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Innovator extraordinaire, Sean Ianchulev

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A tale of jealousy, rivalry and pride... The unfolding story of the capsulotomy over time

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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

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

Reference

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.

• England and Wales’ National Institute for Health and Care Excellence’s (NICE) has released a Final Appraisal Determination (FAD) in which Ozurdex (dexamethasone 0.7mg intravitreal implant in applicator) is recommended as a “cost and clinically-effective treatment option for people with sight-threatening posterior non-infectious posterior uveitis.”

• 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
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

Reference
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 ($r=0.33$, $p<0.001$). “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 ($r=-0.22$, $p<0.02$). 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.”

References
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 PDR 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.”

References
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.”

References

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.
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!

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References

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THE CAPSULOTOMY: FROM THERE TO WHERE?

THE STORY UNFOLDS...

BY RICHARD PACKARD
The capsulotomy has a fascinating history – one tinged with jealousy, rivalry, fashion, evolution, revolution and even nationalistic pride – and it’s a story that’s got a great deal more to tell.

It started with the Frenchman, Jaques Daviel, who ushered in the modern era of cataract surgery, abandoning couching (Box 1) for the first extracapsular cataract extraction (ECCE; Box 2). The British, for predominantly patriotic reasons, preferred couching (Box 3), but ECCE was always going to win out. Albrecht von Graefe improved it in 1850 with his eponymous knife (Box 4) and, extraordinarily, his technique lasted for over a century. That’s not to say that competing approaches weren’t developed along the way – Ignacio Barraquer devised the suction cup-based erisophake in 1917, which enabled rapid intracapsular extraction of the lens (Box 5), but its uptake was limited. So the von Graefe method persisted into the 1970s.

The late 1950s and early 1960s saw lensectomy return to an intracapsular approach, thanks to a combination of Joaquin Barraquer’s enzymatic zonulolysis approach and cryoextraction of the lens (Box 6). Around that time, Cornelius Binkhorst, one of the pioneers of lens implant surgery, realized that to make intraocular lenses (IOLs) work, you needed to move away from fixation to vital tissues and use the capsule instead. And that’s why he developed his two-loop iridocapsular lens – and he tried many different shapes of capsulotomy to get the best fixation (Box 7). We all know the story of how Charles Kelman introduced phacoemulsification in 1967 – and Charlie devised a new way to make the capsulotomy, using a hooked cystitome: the Christmas tree (Box 8).

However, Kelman was performing anterior chamber phaco – and, to do that, you need to prolapse the nucleus into the anterior chamber. Dick Kratz decided that he would like to perform phaco more in the posterior chamber, so he came up with the “can opener” capsulotomy in the 1970s, which resulted in a ‘roundish’ opening (Box 9).

“The British, for predominantly patriotic reasons, preferred couching, but ECCE was always going to win out.”

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**Box 1. Couching**

Stabilize the eye with your thumb; introduce the needle perpendicularly into the eye, entering three millimeters behind the limbus. Gradually push forward with a rotating movement. Move the needle tip downwards to disrupt the lower zonule. Push the lens down into the vitreous with some slow sweeping movements. At least it is minimally invasive…

**Box 2. Daviel’s ECCE technique for opening the capsule and extracting the nucleus, first described in 1747**

Davel used a keratome and a pair of scissors to create a corneal flap, a cystitome to “circumsize” the capsular bag, a blunt spatula placed between the lens and iris to free the lens – and two fingers, gently pressed on the lower lid to express the nucleus.
Box 3. The UK vs. Europe

Given “Brexit”, you might not be surprised to learn that the British medical establishment were very skeptical of Daviel’s new ECCE technique, when it was introduced.

Percival Pott, a surgeon at St. Bartholomew’s Hospital, known for Pott’s disease (tuberculosis of the spine) and Pott’s fracture of the ankle, decided to publish in 1771 that, as far as he was concerned, cataract extraction was just a passing fashion, and he would continue to advocate couching the lens.

Their European colleagues, of course, viewed things differently. Austrian surgeon, Joseph Beer, said, “Some of the English ophthalmologists rejected the extraction method in order to please Mr. Pott, others in order to stand out among the crowd. A third group did it out of national pride and out of hate of all things French. And a fourth group did it because they had bad results due to clumsiness.”
Box 4. Von Graefe sets the standard for more than a century

In 1850, Albrecht von Graefe refined the corneal flap procedure using his eponymous knife, and introduced a peripheral linear incision superior to the cornea; the shift in location from 6 o’clock to 12 o’clock further meant that the eyelid protected the wound, reducing infection and halving the failure rate from 10 to 5 percent.

Box 5. Ignacio Barraquer debuts the erisophake in 1917

Anesthesia, incision, application of the erisophake (a special cup and suction apparatus) then removal of both lens and instrument made for a very rapid procedure. Many surgeons visited Barraquer to learn the technique, but most continued to perform von Graefe’s method.

