DECEMBER 2017 # 48

the Ophthalmologist™

The Innovators

A showcase of the brightest technology of 2017

BIOMECHANICS MEETS TOMOGRAPHY

HEY CORVIS ST
I just took a look at the tomography.
These values call for caution.
I don't think I would operate.

HI PENTACAM
The biomechanics looks good, though.
The cornea is very stable.
I don't see any problem with operating.

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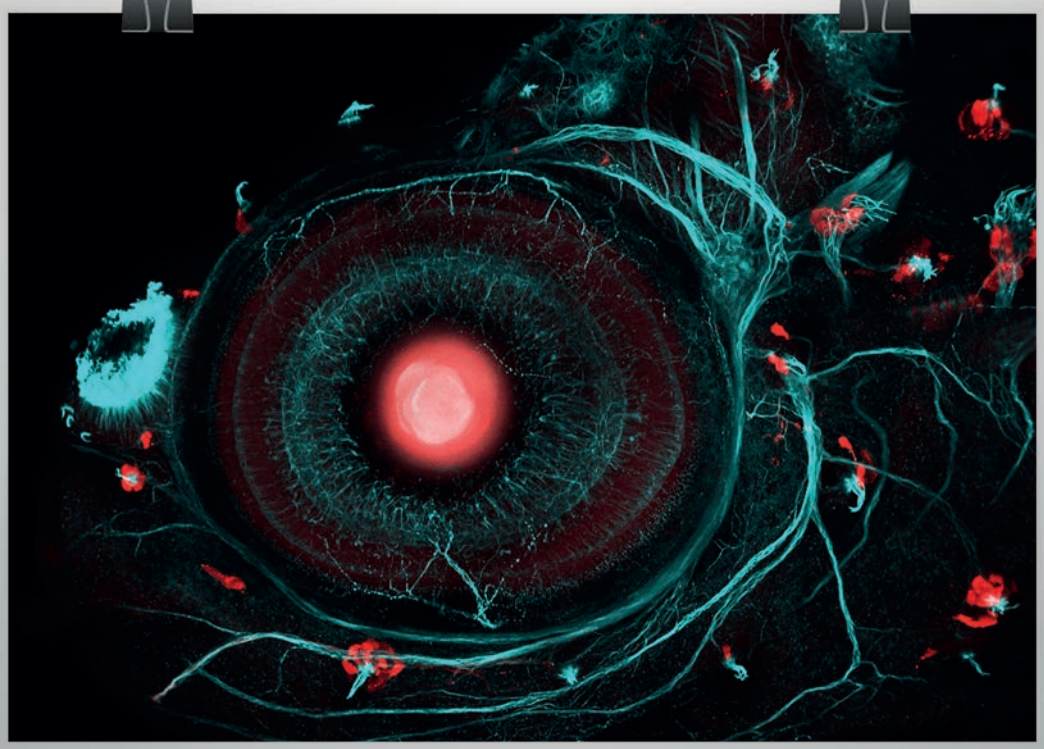
Image of the Month



Embryo Eye

This is an eye of a four day-old zebrafish embryo, with the lens showing red from a fluorescent reporter transgene inserted into the genome using CRISPR/Cas9 technology. The transgene is also expressed in the cells of developing mechanosensory organs - neuromasts, whereas neuronal tracts in the head are labelled in cyan by antibody staining and imaged by confocal microscopy. The image was selected as one of the winners of the Wellcome Trust Image Awards 2017.

Credit: Ingrid Lekk and Steve Wilson, University College London.

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

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Upfront

On The Cover

A representation of the colorful world of innovation.

the Ophthalmologist

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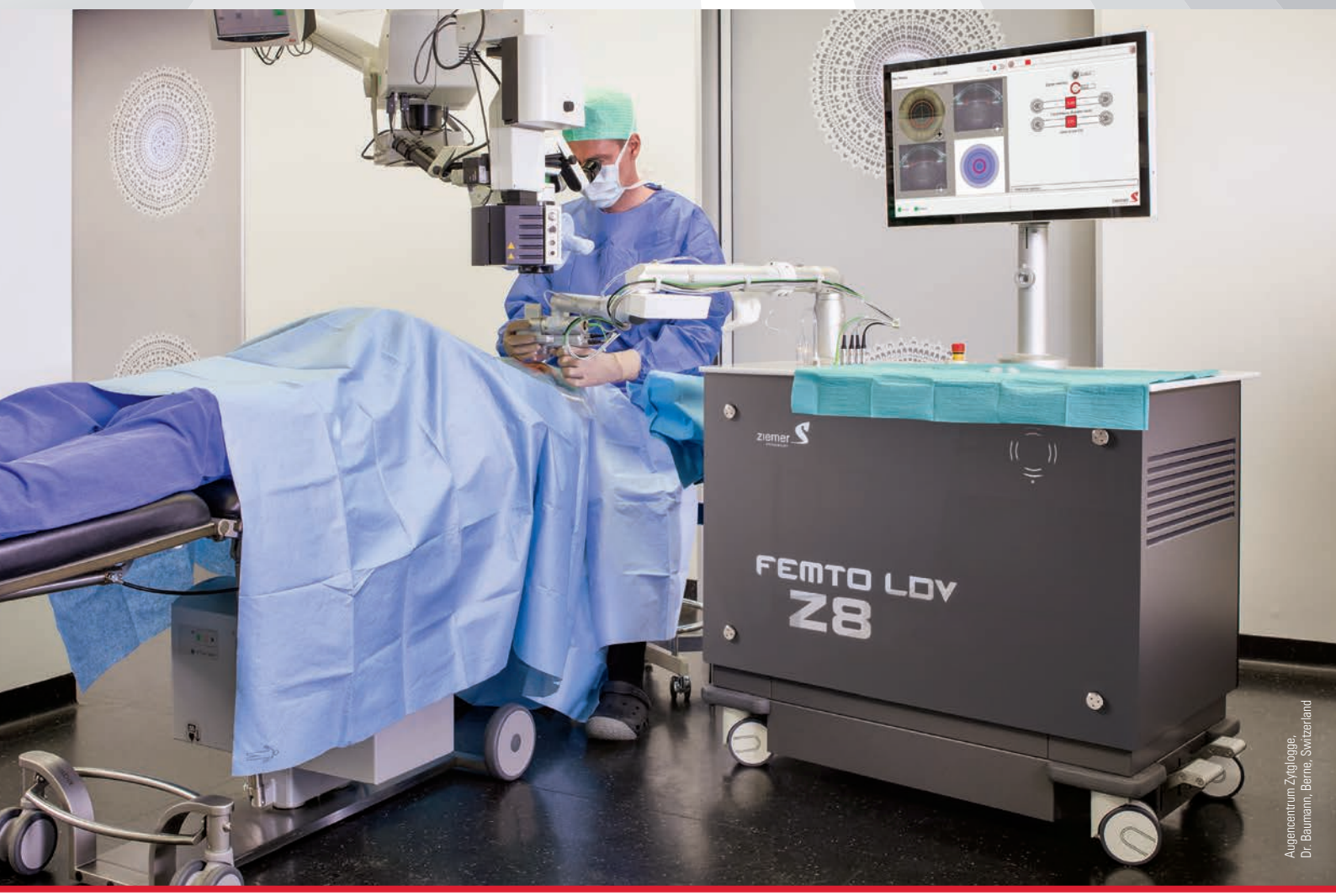

