present to ophthalmic practices. Managing OSD can be challenging because the signs and symptoms are variable and often poorly correlated, and the etiology is diverse.

For many years, the mainstay of OSD treatment has been topical eyedrops, beginning with artificial tears and for more severe cases, topical cyclosporine A or corticosteroids. In recent years, we have seen significant advances in diagnostic technologies, with new point-of-service tests to measure tear osmolarity and inflammatory markers, and we can now perform meibomian gland imaging with dedicated instruments. But new treatment options have been slow to emerge. Recently, lifitegrast (Xiidra, Shire Ophthalmics) was approved in the US to treat the signs and symptoms of dry eye. Lifitegrast is an integrin antagonist that binds to lymphocyte function-associated antigen 1 (LFA-1) on T-cells to block the interaction of LFA-1 with intercellular adhesion molecule 1 (ICAM-1) – a cell surface protein that is overexpressed in patients with dry eye disease. In so doing, it is believed to inhibit T-cell activation and migration, and stop or reduce the secretion of inflammatory cytokines. Clinical studies have shown that its onset of action is less than two weeks (1). However, addressing inflammation doesn't necessarily solve the entire spectrum of symptoms associated with OSD. The hunt for other adjunctive therapies continues…

At a Glance

- *Ocular surface disease has traditionally been treated with artificial tears and topical cyclosporine A or corticosteroids*
- *Such topical medications comes with the specters of poor treatment compliance and tolerability issues, as well as difficulties with effectively delivering medication to the ocular surface*
- *In recent years, ocular surface disease and dry eye have become increasingly common complaints at ophthalmic practices*
- *New treatments and technologies are evolving to redefine the eyedrop.*

Challenges of topical therapy

One of the reasons that we have seen so few new agents for OSD is the pharmacological challenges associated with drops for the ocular surface. Certainly, the cornea is easily accessible, but designing a drop that stays in contact with the cornea long enough to have an effect – while not causing discomfort, toxicity, or visual disturbances in the process – has been challenging. A standard eyedrop contains about 40–50μL of fluid, which is sufficient volume to activate a blink reflex that rapidly clears the drop from the surface within 15–30 seconds of instillation, through spillover and drainage through the lacrimal system (2). It is estimated that only 1–7 percent of an eyedrop's medication has a therapeutic effect on the target tissue (3). Gels and ointments might have a longer dwell time on the cornea, but because they create an uneven refractive surface they also significantly distort vision, making their use during waking hours limited.

"Another challenge with eyedrops is that many compounds, including cyclosporine, are poorly soluble."

Another challenge with eyedrops is that many compounds, including cyclosporine, are poorly soluble. Current formulations of topical cyclosporine get around this problem by suspending the drug in an oil-based emulsion, but the

patient has to shake the drops before use, and multiple excipients are needed to buffer the drug and maintain suspension, with each additional excipient having the potential to affect tolerability or efficacy. Finally, even if a new topical medication can overcome the hurdles of solubility and efficacy, we know that patient compliance with eyedrops is relatively poor, even when they are prescribed an agent to treat a sight-threatening disease like glaucoma (4). In many cases, blurred vision, stinging, and other tolerability issues contribute to poor adherence.

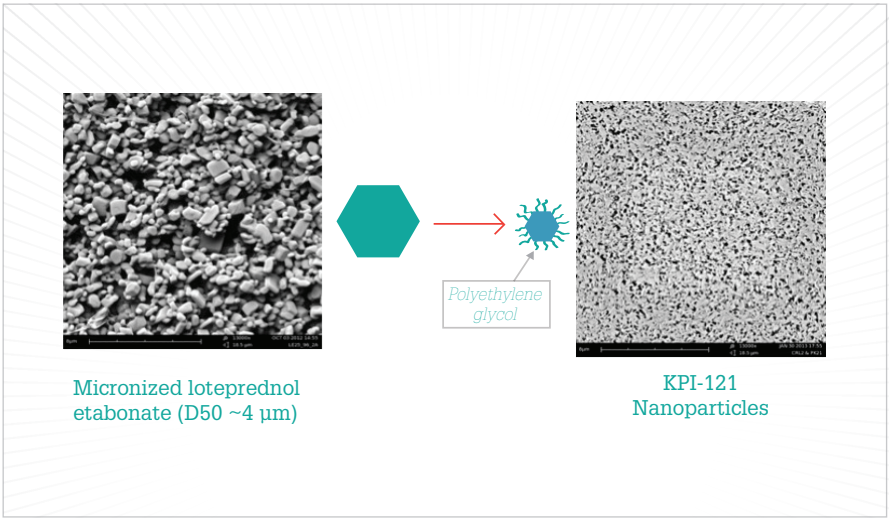

Figure 1. Smaller steroids: current micronized formulations of loteprednol etabonate (LE) get stuck in the mucus layer of the tear film; the drug particles aggregate – and they're distributed poorly and eliminated quickly, however polyethylene glycol (PEG)-coated LE nanoparticles easily penetrate the mucus layer of the tear film, thereby enhancing drug delivery and retention on the ocular surface.

New approaches

What if traditional eyedrops could be replaced with a longer lasting form of drug delivery? Sustained release implants and reservoirs have certainly been an area of intense focus in vitreoretinal therapy, but these do not easily lend themselves to corneal applications. There is a hydroxypropyl cellulose insert for sustained-release treatment of dry eye (Lacrisert, Bausch + Lomb) that has been available for many years. Certainly, some patients rely on the lubrication that this insert provides for relief, but in my opinion it is a last-resort choice because the intermittent blur caused by the sustained release of methylcellulose has a significant impact on vision. Other delivery device approaches have also been trialed. An intracanalicular depot that slowly releases dexamethasone (Dextenza, Ocular Therapeutix) recently completed a Phase III pivotal trial (NCT02736175) of its use for the control of postoperative ocular inflammation and pain after cataract surgery. As Dextenza met endpoints for decrease in inflammation, I expect that the indication for its use will expand. An iontophoresis device that delivered dexamethasone phosphate (EGP-437; EyeGate Pharma) has showed statistically significant improvements in signs and symptoms of dry eye in response to a controlled adverse environment challenge in a Phase II trial, but failed to achieve the target endpoints (corneal staining and ocular discomfort) (5).