CAPSULOTOMY’S FUTURE

CAPSULASER

The Capsulaser device (Excel-Lens; Box 13) is a small laser that is attached under the surgical microscope, and is connected to a small, shoebox-sized console. It’s a continuous laser, rather than a pulsed laser, and it scans in a single circular pattern over a period of one second to create the curvilinear capsulotomy opening. It requires the anterior capsule to be stained with Trypan blue, which creates a chromatically selective target for the laser. The irradiation changes collagen IV to elastic amorphous collagen, and this phase change results in not only a smooth edge but also a very elastic capsular rim (the capsulotomy can be extended from 5 to 12 mm without fracture or tear). And thanks to how the laser works, it’s almost impossible not to get a free cap.

The preliminary results have been good, there’s been no pupil construction after laser use, no untoward anterior chamber activity postoperatively, and in a case series of 20 patients, their corneas remained clear out to 18 months, with similar endothelial cell counts to patients that underwent normal cataract surgery. Also noteworthy is that these capsulotomies have remained well centered and have not contracted at all — meaning that there’s been no subsequent change in IOL position. To date, another 400 eyes have been operated upon and the CE mark trial has recently been completed.

The device has also been used to perform posterior capsulotomies in cadaver eyes, and what’s interesting here is that it leaves the anterior hyaloid intact.
There are also now thermomechanical devices being developed for anterior capsulotomy: you are probably aware of the Zepto device (Mynosys; Box 14). It consists of a soft, foldable clear suction cap that contains a nitinol capsulotomy ring that’s inserted through a 2.2 mm clear corneal incision using a disposable handpiece. Once in the eye and aligned over the visual axis, a push rod is retracted and the device unfolds into a circular shape, whereupon the surgeon can center the device and apply suction. A pulse of electrical energy is delivered in milliseconds to the nitinol ring, triggering a rapid phase transition of water molecules that are trapped between the device and the capsular membrane – instantaneously creating a cleavage plane in the capsular membrane, making a strong capsulotomy. It is CE-marked and now available in Europe.

**APERTURECTC**

Mark Packer has been involved with ApertureCTC (International Biomedical Devices; Box 15) – another thermal device, which is currently under preclinical evaluation. It’s similar to Zepto in many respects, but lacks the suction cup. It consists of a reusable handpiece and a disposable 1.2 mm diameter tip that houses a circular 5.25 mm filament, which can be deployed once the tip is in situ. This is gently depressed on the capsule, a foot pedal is used to deliver a millisecond pulse of thermal energy, which melts the collagen and creates a perfectly round capsulotomy – and with it a smooth, strong and elastic capsular opening. The manufacturers report that multiple filament dimensions are available, ranging from 4–6 mm.

**CAPSULOTOMY’S EVOLUTION**

The role of the capsulotomy has changed with cataract surgery over the last 270 years – from a crude opening to give access to the nucleus for its removal, through various iterations of cystitomes and forceps to create different shapes of opening for IOL support, to CCC for those anterior and

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**Box 6. Joaquim Barraquer discovers alpha-chymotrypsin’s ability to dissolve zonules (1958)**

This, combined with Tadeusz Krzawicz’s cryo probe (1961) – and its subsequent improvements by Percy Amoils (1965) – turned the tide back to intracapsular cataract extraction.
Box 7. Binkhorst’s experimentation

Cornelius Binkhorst (a) realized that good fixation away from vital tissues was critical, designed the iris-fixated four-loop lens (b) for use after intracapsular surgery, and devised a new way to do capsulotomy with a hooked cystome to achieve best fixation (d).

Box 8. Charlie Kelman’s Christmas Tree

Kelman introduces phacoemulsification in 1967 – and devises a new way to do capsulotomy with a hooked cystome to achieve best fixation (d).

Box 9. Dick Kratz’s can-opener approach

Dick Kratz decided that posterior chamber phaco was safer than in the anterior chamber and devised the can-opener capsulotomy and his iris plane phaco technique. One of the issues at the time was whether or not the IOL should go in the capsular bag or into the sulcus – you couldn’t guarantee that the can-opener capsulotomy would keep the lens in the bag.
Box 10. The origins of the CCC

Calvin Fercho from Fargo, North Dakota, started using a continuous tear capsulotomy in the late 1970s, and this was the predecessor of what became termed “continuous curvilinear capsulorhexis” (CCC), which was developed and taught by Howard Gimbel, Thomas Neuhann and Kimiya Shimizu in the mid-1980s. The CCC significantly reduced intraoperative complications, such as anterior capsular rim tear, and improved IOL centration and sequestration in the capsular bag.

The arrival of Peter Utrata’s eponymous forceps in 1988 helped make CCC more controllable and easier to perform for many surgeons.