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HUMANITY IN SCIENCE AWARD

the Analytical Scientist

In partnership with

KNAUER

Richard Jähnke

Meet the Winner

Richard Jähnke

Richard Jähnke from the Global Pharma Health Fund (GPHF) has received the 2017 Humanity in Science Award for "development and continuous improvement of GPHF Minilab™ (www.gphf.org), which represents a breakthrough for the rapid and inexpensive identification of substandard and falsified medicines in low- and middle income countries in Africa, Asia and Latin America".

Richard received his award at a special jubilee reception in Berlin, Germany on October 2, 2017 hosted by KNAUER to celebrate the company's 55th birthday this year. Richard's work will feature in an upcoming issue of The Analytical Scientist.

Could it be you in 2018?

Analytical science has been at the heart of many scientific breakthroughs that have helped to improve people's lives worldwide. And yet analytical scientists rarely receive fanfare for their humble but life-changing work. The Humanity in Science Award was launched to recognize and reward analytical scientists who are changing lives for the better.

Has your own work had a positive impact on people's health and wellbeing? Details of the 2018 Humanity in Science Award will be announced soon.

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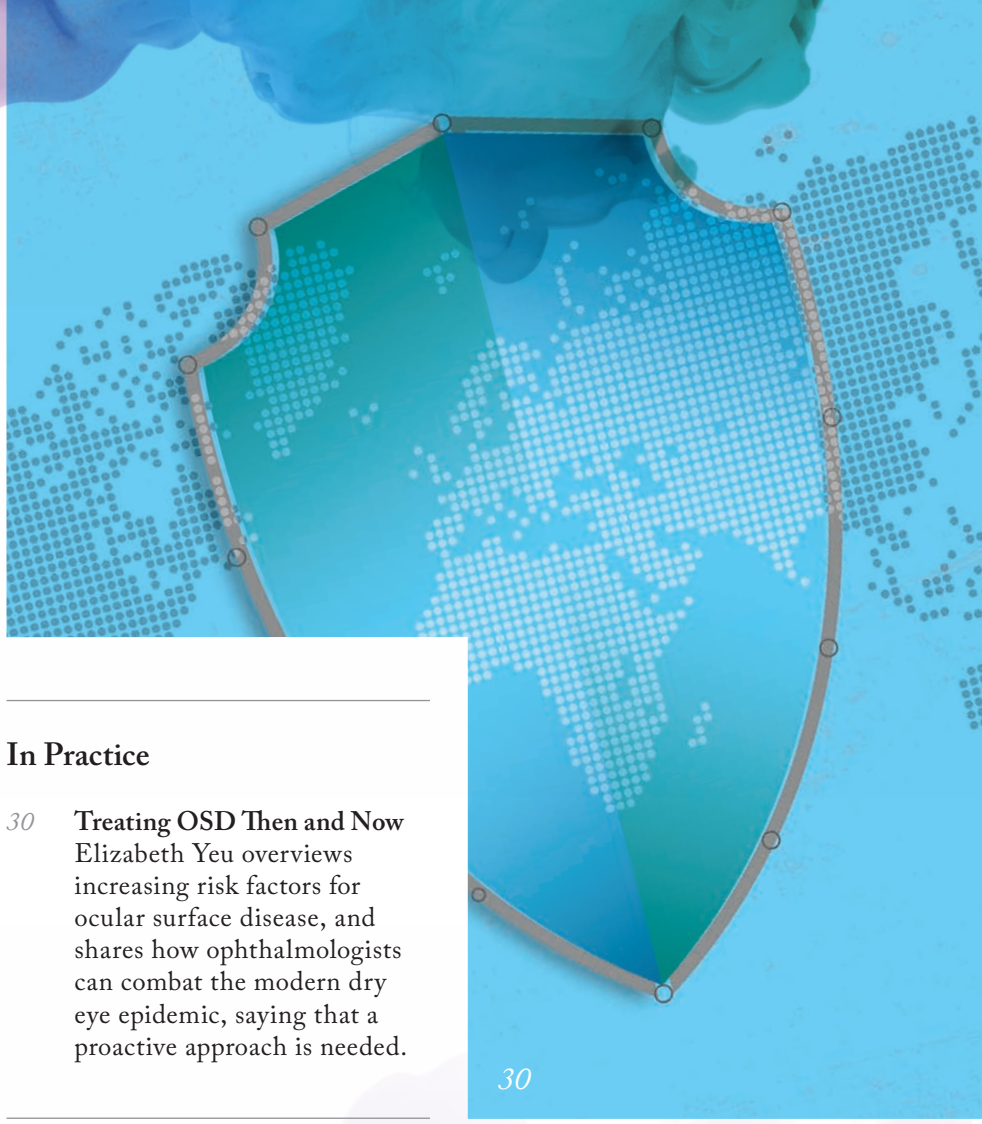

In My View

Feature

In Practice

NextGen

Profession

Sitting Down With

The ICO-Allergan Research Fellowship

THE ICO-ALLERGAN RESEARCH FELLOWSHIP

The ICO-Allergan Research Fellowship is supporting research that recognises innovation and advances the scientific understanding and clinical management of ophthalmic diseases from across the globe. As part of this fellowship the ICO and Allergan are delighted to be able to support a one-year research fellowship, to the value of $50,000.

The fellowship is open to young ophthalmologists (those under 40 years of age at the time of application) from around the globe, offering the chance to continue their research at a chosen university; preferably in a foreign country to where they live. Applications will be accepted for research work in the following subspecialties:

- Neuro-ophthalmology
- Pediatric ophthalmology
- Glaucoma
- Retina
- Tumours
- Uveitis
- Dry eye
- Cornea

HOW TO APPLY

Applications will open on 1st October 2017. For more information about the fellowship criteria and how to apply, interested applicants should visit the ICO's Education page – www.icoph.org/fellowships
Applicants will need to submit the following items with their applications:

- Copy of specialist exam
- Detailed CV
- Description of previous work in the field of the application
- Endorsement of the current Program Director
- Detailed description of how research work should be continued during the fellowship
- Feasibility confirmation of chosen host university
- A sustainability statement

APPLICATION DEADLINE

Submissions must be received by 15 January 2018. The fellowship winner will be chosen and notified at the Association for Research in Vision and Ophthalmology (ARVO) meeting (29 April – 3 May) and will be officially announced at the World Ophthalmology Congress (WOC) meeting in June 2018.