Nanoparticle technology provides a promising avenue for delivery of established drugs to the cornea and tissues beyond. Research has shown that a mucoadhesive nanoparticle drug delivery system prolongs the precorneal residence time of encapsulated cyclosporine A by adhering to mucous membranes (6). OTX-101 (Seciera) is a novel nanomicellar formulation of cyclosporine A 0.09%, acquired from Auven Therapeutics by Sun Pharma, who recently announced results from a multicenter, randomized, double masked, vehicle-controlled Phase III confirmatory study. After 12 weeks of treatment, OTX-101 showed statistically significant improvements over the vehicle control in Schirmer's score and several key secondary endpoints (7).

Similarly, Santen has a cationic nanoparticle water/oil micelle vehicle, Novasorb, which contains a positively charged surfactant and is electrostatically attracted to the negatively charged mucins on the surface of the eye, aiding retention. The vehicle is used alone for the treatment of dry eye symptoms (Cationorm), and when cyclosporin A is embedded in the oily core of the droplets (Ikervis) – although both products are currently only available in certain European and Asian markets (8,9).

Kala Pharmaceuticals is developing mucus-penetrating nanoparticle technology (KPI-121) that delivers loteprednol etabonate (an ester steroid) over approximately five days. Though topical corticosteroids have long been recognized as a highly effective treatment for the ocular surface, clinicians have been wary of their long-term use because of risks of IOP spikes and cataract development. But when loteprednol etabonate is formulated into tiny (200–400 nm) mucous-penetrating particles (Figure 1), it can get to target tissues very effectively without causing unwanted side effects; Phase II trials evaluating KPI-121 in 150 patients with a clinical diagnosis of dry eye showed significant improvements in conjunctival hyperemia and ocular discomfort at two weeks, with no difference in IOP between the drug and vehicle observed (10). Phase III trials of KPI-121 are now underway (NCT02813265).

Varying the vehicle

For perhaps the first time, we are also beginning to think of the eyedrop vehicle itself – something that was of only minor interest in the past – as a delivery system. For instance, Imprimis Pharmaceuticals are using a new technology in their LessDrops formulation that allows combination of multiple postoperative medications into a compounded single drop; active pharmaceutical ingredients that wouldn't ordinarily mix can be solubilized into a well-distributed particle suspension. More relevant to the treatment of OSD, a non-aqueous, preservative free drug delivery system based on semifluorinated alkanes (EyeSol, Novaliq) has been shown to enhance the solubility, suspensibility and stability of drugs such as cyclosporine A, and has a well-established ocular safety profile (11–15). From this technology stems NovaTears, a multi-dose, preservative-free lubricating drop that has been commercially available in Europe since 2015. The low surface and interface tension from the non-aqueous drop allows it to spread quickly and uniformly over the entire ocular surface without relying on blinking for distribution; the drop volume is one-fourth that of a standard eyedrop at ~10 μL which makes it less prone to spillover. In a recent prospective, post-market multicenter study of the lubricating drop in patients with evaporative dry eye disease (n=30), significant improvements from baseline were observed at six weeks in four of five measures assessed, including a 21 point decrease in the Ocular Surface Disease Index score (13). NovaTears, with the addition of omega-3 fatty acids, is anticipated to be approved in Europe by the end of 2017. The company is also developing a cyclosporine A formulation in the EyeSol vehicle, CyclASol, and a recently completed Phase II trial in 207 patients with moderate to severe dry eye showed significant improvements in corneal staining compared with vehicle (16); pivotal trials should be initiated by 2018.

The ongoing need to redefine the eyedrop

OSD is a difficult and frustrating problem to treat, yet so very prevalent in our practices. Despite the many challenges in developing new topical therapies, it is absolutely essential that we continue to evaluate new treatments that can improve patient signs and symptoms. As we continue to search and investigate new compounds, I am encouraged that new drug vehicle and drug delivery technologies offer the promise of better efficacy, less frequent dosing (and so less dependent on patient compliance), and better tolerability.

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Profession

Leadership
Talent Development
Career Planning

Redefining POAG

Why it's time to take the "P" out of POAG and consider the secondary causes behind the disease

By Louis Pasquale

How long have we been confused about primary open-angle glaucoma (POAG)? The answer is a really long time, and even the term glaucoma is a misnomer; its origin stems from the ancient Greek, glaukos, which likely referred to the dull sheen or "glaze" of blindness that arises from a swollen cornea or cataract – both of which can be caused by chronic intraocular pressure (IOP) elevation (1).

Fast-forward to the present day and there's a myriad of terminology related to POAG that doesn't reflect the complicated etiology of the disease (see sidebar: "POAG Terminology through Time"). Even the name "POAG" is bad because it fosters the suggestion that there is no secondary cause of the disease. But it needs to be secondary to something.

I think it's time to take a new approach and redefine POAG. My goal is to break it down into its different components and really understand what is going on. Over many years of study, I have learned that it is likely to be several different diseases, and I believe the best approach is to identify the different subtypes and their unique risk factors. We have much to learn, but here is what we know so far...

Replacing "P" with "PC"

The first POAG subtype to treat as a separate entity is paracentral open-angle glaucoma (PC-OAG). The main feature of this subtype is that disease attacks the center of vision, causing early paracentral visual field loss. When studied by OCT, many of these patients have triangular defects in their pre-laminar optic nerve tissue – almost like a little man with a shovel dug out a trench in the superficial optic nerve head. Another feature of this subtype is that patients typically have lower IOPs than those observed in patients with peripheral visual field loss. However, because many patients with PC-OAG may also have pressures in the normal-tension glaucoma or high-tension glaucoma ranges (2), stratifying patients by IOP may not be serving us well. Instead, we should perhaps consider other biomarkers, such as disc hemorrhages, which have been found to present at a higher frequency in patients with PC-OAG (2).

Genetically, we know that impaired nitric oxide (NO) signaling plays an important role in PC-OAG. Caveolin is a membrane protein that interacts directly with endothelial nitric oxide synthase (eNOS) to regulate NO production, and genomic variants in the CAV1/CAV2 region associate with the PC-OAG subtype (3). This, together with research showing that IOP is elevated and outflow facility reduced in eNOS knockout mice (4), means that we now know that NO signaling is very important for the regulation of IOP – and it's why we're seeing potential new drugs on the horizon that target NO and associated pathways. Until these drugs make it into the clinic, what are the options for patients with PC-OAG? A low target IOP is needed for these patients (16 mmHg is too high) and many may need even lower target IOPs in the range of 10–12 mmHg. Additionally, observational research suggests that dietary nitrates might favorably reduce the risk of POAG (5), particularly for PC-OAG, and there's certainly no harm in trying to get patients to eat more leafy green vegetables!