1982

Box 11. The YAG laser

Daniele Aron Rosa tried her newly invented YAG laser for anterior capsulotomies back in 1982. The main drawback was that the surgery had to be carried out immediately – the soft lens matter “fluffed” up and IOP rose greatly after application of the laser.
Box 12. Zoltán Nagy performs the first capsulotomy with a femtosecond laser in 2008

But how does the femtosecond laser compare with manual capsulorhexis for accuracy? In one study, 100 percent of LenSx procedures achieved an accuracy of ±0.25 mm.

Only 10 percent of manual procedures achieved an accuracy of ±0.25 mm. No radial tears.


Box 13. The CapsuLaser device

(a) Present on the surgical microscope; (b) the console; (c) the process of laser capsulotomy; (d) the smooth edge of the disk; (e) Stronger capsulotomy than a manual CCC.
posterior capsules to contain the IOL. And now we have many devices from lasers to metallic thermal instruments to automate the creation of perfectly round consistent central capsulotomies – which should offer more effective lens position predictability.

Of course, IOLs have evolved with the capsulotomy, and a new generation of IOLs are being developed take advantage of this; for example, the Oculentis FEMTIS IOL with its small flaps – “rhexis clips” – that lock the lens inside the capsulotomy; or the Masket ND IOL (Morcher), which has a groove that fits inside the anterior capsulotomy. Could it be that the combination of these new, lower cost approaches to capsulotomy – plus a new generation of IOLs that rely on the properties of capsulotomies made by these devices – will soon consign manual CCCs to the history books too?

Richard Packard is a consultant ophthalmic surgeon and Director of Arnott Eye Associates in London, England, and was the senior surgeon at the Prince Charles Eye Unit, King Edward VII Hospital in Windsor, and is credited as “almost single-handedly removing phaco from the blacklist in the UK giving the procedure credibility and validation.” He implanted the world’s first foldable soft lens in rabbits and has lectured and operated in 59 countries – often with Charlie Kelman, and has chaired the ESCRS’ video competition panel since 2000. He reports that he is a consultant and equity holder in Excel-Lens, and consults for Core Surgical and Shire.

This feature is adapted from the presentation, “The capsulotomy from there to where? The story unfolds…” given at the Cataract Surgery: Telling It Like It Is! annual meeting, held in Naples, FL in January 2017.

Box 14. The Zepto capsules system

The disposable capsulotomy tip (a) consists of a foldable, soft, clear suction cup containing a nitinol ring that can enter through a 2.2 mm incision, and expands to create a 5.2 mm circular capsulotomy. The tip is delivered through a disposable handpiece, pictured in (b) above the device’s console.

Box 15. ApertureCTC

Similar to Zepto, but without the suction ring, the disposable tip (a) is intended to be introduced through a 1.8 mm incision, and will come in sizes between 4.5 mm and 6.5 mm (in 0.5 mm increments), placed on to the capsule and activated to make the thermal capsulotomy. A render of the device’s console is shown in panel (b).
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Single Incision: Multiple Advantages

SooSan Jacob shares how and why to perform stab incision glaucoma surgery (SIGS) in patients with open-angle glaucoma.
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?

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...
“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.”

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 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 fibroed 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 peribulbar 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 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,
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).

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!

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.

Soosan Jacob is a senior consultant ophthalmologist at Dr. Agarwal’s Eye Hospital and Eye Research Centre in Chennai, India.

References
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
NextGen

Research advances
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Redefining the Eyedrop
Stephen Lane examines how the challenges of effectively delivering topical eye medication is being overcome.
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...

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 eye drop 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.

“At a Glance

• Ocular surface disease has traditionally been treated with artificial tears and topical cyclosporine A or corticosteroids
• Such topical medications come 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.

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

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. 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.

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 cyclosporine 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, CycASol, and a recently completed Phase II trial in 207 patients with moderate to severe dry eye showed significant improvements in conneal 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.

Stephen Lane is Clinical Professor of Ophthalmology at the University of Minnesota and Medical Director of Associated Eye Care in Stillwater, Minnesota, USA.

Financial Disclosures: Lane reports that he is Chief Medical Officer of Aikon, and is a consultant for Novaliq GmbH, Shire Ophthalmics, Ocular Therapeutics, Bausch + Lomb, and Kala Pharmaceuticals.

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Redefining POAG
Primary open-angle glaucoma: one disease or many? Louis Pasquale tackles the myths and misnomers plaguing the study of glaucoma.

Balancing the Cost of Success and Failure
Ian Catchpole shares his story on working with sustained-release anti-VEGFs, and how publishing negative results can stop duplication of disappointments.
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
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 PC-OAG 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.

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

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.

Louis Pasquale is Director of the Glaucoma Service and Telemedicine at Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, USA. Financial disclosures: Paid Consultant for Bausch + Lamb and Eyenovia. Travel support from The Glaucoma Foundations in New York and San Francisco.