FURTHER INFORMATION

For further information about the fellowship, please contact the ICO Fellowships office.

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INT/0616/2017d & Date of Preparation: October 2017

Heidelberg Man

Another lament to the loss of a leading figure in ophthalmology.

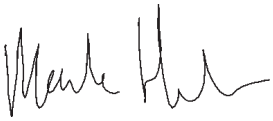
The sad news this month is the passing of Dr. Gerhard Zinser at the age of 63 years. If you've ever performed retinal imaging, the chances are you've heard of him, and it's very likely that you've used an instrument that owes something to his work – the Heidelberg Retina Angiograph, the Heidelberg Retina Tomograph, or the Spectralis OCT (and the software that produces the images for these instruments) are the big-ticket items. More generally, if you use confocal laser scanning to image the retina or the optic nerve, Gerhard didn't invent the technique – but he was instrumental in taking it out of the laboratory and in to the clinic.

In fact, this is a Heidelberg story: born in the nearby German town of Speyer, Gerhard lived there until his passing. His first degree (a MSc in Physics), PhD (Natural Sciences; applied optics) were both received from the University of Heidelberg, and his post-doctoral research (examining 3D light-microscopic image acquisition and processing) was performed at the nearby German Cancer Research Center. In 1990, he and Christoph Schoess founded a tech startup called Heidelberg Engineering. As an editor, I baulk at seeing anything that comes across as a billet-doux to a single company, but in the case of Gerhard and what he's achieved over the years, he truly is a Heidelberg Man.

From my perspective, Heidelberg Engineering appears to be a formal – almost stereotypically German – company. But if you speak to those who work there, in many respects, it really isn't. They talk about the company's culture: a flat hierarchy, and for anyone who has ever spoken or learned German, here's something big: everybody uses the informal 'Du', rather than the formal (and more common) 'Sie'. It's certainly worked for them – and that's down to Gerhard and Christoph. I think the combination of German, Engineer and Physicist is what prompted this comment from the first ophthalmologist I spoke to (Pearse Keane) after I heard the news: "I never met him, but it's clear to me that his character is reflected in Heidelberg Engineering, with their focus on high-quality engineering and precision."

So I implore you – even if you're an employee of a competitor, or a dyed-in-the-wool user of a different company's product – think of Gerhard when you next raise a glass. Toast him, and remember what he's helped reveal of the retina.

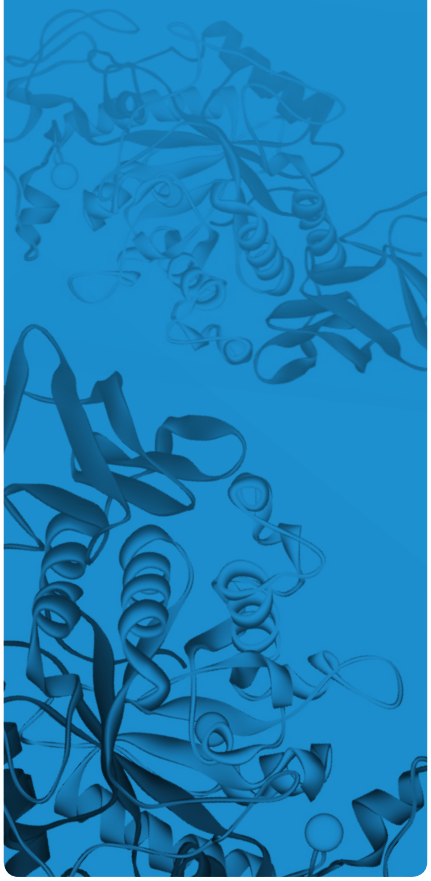
Mark Hillen
Editor



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



A New Dry AMD Target?

A US research team have identified a novel enzyme that appears to play a role in disease progression

Dry AMD – it's one of ophthalmology's modern mysteries. And it represents a huge unmet need; there are currently no available treatments for the disease, and recent hopeful candidate lampalizumab failed to meet its primary endpoint at Phase III (1). Because the mechanisms driving disease progression remain elusive, sourcing candidates is tough. But now, there is a new lead to chase: cGas.

cGas – or cyclic GMP-AMP cyclase – is a DNA sensor enzyme that is thought to function in the immune response to viruses. A multicenter team have, however, identified that the enzyme may also play a role in dry AMD disease progression by driving interferon signaling, which leads to mitochondrial-damage-induced inflammasome activation and, ultimately, retinal pigmented epithelium (RPE) degeneration (2). Jayakrishna Ambati from the Center for Advanced Vision Science at the University of Virginia, USA, and corresponding author on the associated publication shares the details.

What inspired your recent research direction?
Previously, we demonstrated that the inflammasome is a critical driver of retinal cell death in dry macular degeneration (3). We sought to determine the precise mechanisms by which inflammasome activation occurs in this disease, which led us to discover that activation occurred via the "non-canonical" Caspase-11 pathway.

What impact could your work have on the management of dry AMD?
Our work identifies cGAS as an extremely early event in the process by which retinal cells die in macular degeneration, which provides a strong rationale for developing therapies that can block cGAS or its effects. In addition, there is also potential to develop new imaging technologies to directly image inflammasome activation in the living human eye, which could identify patients with active disease who might be ideal candidates for therapy, as well as provide a means of monitoring treatment activity.

Did you suspect cGAS from the outset?
No. We were surprised because cGAS is a viral sensor, and there is no apparent viral involvement in macular degeneration.

Next steps?
Previously, we demonstrated that nucleoside reverse transcriptase inhibitors (NRTIs; a class of drugs already on the market for treatment of HIV/AIDS and hepatitis B), and modified NRTIs known as Kamuvudines, block inflammasome activation and prevent retinal death in relevant models of dry AMD (4). Inflammasome Therapeutics has licensed this technology and is moving rapidly to commercialize it. It turns out that NRTIs and Kamuvudines also block the function of cGAS and the non-canonical inflammasome as they relate to dry macular degeneration; hence, we are investigating the mechanisms by which these drugs have these multifaceted effects.