Replacing "P" with "AD"

The next POAG subtype is a very important entity and one we should be

At a Glance

- *Glaucoma specialists have been confused by POAG for too long, and this may be because it is actually multiple heterogeneous diseases*
- *It's time we redefined the disease, and discuss the potential different subtypes and how best to manage them*
- *Patients with paracentral open-angle glaucoma should have low target IOPs, and patients with African-derived open-angle glaucoma should be screened and monitored alongside their children and family*
- *There remains much to learn, and we need to continue to find the different disease subtypes to better serve our patients*

"I think it's time to take a new approach and redefine POAG."

recognizing more: African-derived open-angle glaucoma (AD-OAG). We think of POAG as a disease of the elderly, and a common misconception is that it won't be found in people below the age of 40 years. However, research performed in South Florida has shown that at least one African-derived population is likely developing glaucoma a decade or two earlier than their Caucasian counterparts (6).

Take for example a case of an African-American man with a positive family history of glaucoma (see box "A Case of AD-OAG"). Of note, this patient was only 32 years old, his IOPs weren't particularly high (18–24 mmHg), central corneal thickness (CCT) measures were low, and there was no evidence of a secondary glaucoma upon examination. So what do we do differently for this type of patient? We get them and their family on our radar – they're all high-risk patients who need intervention, even their children. Research into the genetics of AD-OAG is spearheaded by Joan O'Brien, Mike Hauser and others. Constance Okeke is championing the effort to educate all patients about the importance of a positive family history of glaucoma, with emphasis on counseling young AD-OAG patients that their siblings and even their children should be under ophthalmic surveillance.

But we can do more – we need to deepen our understanding of AD-OAG because there are pathophysiological differences between African-Americans and Caucasians. For instance, a well-executed study examined over 10,000 disc photographs and showed that people of African descent had a reduced risk of disc hemorrhage compared with Caucasians (7). This is intriguing because disc hemorrhages are a structural biomarker for disease progression; yet, they occur less commonly in African Americans with open-angle glaucoma who are more likely to go blind from glaucoma than Caucasians with open-angle glaucoma. The reasons for this tendency are currently unclear, but these findings suggest that retinal hemodynamics might differ between these two populations, and we need to understand more so that we can improve the care of our patients.

Going backwards to move forwards

As PC-OAG and AD-OAG subtypes have unique themes, putting these patients together in one basket with other patients with glaucoma means we'd be missing opportunities to learn more about each of them. To find new drug targets for POAG, we need to entertain candidate mechanisms of the disease – of which there are many (see sidebar: "Candidate Disease Mechanisms for POAG"). The best way to identify these might be through a reverse engineering cycle of discovery (Figure 1a).

The following case helps demonstrate the concept of reverse engineering:

- At 47 years of age, a female patient was identified as a glaucoma suspect because of cupping.
- Her OB/GYN history, which many of us ophthalmologists tend to ignore, was remarkable. She experienced pre-eclampsia at 30 years of age, and underwent a hysterectomy and bilateral oophorectomy at the age of 53.
- At 61 years of age, the patient noticed she'd lost the superior part of her visual field in her right eye. IOP was 21 mmHg in both eyes and examination showed excavation of the neuroretinal rims in both eyes, but worse in the right eye.
- Visual field assessments showed superior paracentral scotoma in the right eye, and superior nasal step and nasal step in the left eye.

POAG Terminology through Time

Pre-1970 terminology
- Chronic simple glaucoma
- Wide-angle glaucoma
- Glaucoma simplex

Post-1970 terminology
- Normal tension glaucoma
- Low pressure glaucoma
- High tension glaucoma
- Open-angle glaucoma

You may be thinking "this sounds just like the PC-OAG subtype," but I would like to draw attention to her GYN history and mention that estrogen is a big driver of NO synthase 3 activity. It also has a role in glaucoma-related traits, as indicated by several studies: retinal ganglion cells express estrogen receptors (8), and optic nerve structure and retinal sensitivity on visual field tests both vary as a function of the menstrual cycle (9, 10); IOP decreases during pregnancy despite the fact that CCT increases in the third trimester (11); and a post-hoc analysis of a randomized controlled trial (RCT) has shown that post-menopausal estrogen hormone therapy was associated with lower IOP (12). But what about POAG? Several studies indicate an increased risk of the disease in women with a reduced estrogen exposure during their lifetime (13–19). Estrogen has also been shown to preserve visual function

Candidate Disease Mechanisms for POAG

- Endothelial cell dysfunction with impaired NO signaling
- Estrogen deficiency
- Mitochondrial dysfunction
- Neuroinflammation
- Insulin resistance
- Oxidative stress
- Ocular connective tissue disorder