References

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

Eye exam
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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.

**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...
generated enough interest within the newly formed GSK Ophthalmology group that they thought it 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.

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.

Ian Catchpole is a GSK Fellow, Cell & Gene Therapy, and is based in their Stevenage campus in Hertfordshire, England.

References
The Impatient Innovator

Sitting Down With... Sean Ianchulev, Professor of Ophthalmology at New York Eye and Ear Infirmary of Mount Sinai; Founder and CEO, Eyenovia; and Founder and Chairman of the Board, Iantech Medical.
You’re a true innovator – where does that stem from?
I come from an academic background, but I’m very impatient and find the academic approach to product development too slow, which is partly why I work closely with industry. Such collaborative approaches are increasingly necessary, because product development is now so complex. If you want to get even a simple device into patients today, you need to partner with people from many disciplines: engineering, medicinal chemistry, quality, manufacturing, and venture capital. It’s no longer as easy as coming up with a Sinskey hook and trying it on patients! For example, even something as safe and non-invasive as intraoperative aberrometry took more than 10 years and millions of dollars of development to get to patients. On the pharmaceutical side even more so – when I was at Genentech and led the clinical development of Lucentis, it needed more than a decade and hundreds of millions of dollars to get it into the clinic. Product development and commercialization are non-trivial parts of the science and innovation process, which is like launching a mission in space – thoughtful, well-planned and disciplined development are required, and this costs real money.

Which of your innovations do you consider to be the most disruptive?
Intraoperative aberrometry is a good example. When I came up with the idea, I tried it on my patients using a simple auto-refractor during cataract surgery in 2003. It was so powerful and predictive that even 20 patients were enough to get a signal. Getting clinical information early in the process was critical – we published the original series in JCRS. Little did I realize this would break down a 50 year-old paradigm of pre-operative biometry, which had changed only incrementally since the 70s – from the time of Fyodorov’s IOL fundamental models. There have been many permutations and improvements in preoperative formulae since then, but intra-operative aberrometry was based on a categorically different paradigm – in-theater measurement of aphakic autorefraction. And now aberrometry has been used to improve care for more than half a million patients, and counting – the method is almost ubiquitous. Similarly, when I joined Eugene de Juan and Transcend Medical to develop the CyPass Micro-Stent nine years ago, people couldn’t see the point – they were happy with their trabeculectomies and tubes. But today, microstents have revolutionized glaucoma treatment, and MIGS is the fastest growing category in ophthalmology. You simply don’t know where innovation will take you, and building market models is often so treacherous – it is necessary, but often gives investors a false sense of security as they are trained in excel spreadsheets and data analytics. From my experience, all the technologies I have been involved in exceeded estimates by a factor of at least 10. On the venture side, I have seen the flip side of the coin as well – when beautiful and intricate forecasting models come to naught. So, I trust my clinical gut and try to ask one simple question – how can I make patients’ and physicians’ lives better? What is the clinical utility? And then disruption and adoption seem to follow.

What’s the biggest challenge in ophthalmology today?
First, we need more bright, entrepreneurial ophthalmologists to get involved and step out of the clinical practice treadmill. Ophthalmology has genericized itself both technologically and practice-wise; it is all about volume and less about differentiation and eminence. There are so many ideas out there – I get approached every week by a colleague or resident who have had a light bulb go off. But an idea is just the beginning – it needs to be matured into a solution, the solution developed into a product and ultimately into a business which can scale and touch many patients, and that takes a village, or as the Transcend team say, it takes a tribe! I think we need to get more efficient and smarter about how we practice medicine. My team published a study in Ophthalmology 18 months ago, where we analyzed a database of 20,000 office-based cataract surgeries, and found it to be pretty safe – not a single case of endophthalmitis. This gave some people heartburn, but it has tremendous implications: avoiding the OR frees up OR space for other procedures, and aligns cataract surgery with refractive surgery in terms of how it’s done. It reduces resource use and improves efficiency – leaving the OR rooms for the more major procedures which need it.

What advice would you give to aspiring innovators?
Follow your passion and trust yourself. Doctors are not always the greatest businessmen, but being able to wear a clinician’s hat when judging new technologies – to really understand their clinical utility – is tremendously helpful. But you can’t know from the outset which ideas will result in paradigm shifts; you have to persevere – and for that you need passion.

An extended version of this interview is available online at: top.txp.to/issues/0617/802

Sean Ianchulev reports the following relevant disclosures: Founder and Chairman of Iantech, Inc; Founder and CEO of Eyenovia, Inc; Advisor to Alcon-Novartis; and a partner of PME Ventures.
THE NEXT STEP FOR POWERFUL IOP LOWERING

• Up to 40% vs baseline
• Low level of hyperaemia (7%)
• One drop once daily