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1. *Roche. "Media Release". Available at: http://bit.ly/2jdN8Xx. Accessed: December 4, 2017.*
2. *N Kerur et al., "cGAS drives noncanonical-inflammasome activation in age-related macular degeneration", Nat Med, [Epub ahead of print], (2017). PMID: 29176737.*
3. *V Tarallo et al., "DICER1 loss and Alu RNA induce age-related macular degeneration via the NLRP3 inflammasome and MyD88", Cell, 149, 847–859 (2012). PMID: 22541070.*
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How Low Can You Go?

Optimizing ROP treatment by scaling back the dose

The vascularization that presents in premature babies with retinopathy of prematurity (ROP) requires prompt treatment to prevent retinal detachments and blindness. Currently, ROP is treated by conventional laser therapy, with vitrectomy required when disease fails to regress. But what about using anti-VEGF agents, such as bevacizumab, to dampen down neovascularization? David K Wallace of Indiana University School of Medicine, Indianapolis, USA, performed a dose de-escalation study and discovered that less is more.

"Bevacizumab, when injected intravitreally, can reach the systemic circulation and cause large and persistent reductions in serum VEGF levels," said Wallace (1). "This is important because developing infants need VEGF for vascular growth in important structures like the brain and lungs for example." Bevacizumab has been investigated previously for ROP, with 0.625 mg – half the adult dose – being administered in the BEAT-ROP study (2). However, this is likely still too high: "It has been estimated that this may be as much as 10,000 times the drug we need to bind VEGF in the vitreous," said Wallace.

To determine a lower dose of bevacizumab that is effective and could be tested in future larger studies, they performed a multi-center dose de-escalation study in which successive cohorts of infants with ROP received lower concentrations of bevacizumab. Study eyes were administered investigational (reduced) doses, whilst fellow eyes received the last dose to be found effective in the study; progression to the next lower dose was based on achieving successful results with the previous dose. Dosing schedules in the cohorts was as follows (study eye, fellow eye):

- Cohort 1: 0.250 mg, 0.625 mg
- Cohort 2: 0.125 mg, 0.250 mg
- Cohort 3: 0.063 mg, 0.125 mg
- Cohort 4: 0.031 mg, 0.063 mg.

In total, 61 infants were treated (mean gestational age, 24.9 weeks), with 58 completing examinations at four weeks. All type 1 ROP study eyes treated with 0.25 mg (11/11), 0.125 mg (14/14) and 0.031 mg (9/9) bevacizumab showed successful treatment at four weeks; of the 24 infants treated with 0.063 mg, 21 showed success. Of all 61-treated infants, three had early failure (5 percent) and 11 (18 percent) were re-treated for a late recurrence of ROP. At ≥6 months, 54 patients had regressed ROP, and one infant each had progressed to retinal detachment stage 4a and stage 5. "Doses of bevacizumab as low as 5 percent of that which was administered, and considered the standard dose, in the BEAT-ROP study were effective in treating ROP" said Wallace. In terms of adverse events, he reported that mild vitreous hemorrhage occurred in one study eye, and that five infants died from pre-existing conditions that were not related to treatment.

Referring to the suppression of serum VEGF – which was found to be reduced at both 2- and 4-weeks after injection – Wallace said: "We'd like to see less effect on VEGF levels as we go to lower doses, as all the doses tested so far still suppress VEGF and give us concern about the possible systemic side effects." Their next steps? "We are going lower in terms of dose, as well as following these babies forwards to 24 months to obtain neurodevelopmental tests."

References

1. *DK Wallace, "Lower dose intravitreal bevacizumab for ROP". Presentation at the American Academy of Ophthalmology annual meeting, November 13, 2017; New Orleans, USA.*
2. *HA Mintz-Hittner et al., "Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity", N Engl J Med, 364, 603–615 (2011). PMID: 21323540.*

Red Light Means Go?

A recent trial shows promise for a new ocular melanoma therapeutic

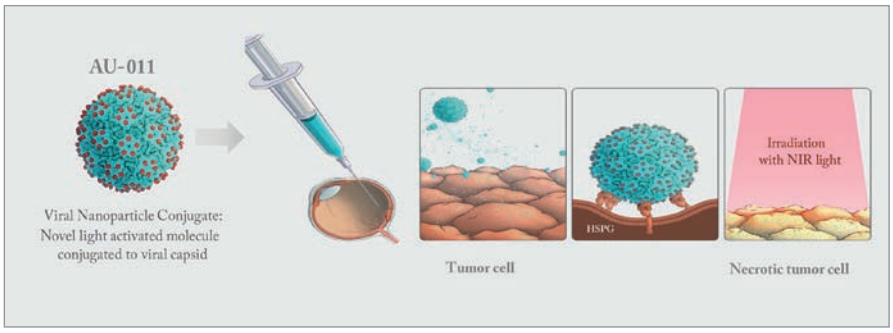

Figure 1. AU-011 mechanism of action. NIR, near infra-red. Credit: Aura Biosciences.

Choroidal melanoma represents a serious unmet medical need; despite receiving radiotherapy, 25 percent of patients with the disease develop metastatic disease after five years (1).

Enter AU-011 – a viral nanoparticle conjugate comprising a novel light-activated molecule conjugated to a viral capsid that is currently under investigation. When injected into the vitreous, AU-011 binds to heparan sulfate proteoglycans on the surface of tumor cells. Stimulation with near-infrared light (689 nm) activates the drug, disrupting the tumor cell membrane and causing subsequent necrosis of the tumor (Figure 1).

Initial studies in rabbits have demonstrated that a therapeutic dose of 50 µg induced complete necrosis of melanoma in 80 percent of animals (2). But what about in humans? Carol Shields of Wills Eye Hospital, Philadelphia, USA, recently shared interim results from a Phase Ib/2 trial of AU-011 at the recent Annual Meeting of the American Academy of Ophthalmology in New Orleans (2).

Six patients with small-medium choroidal melanoma (2–3.4 mm in thickness with evidence of documented growth or sub-retinal fluid) were enrolled into the open-label ascending single and repeat dose clinical trial, with three patients each receiving a single dose of 20 or 40 µg. The primary endpoint, safety by multimodal imaging, was met. Though no serious adverse events were found, Shields reported that there was some inflammation in the anterior and posterior segment that led to increased IOP in three patients. "We wonder if this could be a sign of new stimulation from this medication," said Shields. Visual acuity for all patients was preserved within five letters of their pre-treatment vision.

The secondary endpoint was preliminary efficacy at 3–6 months, assessed by B-scan ultrasonography of tumor height. Five of the six patients showed stable disease and one patient showed tumor growth that required plaque radiotherapy. Shields also noted other related findings to the treatment: "tumor change in color, loss of orange pigment, loss of melanin and reduction in macular fluid."