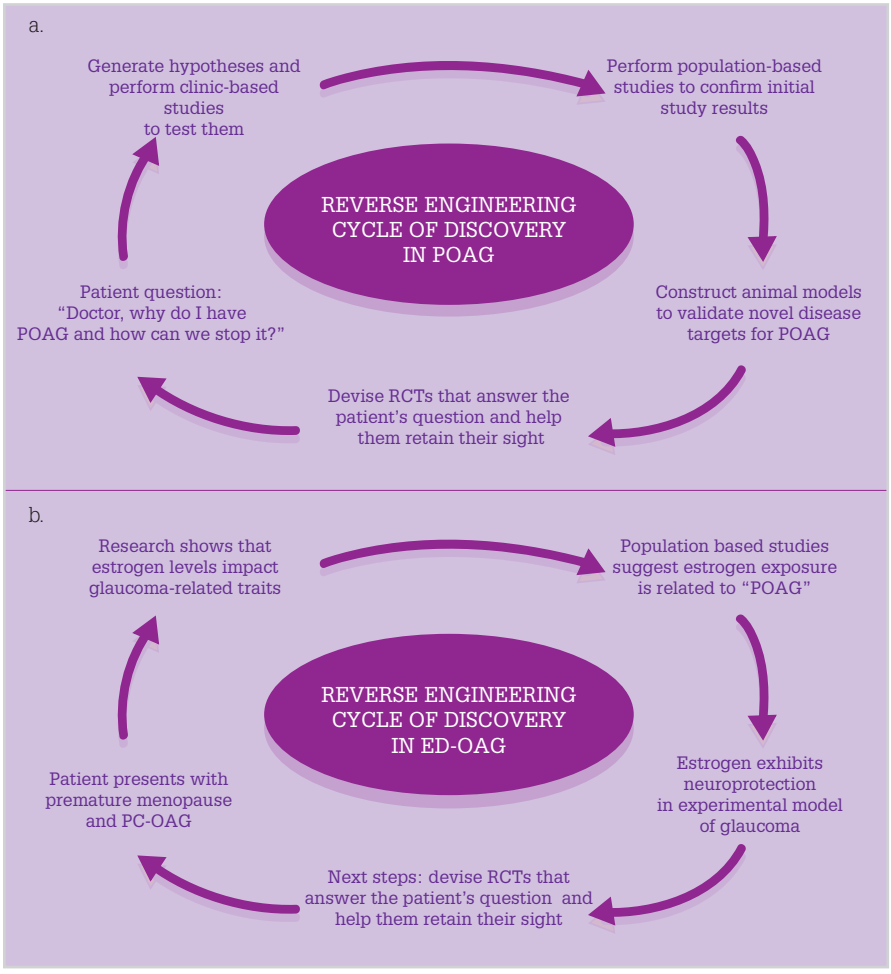

Figure 1. Reverse engineering cycle of discovery in (a) POAG and (b) ED-OAG. ED-OAG, estrogen-deficient open-angle glaucoma; PC-OAG, paracentral open-angle glaucoma; POAG, primary open-angle glaucoma; RCT, randomized controlled trial.

and structure in a rat model of open-angle glaucoma (20). So when looking at the reverse cycle of engineering, this patient might actually have estrogen-deficient POAG (ED-OAG) because of her GYN history (Figure 1b), and the next steps would be to figure out how to leverage this information to design RCTs that answer the question of how we can help this patient safely improve the local estrogen levels in her eyes and retain her sight. Of course, we are far from being able to achieve that goal at the current time.

Some parting thoughts

Clinically, there is much to think about with POAG, and we need to see the bigger picture. POAG may be associated with increased IOP, but the majority of patients with the disease do not have IOPs exceeding 35 mmHg.

So when confronted with a patient with "POAG" who has very high pressures, you should be considering other causes of elevated IOP such as steroid exposure or exfoliation. Physiological cupping should also be treated with caution because many genetic markers for a large cup-to-disc ratio are also markers for POAG (21), and these patients should be monitored for the development of glaucoma. In the future, we'll hopefully know the full complement of genes dictating optic nerve cup and shape, and be able to use this information to predict which patients might get POAG. Caution should also be merited in cases of rapid visual field progression because this is rare in patients with POAG – if you're seeing this, seek alternative causes for rapid progression. Asking about steroid use, and eye rubbing could be informative. Performing a diurnal curve to look for IOP spikes and neuroimaging might also reveal why some patients are deteriorating at a rapid rate.

Let's help our patients…

I've defined subtypes of POAG that I believe exist. They each have different features, different genetic markers that point to specific biochemical pathways in their disease – different etiologies that dictate how best they should be managed. To achieve a precision medicine approach to treatment, we need to perform more

research to find all the different subtypes, and we need to accept that some patients may have overlapping features of several different subtypes of the disease. Let's help our patients by taking the "P" out of POAG. I said that it has to be secondary to something – in fact, it is secondary to many things.

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A Case of AD-OAG

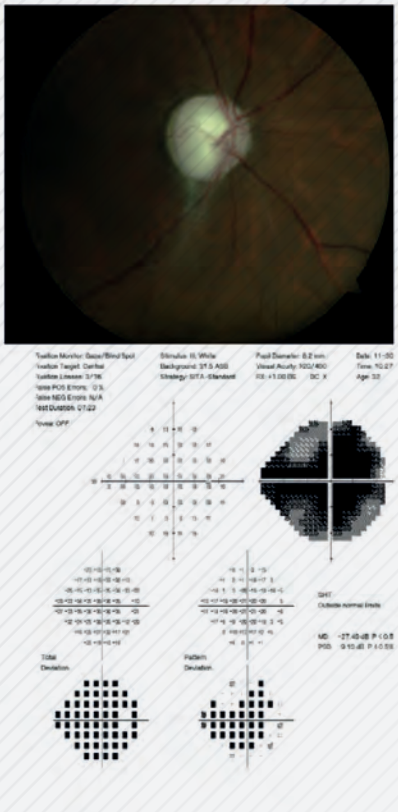
Background

- Male, 32 years old
- Last eye exam was eight years ago; routine eye exam revealed loss of vision in right eye
- Patient knew OD vision was "weak," but it hadn't been affecting his daily activities

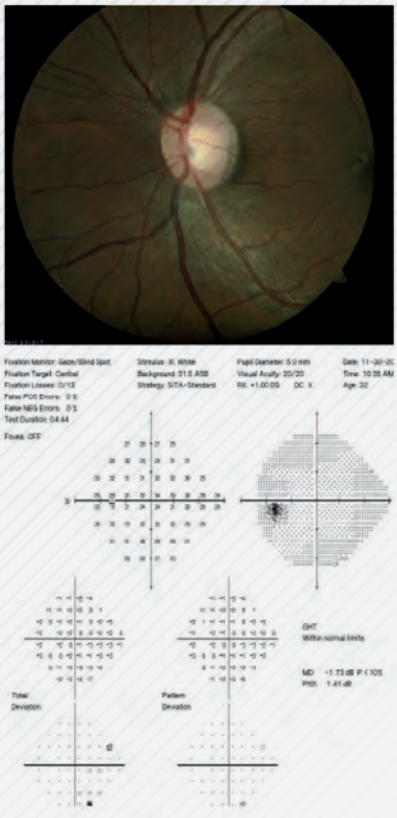
Eye exam

- Vision: 20/600 sc OD; 20/20 sc OS
- IOP: 24 mmHg OD; 18 mmHg OS
- CCT: 512 µm OD; 522 µm OS
- Slit lamp examination unremarkable
- Gonioscopy: Gr III open 360° OU with 1+PTM

OD



OS



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Balancing the Cost of Success and Failure

Publishing negative results might not flatter – but it does matter

By Ian Catchpole

Late on in my career at GSK, my colleagues and I published a paper (1). It could have been groundbreaking. In some ways it was. We were seeking a better way to treat wet AMD – one that would obviate much of the burden of monthly clinic visits for intravitreal injections of anti-VEGF therapy that we see today. Despite solving many problems along the way, ultimately, the project failed – but we should all learn from its failure. Let me tell you my story.