Shields closed her presentation with a nod to the scientists behind AU-011. "I'd like to acknowledge the scientist John Schiller, inventor of the HPV vaccine, who modified that technology to adapt it to this new drug, as well as Elisabet de los Pinos – the mastermind behind this drug, who is taking it from bench to bedside."

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1. *M Diener-West et al., "Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26.", Arch Ophthalmol, 123, 1639–1643 (2005). PMID: 16344433.*
2. *CA Shields, "A Phase 1b clinical safety study of a novel tumor targeted therapy (AU-011) for the treatment of primary choroidal melanoma". Presentation at the American Academy of Ophthalmology; November 11, 2017; New Orleans, USA.*

Quite a Stretch

Can brolucizumab extend the AMD anti-VEGF treatment interval?

RTH258. "Son of Lucentis." The drug is brolucizumab – a single-chain antibody fragment, a potent inhibitor of VEGF, and it's claimed to be "the smallest known active unit of an antibody." It also holds the potential of a 12-weekly treatment interval for the treatment of AMD, which, if true, clearly means fewer hospital visits for patients and an easing of the burden for the healthcare professionals that have to run the clinics. Last month, at the American Academy of Ophthalmology annual meeting in New Orleans, Pravin Dugel presented the much-anticipated 48-week data from the 96-week, Phase III evaluation of two doses of the intravitreally-administered anti-VEGF drug compared with aflibercept for the treatment of neovascular AMD in the HAWK and HARRIER trials (1).

The trial design, treatment regimens and disease activity assessments are depicted in Figure 1, and consisted of two phases: an initial 16-week matched regimen period to provide a head-to-head comparison of brolucizumab (3.0 or 6.0 mg) and aflibercept 2.0 mg, which was followed by brolucizumab being dosed in 12-weekly intervals (q12w) – reduced to 8-weekly

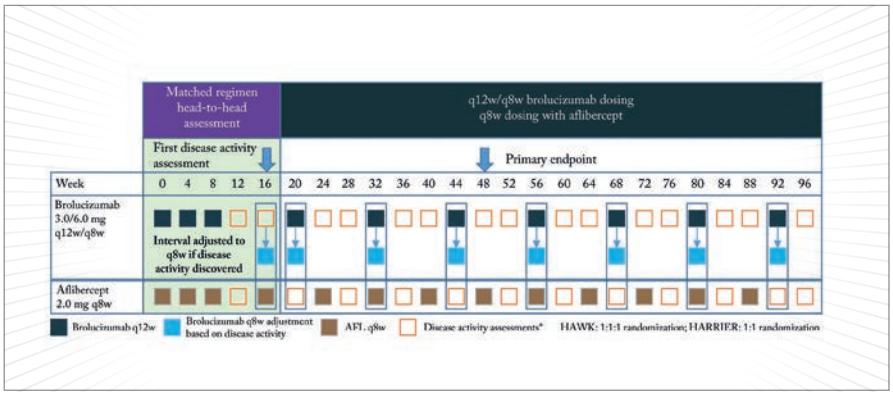

Figure 1. HAWK/HARRIER trial design. **Disease activity assessments were conducted at pre-specified visits by the masked investigator, supported by protocol guidance based on dynamic functional and anatomical characteristics. Additional assessments and potential dosing interval adjustments occurred at weeks 28, 40, 52, 64, 76 and 88 in the HARRIER study.*

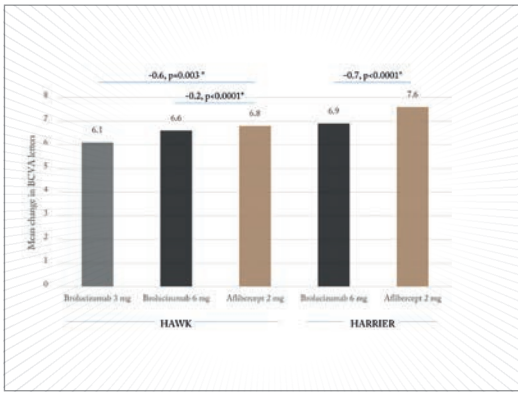

Figure 2. Mean change in BCVA letters at week 48 in the HAWK and HARRIER trials. Brolucizumab (q8w/q12w) was non-inferior to aflibercept at both doses for this endpoint. **Noninferiority with a 4.0 letter margin vs aflibercept; noninferiority for change in BCVA from baseline averaged over period of Week 36–43 in HAWK (brolucizumab 3.0 mg p=0.0001; brolucizumab 6.0 mg (p<0.0001) and HARRIER (p<0.0003) vs. aflibercept).*

intervals (q8w), if signs of disease activity were noted. Patients randomized to receive aflibercept were administered q8w doses for the rest of the study.

So what does the 48-week data show? Brolucizumab met the primary (non-inferiority) endpoint: change in BCVA from baseline to week 48 (Figure 2). Not all patients were able to maintain the q12w brolucizumab treatment interval – in HAWK, 52 and 57 percent of patients remained on q12w for the 3.0 and 6.0 mg doses, respectively. And in HARRIER (which evaluated only the 6.0 mg brolucizumab dose), 52 percent of patients remained on the longer interval by week 48. However, the visual gains achieved by all drugs and dosing arms were robust in the head-to-head assessment period, and were maintained out to week 48. Additionally, significantly ($p<0.05$) fewer brolucizumab-receiving patients displayed disease activity at week 16 (HAWK: 27.4, 23.5 and 33.5 percent for brolucizumab 3.0 mg, 6.0 mg and aflibercept 2.0 mg, respectively; HARRIER: 21.9 vs. 31.4 percent). In both trials, the novel agent was also found to have achieved superior reductions in central subfield thickness measurements in both the head-to-head and maintenance phases, and significantly fewer brolucizumab-receiving patients had intraretinal, subretinal or sub-RPE fluid on assessment at week 16 or 48. In terms of safety, ocular, non-ocular and serious adverse event rates were similar across treatment groups.

Can brolucizumab stretch those treatment intervals out beyond what's currently achievable? On the basis of the HAWK/HARRIER trial data, it seems that for some patients, at least, the answer could be "yes." Dugel stated in his presentation that further details of the HAWK and HARRIER trials will be presented in future congresses – and it was clear that those details are keenly awaited.

Reference

1. *PU Dugel et al., "HAWK & HARRIER: 48-week Results Of 2 Multi-Centered, Randomized, Double-Masked Trials of Brolucizumab Versus Aflibercept For Neovascular AMD", presented at: The American Academy of Ophthalmology 2017 Annual Meeting on November 10, 2017, New Orleans.*

Andrew Moshfeghi's take

Though the HAWK and HARRIER studies (1) provided compelling evidence of a potentially significant biologic effect of brolucizumab for patients with neovascular AMD, there are some preliminary concerns with respect to the way the data were presented. For one, the proportion of patients who completed the study protocol was not shown – as one would normally expect to see in an initial presentation of pivotal clinical trial data. This is particularly relevant to these studies with their complicated treatment regimen assignments for the brolucizumab cohorts. As a result, it is unclear how many subjects may have been exited from the studies (in each of the cohorts) as a result of needing treatment more frequently than every eight weeks. Because we don't know how many subjects were exited for this reason (or for other reasons), it is difficult to interpret the potential impact this may have had on the reported treatment effect. Furthermore, the data were not presented in a way that allows one to discern the treatment effect of the brolucizumab cohort dosing strategies. Rather, we were left only to draw efficacy and safety conclusions on the basis of pooled brolucizumab data with their varied dose and treatment frequency regimens.

Andrew Moshfeghi serves as Associate Professor and Director of the Clinical Trials Unit for the Department of Ophthalmology at the USC Eye Institute.

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

Get Involved

My words of wisdom on working with industry to drive ophthalmic innovation

By Richard Lindstrom, Founder and Attending Surgeon, Minnesota Eye Consultants, Minneapolis, Minnesota, USA

I am passionate about innovation and next-generation technology in ophthalmology, in terms of both the initial development and the translation from bench to bedside. And who is best-placed to direct industry where to invest or to help them develop the next-generation technology, as well as teach others how to use it? Ophthalmologists, of course.

I know it might be controversial to some, but I am a strong advocate of properly designed and well-intentioned collaboration between the industry that develops the products and the ophthalmologists who use them. A powerful innovation cycle needs a quality physician – the individual who is working in the 'arena' and fully aware of the problems. Ophthalmologists can inform industry colleagues what the unmet needs are and help them find ways to resolve them. Then they are able to assist with the challenges of developing a product to address those unmet needs, bringing it to market, and sharing best practice.

Clinicians can start helping to drive the cycle of innovation by simply not being 'intimidated' when an opportunity presents itself. But we can also be proactive. We spend our days seeing patients and being confronted with unmet needs. And with hundreds of thousands of ophthalmologists worldwide, there are many problems that are being seen – and all need to be solved. The next step is to seek a solution, which can begin by us getting inventive or by looking for talented collaborators – such as those in industry or engineers – to see if they know of a novel way to solve the problem at hand. Next comes expansion of the idea, potentially through recruiting more partners to help, and working through the innovation cycle.

It's true that 'shepherding' through the whole innovation cycle – from idea to reality to commercialized product – can take 10 or 15 years, so I can understand why some physicians don't want to get involved in the process; it does takes a lot of time and effort. But it can also be incredibly rewarding. And if a clinician is committed and believes in an idea, it is absolutely possible – as proven by the fact that I have been through the process multiple times!

"A powerful innovation cycle needs a quality physician."

One main challenge in ophthalmic innovation is how we best help the proactive entrepreneurs – those individuals who have come up with ideas to tackle unmet needs. Such people invariably need some help getting started. Working together with the Octane Group in Orange County, we created a fund called Visionary Ventures to invest in new technologies in ophthalmology. In addition, my good friends Bill Link, Andy Corley, Matt Larson and I have founded Flying L Ventures. To date, these two

entities have invested together in SightLife Surgical, RxSight and Equinox. Visionary Ventures has also invested in Mynosys, Iantech, TearClear, and TearFilm.

As well as helping new and interesting startups, such as Mynosys and Iantech, we had a completely new, "out-of-the-box" idea to help one key area that has been neglected for investment – cornea. Cataract, glaucoma and age-related macular degeneration (AMD) all receive a lot of investment, but because we only perform around 50,000 corneal transplants a year in the USA, it is a smaller opportunity. We saw it as an unmet need, and together with the director of the world's largest eyebank – SightLife – we conceptualized a unique model where a for-profit entity (SightLife Surgical) is owned by a not-for-profit entity (SightLife). SightLife's primary mission is to eradicate corneal blindness in the world, and it's hoped that money made from running a successful company might accelerate their mission. So far it is working quite nicely, and I am really excited by it. It's a fascinating new model that will bring innovation investment into a field that has been somewhat neglected – and it will be of real benefit to patients with corneal disease.

What will continue to drive ophthalmic innovation? Essential collaborations between clinicians and industry, plus the right kind of support for ideas born of those collaborations. I certainly plan to continue pursuing collaborations with industry as long as I can – and I hope I inspire others to do the same.

A Whole New World

There's a need to open up new opportunities for retinoblastoma care. Here's how we're approaching the challenge

By Jesse L. Berry, Associate Director of Ocular Oncology at Children's Hospital Los Angeles (CHLA) and Assistant Professor of Ophthalmology at CHLA & the USC Roski Eye Institute, University of Southern California, USA

We say we are in an era of precision medicine. But what can one do when the very information needed to make these informed, directed, personalized choices cannot be accessed by the clinician? Well, that is the situation we currently face as ocular oncologists for retinoblastoma (Rb).

Despite critical advances in how chemotherapy is delivered, worldwide, nearly 50 percent of advanced eyes with Rb are enucleated and many more affected eyes are legally blind – even with treatment (1, 2). Why? Because there are no known molecular prognostic features that can predict the response of Rb to treatment and clinical features rely primarily on assessing the size of the tumor or presence of seeding (e.g. ICRB Group Classification [3]). These, however, still predict with only 50 percent certainty whether an advanced Group D Rb tumor will respond to intravenous chemotherapy or will require subsequent enucleation due to persistent or recurrent tumor (4). In 2017, for advanced eyes, we have the same predictive value as a coin flip.

The vast majority of Rb arises from somatic, germline or mosaic mutations in the RB1 tumor suppressor gene. And similar to other cancers – such as those found in the breast, lung and prostate – Rb DNA likely harbors specific genetic or genomic changes that will be informative regarding therapeutic response and/or prognosis. And we need this information because currently there is no targeted treatment or personalized medicine approach for Rb, despite it being one of the first cancers with a known genetic etiology for carcinogenesis. Performing genomic analyses on Rb DNA at the time of diagnosis or during treatment would allow, for the first time, clinical correlations with specific tumor mutations, genomic changes and expression profiles that were only previously available from tumor tissue from eyes that had been already enucleated – and never from those eyes that responded to therapy and were saved. This is because evaluating tumor DNA in Rb is challenging because direct biopsy of the tumors is contraindicated due to the risk of extraocular tumor spread and metastatic disease (5). As a result, the Rb field had a long-standing golden rule: the eye is inviolable during treatment, which means that tumor tissue only becomes available after enucleation.