At a Glance

- *Collectively, companies and research institutions have invested millions trying to develop intravitreally administered, extended-release anti-VEGF agents for the treatment of retinal neovascular disease that can act for as long as 6 months*
- *GSK, in collaboration with OctoPlus N.V., developed a novel potent anti VEGF molecule and hydrogel microparticle combination that almost fitted the bill – and was close to a clinical trial. Had it worked, it would have been a paradigm changer.*
- *One of the issues that led to the project's termination was caused by fundamental and poorly understood aspects of primate accommodation, which led to microparticle migration into the anterior chamber*
- *The issues highlighted in this research are relevant for others pursuing the use of particulate injectables for intravitreal ocular delivery, some of whom are not easily able to afford the key experiments in the primate eye needed to de-risk likely similar issues in man*

Discovering ophthalmology

It started back in 2007, when I first worked in the field of ophthalmology. GSK's head of research at the time was Tachi Yamada, and he was interested in the gene therapy area. He knew one of the biggest names in that field – Jim Wilson at University of Pennsylvania – and he enabled GSK to access some of the Wilson group's novel adeno-associated virus (AAV) vectors. We started working with Jim's group and also a number of researchers from the UCL Institute of Ophthalmology in London looking at gene therapy approaches to ocular disease. The opportunities were great – here was an organ where you could actually see the effects of what you were doing! We also started re-profiling existing GSK assets and considering ophthalmic applications for them – this was a therapy area that had great promise! I started going to the ARVO meetings to start trying to understand what kind of problems were out there in ophthalmology: scientifically, clinically, and everything else that we might need to deal with when building an ophthalmic franchise. It was apparent even then (ranibizumab had been approved in the US less than a year before for the treatment of wet AMD) that the large number of clinic visits and intravitreal anti-VEGF injections – one a month, going forward for as long as the drug continued to work – was going to be the big issue, in addition to the hefty cost of the drugs themselves.

Combining drug with delivery platform

Around that time, GSK acquired a company called Domantis that worked on domain antibodies and antibody fragments. As part of that, we acquired certain relatively small anti-VEGF molecules – certainly smaller than ranibizumab. Here was an opportunity to play with drug delivery – i.e. to pack a lot of drug in to a sustained release vehicle and build a long-acting injectable anti-VEGF. So we presented that idea to the GSK equivalent of Dragon's Den – an internal poster presentation and competition session called the Goldfish Awards. We didn't win – but what we presented

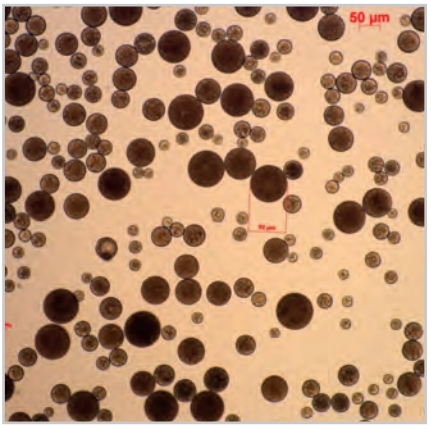


Figure 1. PolyActive hydrogel microparticles. Adapted from (1).

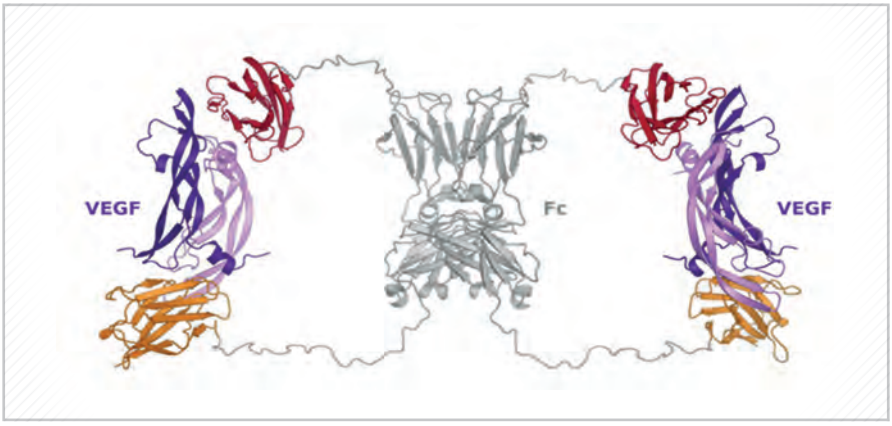


Figure 2. Proposed structure of the dual domain antibody in complex with two VEGF molecules. Adapted from (2).

generated enough interest within the newly formed GSK Ophthalmology group that they thought it that was a good idea to pick it up. We had started reviewing drug delivery options, and came across a Dutch company called Octoplus N.V. (now part of the Dr. Reddy's franchise) who had an aqueous hydrogel drug delivery platform (Figure 1) that not only managed to keep the proteins active for a long time, but also released them with pretty much first order kinetics – i.e. with minimal 'burst' release – over a long period. They hadn't really performed any studies in the eye, so we moved forward together.

Even then, there were stumbling blocks. Our original candidate molecule just wasn't potent enough – so the big challenge was rebuilding the molecule to make it a more potent VEGF inhibitor. What we ended up making (Figure 2) was at least as potent as the most potent anti-VEGF available on the market today, aflibercept (2). We then had to work to find and evaluate a polymer that could keep the protein intact in the distinctly "wet" environment of the eye and release therapeutic levels of it over a 6–12 month period. That was no easy task: the principal technical challenge was to load enough protein material from the antibody fragment into the microparticle itself – you needed to get liquid protein concentrations up to >200 mg/mL (a huge amount) to enable the release of sufficient quantities to be effective for at least 6 months. But we did it.

"The big challenge was rebuilding the molecule to make it a more potent VEGF inhibitor."