However, the golden rule changed in 2012 as Francis Munier – an ocular oncologist in Switzerland – introduced a safety-enhanced procedure to inject melphalan into the vitreous cavity of eyes with Rb and seeding (6, 7). In this procedure, aqueous humor is withdrawn prior to the injection to lower IOP and prevent reflux of active seeds to the injection site. And it has turned out to be safe: no cases of metastatic disease have been reported with this safety-enhanced technique (8). This method of intravitreal chemotherapy as treatment for vitreous seeding in Rb has been an absolute game-changer for managing the disease, not only by providing

a new, highly effective treatment strategy, but also by providing access to the aqueous humor of eyes undergoing treatment. This revolution in one aspect of Rb management has provided a critical opportunity to revolutionize another – the biopsy. We've managed to do just this, and have recently demonstrated that aqueous humor samples can be a 'surrogate' biopsy for Rb as a liquid biopsy. In six samples obtained from three children with Rb (≤3 years at diagnosis), we identified cell-free tumor DNA through shallow whole genome sequencing using a next-generation protocol, and confirmed that the chromosomal alterations in the aqueous corroborated those found in Rb tumors (9).

Our findings provide the proof of concept that, with the aqueous, we have a safe and effective way in which to derive genetic information from the Rb tumor without enucleation. Finally, we can gain access to critical genomic information to help ocular oncologists decide which eyes are likely to be most responsive to therapy – and can thus be salvaged – and those which are higher risk and should undergo primary enucleation. It could also open up an entirely new research domain for Rb as well as other intraocular diseases, as the aqueous humor doesn't only yield tumor DNA, there is also RNA, micro-RNA and possibly other disease markers. In fact, there's a whole new world to explore!

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Jury's Out

Placing the HAWK/HARRIER data in the wider context of nAMD anti-VEGF trial data

By David A. Eichenbaum, Retina Specialist at Retina Vitreous Associates of Florida in Tampa, Florida, and Affiliate Assistant Professor in the Department of Ophthalmology at the Morsani College of Medicine at the University of South Florida

The treatment of neovascular age-related macular degeneration (nAMD) has been transformed by the introduction of intravitreal anti-VEGF therapy. Since the introduction of this class of treatment in 2005 with off-label bevacizumab, the field has both embraced anti-VEGF therapy but also continuously tried to reduce the frequency of injection treatments, while maintaining the very good visual and anatomic results demonstrated in fixed-interval treatment protocols. It has been demonstrated that, in aggregate, converting patients in a given population to a less-frequent, 12-week injection schedule has not shown nearly as much benefit as higher-frequency, 4- or 8-week treatment (1–10). When study populations that did well in high-frequency dosing groups are allowed to follow-up in extension trials at infrequent intervals and receive few injections, visual acuity drops off fairly quickly over time. Real-world data also supports the finding that infrequent injections of available anti-VEGF injection therapy correlate with decreased acuity, whereas more frequent injections correlate with better vision (10).

Recently, Novartis presented data from the HAWK and HARRIER trials (11), which showed that 57 percent and 52 percent of subjects, respectively, maintained vision at 12-week injection intervals following a 3-injection monthly loading phase. In the protocols, patients were assessed monthly and could be treated at either 8- or 12-week intervals depending upon the presence of disease activity.

The question that was not directly challenged in the HAWK and HARRIER studies is whether or not the current commercially available

agents (bevacizumab, ranibizumab, and aflibercept) have similar efficacy when subjected to the same dosing protocol. HAWK and HARRIER used aflibercept as an active control agent in half the randomized patients, but the aflibercept could only be dosed at 8-week intervals – without an option to extend to 12-week intervals, which the brolucizumab subjects enjoyed. Fortunately, ranibizumab and aflibercept have been extensively studied in a variety of less-frequent injection dosing protocols, and we can look at the patient populations in those previously published studies for some illumination regarding whether the HAWK and HARRIER results imply that a meaningful advance with regards to dosing frequency has been made.

"The question that was not directly challenged HAWK and HARRIER is whether or not the currently available agents have similar efficacy when subjected to the same dosing protocol."

In PIER (3), patients received 3 monthly loading doses of 0.3 mg (n=60) or 0.5 mg ranibizumab (n=61) then quarterly dosing through month 12. Fifty-four percent of patients at month 12 maintained their initial visual acuity gains enjoyed over the 3-month loading period (4). In CABERNET (10), the control group (n=163) received 0.5 mg ranibizumab quarterly after 3 monthly loading doses. At month 12, 71 percent of these patients required no additional therapy and gained a mean 8.2 ETDRS letters from baseline. In EXCITE (5), most patients were randomized to quarterly dosing after a 3-month loading phase. At month 12, approximately 41.6 percent of patients receiving quarterly ranibizumab 0.3 mg (n=120) and 0.5 mg (n=118) maintained their initial gains in BCVA. During weeks 52–96 of the VIEW trials, a subset of patients achieved a dosing interval of ≥12 weeks from the 0.5 mg ranibizumab q4 weeks (n=218; 43 percent), 2 mg aflibercept q4 week (n=284; 54 percent), and q8 week (n=245; 48 percent) groups. At week 96, these patients gained a mean 9.2 (AFL2q8), 8.8 (AFL2q4), and 8.5 (RBZq4) ETDRS letters from BL (6,7).

Cross-trial comparison of over a decade of anti-VEGF studies suggests that approximately 50 percent of patients with nAMD perform well with a 12-week dosing schedule of ranibizumab, aflibercept, or brolucizumab. Our subspecialty is certainly seeking a therapeutic that can reduce the burden of treatment for our patients, and we will welcome brolucizumab as an additional treatment option. However, we need to look at its data in the context of our maturing compendium of knowledge studying anti-VEGF biologics in nAMD before we conclude that brolucizumab will provide an actual reduction in dosing burden.