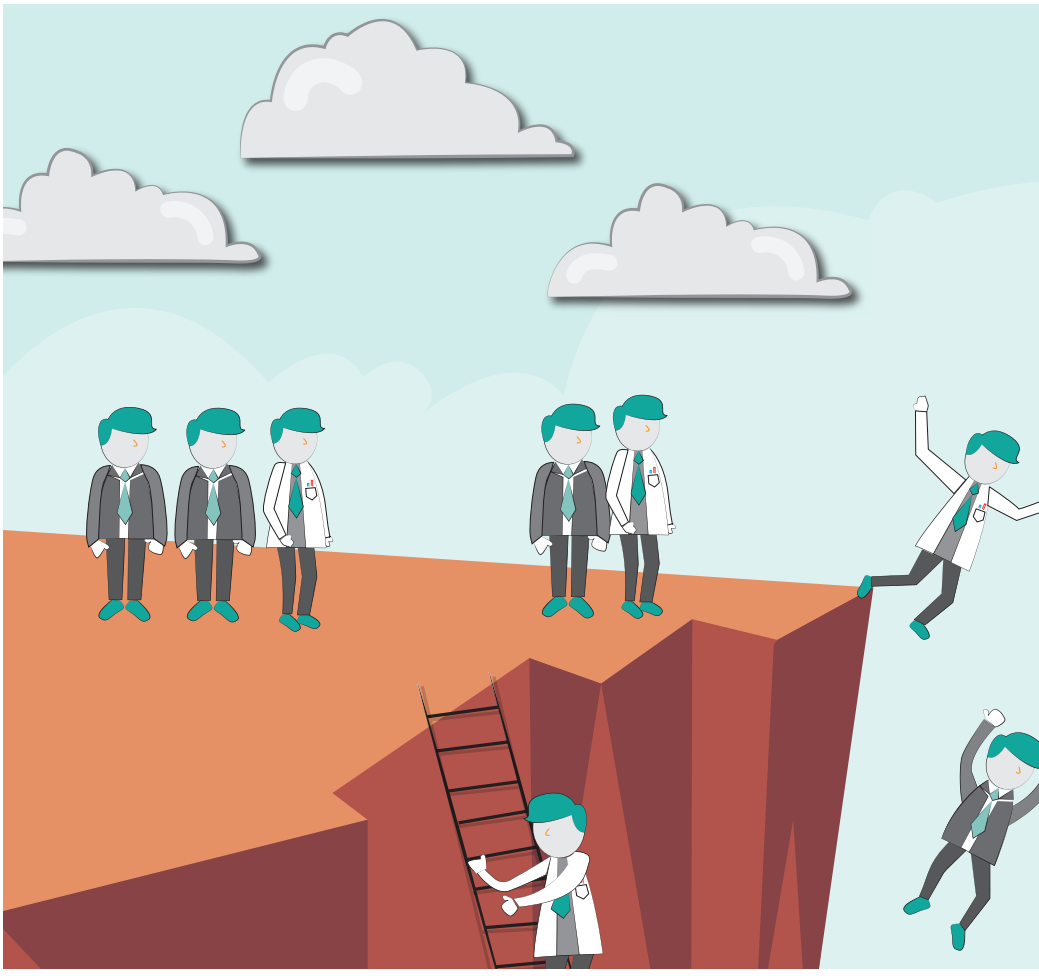
Progressing through the preclinical steps

The next step was preclinical in vivo experiments. We did our first studies in rabbits, as it is the model of choice for studies of ocular delivery. The use of rabbit eyes are not without issue; though the intravitreal volume is relatively large at 1.3 ml, it is still smaller than man (4.5 ml), but with a huge lens, so you need to make sure that injection avoids the lens – and then there were issues with immune responses. Our antibody fragment was a humanized protein: the rabbit's immune system kicked in and generated anti-drug antibodies (ADA) responses post-dose at high frequency which blocked detection of the released anti-VEGF, and it made it challenging to interpret the results. Nevertheless, we gathered together enough data to demonstrate that substantial levels of active anti-VEGF molecule were present in the rabbit vitreous at six months post-dose and to justify progressing to the non-human primate (NHP) model. The cynomologous monkey is far closer than rabbits to humans in terms of ocular anatomy and function – it also seemed likely that the closer similarity to human would help reduce the negative impact and frequency of ADA responses; enabling simpler detection and interpretation of the pharmacokinetics of the released molecule. It turned out that these successful and very expensive experiments both validated many aspects of the approach but also ended the project…

We'd found that in vitro, we could release effective doses of anti-VEGF molecule from the microparticle/ hydrogel, PolyActive, platform over a 12-month period, and in vivo, this translated to at least six months' worth of effective levels of anti-VEGF released in both the rabbit and NHP experiments. We used the NHP laser choroidal neovascularization (CNV) model (the pre-clinical model of

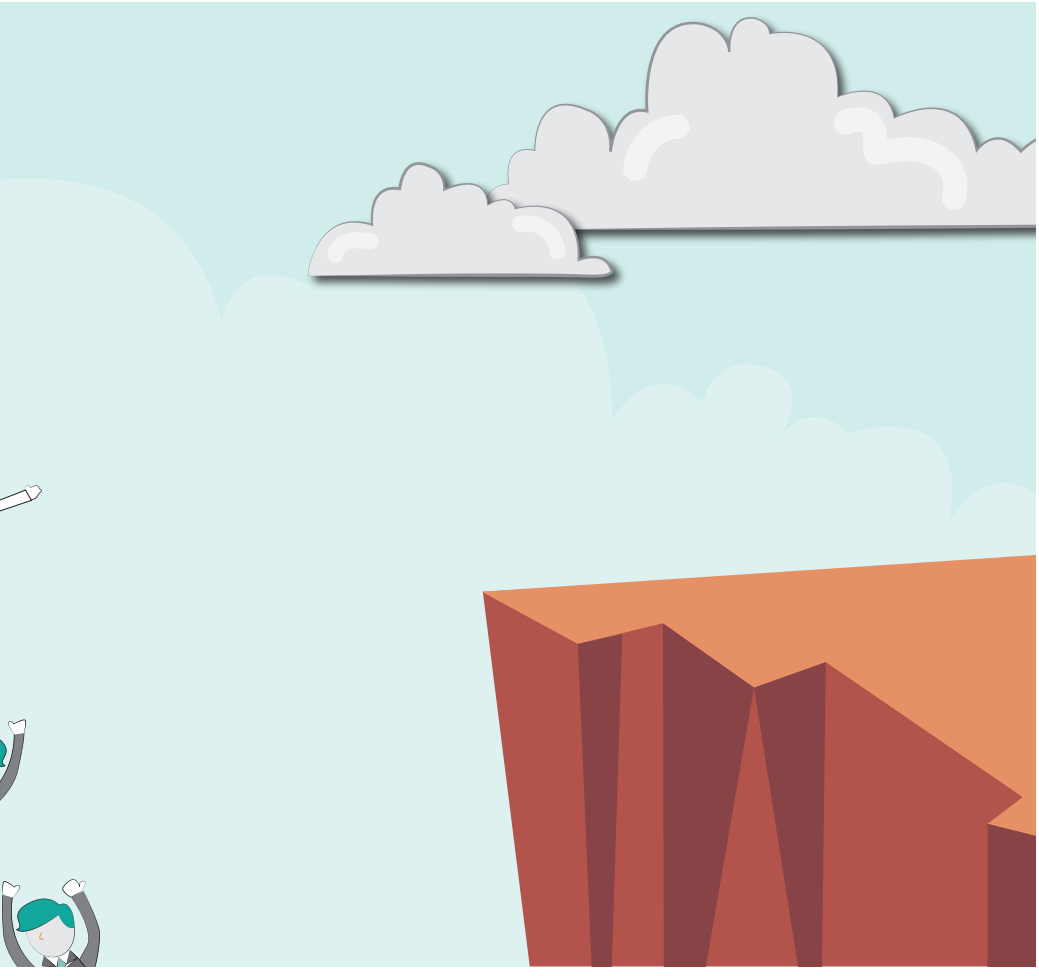
wet AMD used to validate ranibizumab prior to the clinic) to test how successfully our therapy managed to suppress the production of laser-induced leaky new blood vessels: we'd dose the eyes, wait 4–6 months, and challenge the eye with the laser – and found that we still got good protection even 6 months out. In that respect, moving forwards to a clinical trial looked promising. But there were three major challenges that prevented us from doing so – and these represent crucial lessons for any other research group that's trying similar intravitreal particle-based drug delivery systems. It's not always 100 percent success and steps forward into the clinic.

"It's not always 100 percent success and steps forwards into the clinic."



Three big challenges

The first hurdle was ocular inflammation: we were seeing it in the NHP eyes as well as the rabbits. Although both protein and microparticles were prepared at high quality and were shown to have extremely low levels of endotoxin, they were still research-grade materials, i.e., not prepared at GMP grade purity. So it might have been possible to reduce the degree of inflammation by improving the quality of what we were administering, unless the inflammation was solely driven by the particulate nature. But these weren't the only challenges. The second issue was a lack of degradation of the polymer at the same rate as the release of the molecule. The polymer was predicted to last for 6–9 months, based on experiments where similar PolyActive implants had been placed subcutaneously in the rat – but when we looked at the PolyActive material in the NHP eye, it was still there at 6 months, 9 months… and it was only really 12 months after implantation before we started to see any major en masse reduction and degradation. That meant it would be very difficult to re-dose – the accumulation of material in the eye would start to become a problem after only a few doses. But the third and biggest problem was related to the microparticles themselves. They would travel from the vitreous into the anterior chamber. These three issues combined lead to termination of the project. We were quite surprised by the latter observation – we hadn't seen anything like that in our rabbit studies, and it seemed to be driven by the primate (and presumably human) eye's process of lens accommodation-disaccommodation (3). It seems that ciliary muscle-driven lens movement causes fluid to flow between the vitreous and anterior chamber, and the particles get disturbed and caught up in it. And so, despite some great technical achievements along the way – developing a potent anti-VEGF antibody fragment, and being able to concentrate, load and deliver this biologic over a long period with a novel drug delivery vehicle – we fell at this last hurdle.



Being open

Why am I talking about our work, both the successes and its ultimate failure? I strongly believe that negative results, especially those that have such a strong bearing on the future of a field should be published (4). Anyone evaluating a similar drug-delivery method needs to be aware of our work – GSK was not alone in working on this approach. There are still biotech companies developing particle-based drug delivery approaches for intravitreal injection who have not performed NHP studies and are either unaware of our findings or are reluctant to accept the full consequences of them, as it might negatively influence their share price. Also, how many biotech companies and academic groups are receiving funding from research councils or companies to fund costly studies – only to repeat our findings? A huge combined investment has likely already been made with this type of approach by GSK together with other pharma and biotech companies. Although our project didn't work out, there were positive aspects from our study. We clearly demonstrated that hydrogel systems can keep anti-VEGF protein molecules stable and active, and can enable them to be released for over 6 months in the eye at effective doses to treat wet AMD. I hope that others will learn of and from our experience – and not feel the need to cover old ground.

The big questions I'm left with are: how can others build from the positive aspects of our findings and address the remaining issues? Can those working on particulates really take heed of the full message and switch funding and research activities to concentrate on generating similar data to ours with temperature sensitive solidifying erodible gels? If others with a negative data story are reluctant to share knowledge with the field perhaps they should reconsider and think of what other medical research could have been done with the money others spend repeating their mistakes? The answer to that latter question is the true cost of failure.

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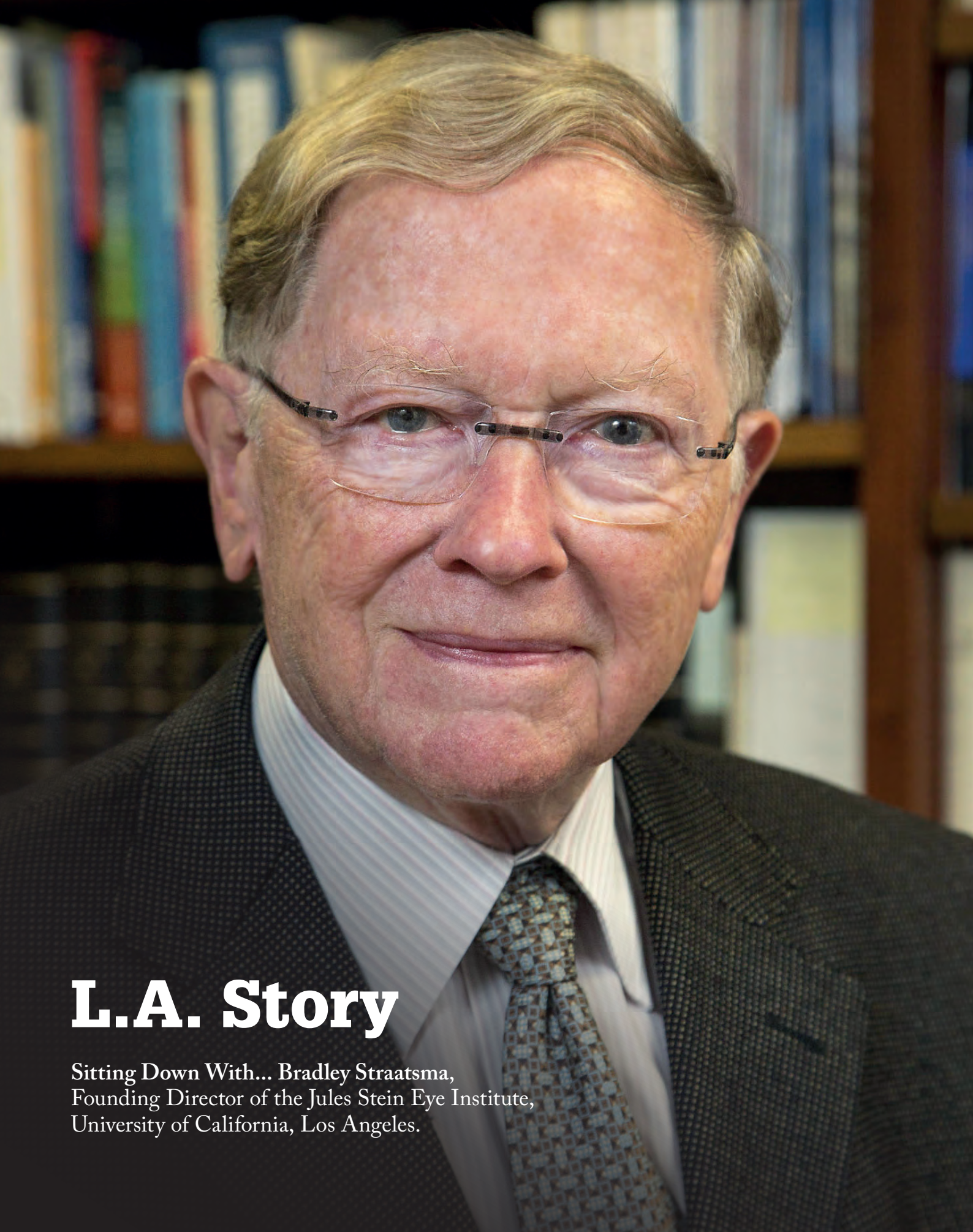

L.A. Story

Sitting Down With... Bradley Straatsma,
Founding Director of the Jules Stein Eye Institute,
University of California, Los Angeles.

You've been the president of many important ophthalmological societies. How and why?

I've been fortunate. I was involved at a time when my participation was exciting for me and useful for the organizations. I was particularly fortunate to be involved in the American Academy of Ophthalmology and Otolaryngology when it transitioned to two separate organizations: the American Academy of Ophthalmology (AAO) and the American Academy of Otolaryngology. It was a natural evolution of the professional roles of the physicians involved, but it was also an opportunity to participate actively in the AAO at the level of its fundamental organization; for example, we established a Washington D.C. office to engage with government in the form of advocacy and that has become increasingly important as the years since then have proven.

What are your views on politics and healthcare?

That's a critical question. Let me tell you about something that happened in 1967. Jules Stein and the leaders of American ophthalmology at the time – Michael Hogan, Edward Maumenee, David Cogan, Frank Newell and I – all appeared before a congressional committee to recommend the establishment of the National Eye Institute (NEI) as a separate unit within the National Institutes of Health. And we did our best to advocate for it. Right after we finished our testimony, the President of the American Foundation for the Blind spoke on behalf of the people who would be impacted by the NEI – and he spoke in a most convincing emotional and factual manner to promote its formation. That taught me a lesson: we should bring into our role of advocacy the populations of patients who are served and aided by fine eye care, surgery, and the advances of science.

What makes you such an effective leader?

I'm not best placed to try to answer that! I enjoy working with people. I try very hard to listen to ideas, but also I always try to have a basic plan, so that there is a concept of what we should be doing – it can always be altered, changed or abandoned. That philosophy was extremely important in the evolution of the AAO and also in the development of the Jules Stein Eye Institute.

Why go to Los Angeles rather than staying in the then far more developed East Coast?

I'm almost smiling and laughing when you bring up the transition from the East Coast to the West Coast! I found that such a difficult decision that I didn't make it until the day the moving van arrived at our apartment in Bethesda, Maryland. It really was a very difficult decision because there were a number of opportunities in the East Coast at much more well-established institutions. But I was impressed with the opportunity offered at the University of California and my wife and family said: let's do it! So we came to California knowing very little about the place. It has turned out to be a most fortunate decision – the university has grown enormously and favorably, and Los Angeles is a lovely community in which to reside.

How did Jules Stein respond when you initially made contact?

The first time I tried to make contact, he declined to meet me. He said that he'd like to do something nationally, and wasn't interested in something that might be limited to a particular location. He then founded Research to Prevent Blindness and, as part of his work with that organization, he developed a program to help Johns Hopkins University; they very successfully built a structure for research. I approached him again, asking him if he would consider supporting a program on the West Coast at a University that was not well known, and also part of the state system. He said that he would look at it. I presented him with a rather detailed plan which he found... satisfactory.

From humble beginnings, the Jules Stein Eye Institute became a world leader. What is the secret to its success?

It stems from the combination of the initial support of Jules Stein and the community of Los Angeles that allowed us to establish a major base within a university that was growing in stature at the same time. We also had extremely capable researchers, educators and physicians on the faculty. The program has grown substantially since that beginning; our formal dedication was in 1966, so last year we celebrated our fiftieth anniversary with a complete remodeling of our buildings to make sure that we really have a vision campus for the future at UCLA.

The Institute broke traditional barriers between departments, fostering wide collaboration...

We recognized that the science of vision was related to neurology, to pathology, to biochemistry, to physiology... to many other departments. The goal was not initially to create a Department of Ophthalmology per se, but to create an organized research unit that would draw together people from a number of disciplines and several departments of the university. Only after we had built the Jules Stein Eye Institute and only after it was operating very effectively did the small division of ophthalmology become a Department of Ophthalmology.

How important is international collaboration today?

Extremely important. Curiously, many of the causes of blindness around the world are basically the same. Cataract, glaucoma, amblyopia, strabismus, diabetic retinopathy, and increasingly macular degeneration. These diseases occur in different cultures – but are increasing worldwide. We have an opportunity – and a need – to work in a larger dimension that brings together all of the information that's available in what we might call "big data" using current terminology. International collaboration is central to achieving that.

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