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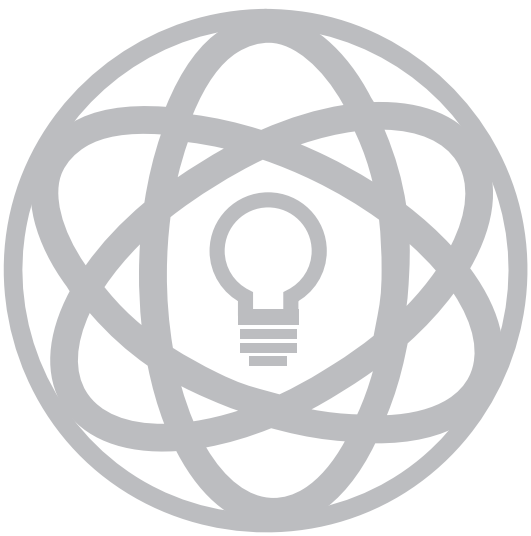
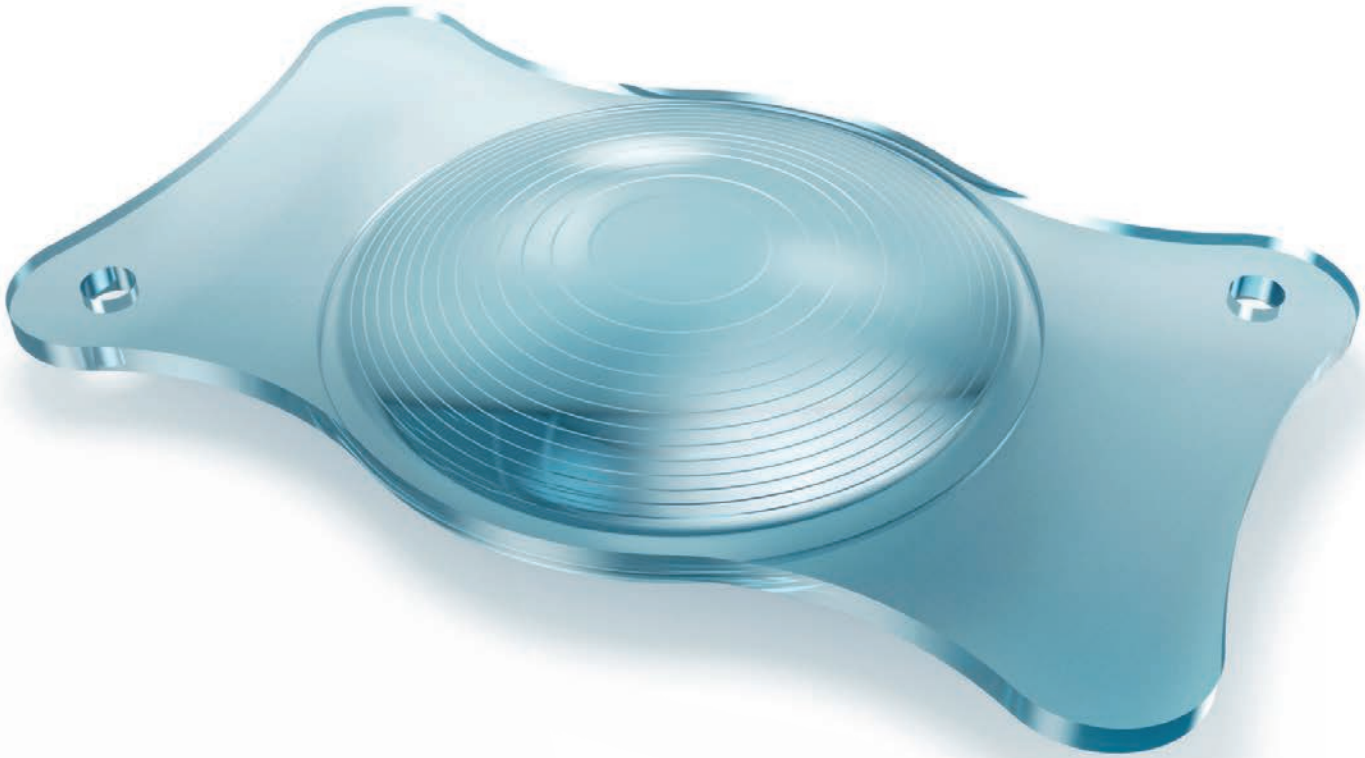


THE INNOVATORS 2017

The field and practice of ophthalmology is constantly being shaped by the driving force of innovation. As one of the most innovative fields in medicine, ophthalmology is often at the forefront of cutting-edge technologies and treatments. Here, some of the leading innovators from the ophthalmic space present their latest and greatest offerings: from imagers and diagnostics, to cutting edge refractive surgery and glaucoma care.

ZEISS AT LARA 829MP

The next-generation EDoF IOL with the widest range of focus



Florian Kretz, Chief Executive Officer and Lead Surgeon at Augenärzte Gerl, Kretz & Kollegen in Ahaus, Germany, says,

"AT LARA from ZEISS offers us an additional option for individualized patient care. It enhances the intermediate visual acuity and offers reduced optical phenomena with increased optical performance for distance and intermediate range."

'Premium' patients expect premium outcomes. When it comes to multifocal IOLs, it's the surgeon's job to give their patients what they've paid for. Both surgeon and patient, therefore, require a premium IOL that can meet the demands (and the high expectations) that are inherent in premium cataract and refractive lens exchange procedures.

Multifocal IOLs – and in particular trifocal IOLs – provide patients with good visual acuity at all distances. But this has come at a cost: the optical compromises inherent in such lens designs can lead to visual side effects like halo and glare. If patients can't tolerate them, the alternative is often placing a monofocal lens. These are safe in terms of visual side-effects, but come with a glaring drawback: patients need to wear spectacles for near and intermediate vision. Extended depth-of-focus (EDoF) IOLs provide an excellent compromise of the benefits of both monofocal and multifocal IOLs: more spectacle independence than monofocal IOLs, with fewer visual side effects than multifocal IOLs. If you have a patient who leads an active lifestyle, who wants to be largely spectacle-independent, who may be particularly sensitive to visual side effects, and who is happy to occasionally wear reading glasses, EDoF lenses could be a great choice. However, such lens designs still involve optical compromises and visual side effects – meaning there's still room for improvement.

It has taken real innovation from ZEISS, including simulations with about 50,000 optical design candidates, to push forward the field of EDoF IOLs: the result is a lens that provides the widest range of focus of any lens of its type on the market today – and simultaneously minimizing visual side effects and contrast loss. That lens is the AT LARA 829MP, with each letter in 'LARA' representing an optical innovation by ZEISS:

L – "Light Bridge" optical design, providing the widest range of focus among EDoF IOLs.
A – Aspheric optics that are biometrically optimized and neutral. The aberration neutral aspheric design supports depth of focus and post-LASIK usage.
R – Reduced visual side effects, thanks to patented Smooth Micro Phase (SMP) technology and an EDoF design that results in fewer visual side effects than multifocal IOLs.
A – Advanced chromatic optics, with a color-optimized optical design for increased contrast sensitivity.

The Light Bridge optical design is based on a unique diffractive optic with two focus additions, creating a continuous focus extension that allows patients to see sharply without visual aid at distances relevant to most of their daily activities.

AT LARA 829MP's aberration-neutral aspheric design and advanced chromatic correction allow for optimized contrast sensitivity. ZEISS' SMP technology combines a diffractive optical design with a unique transition between optical powers. This design allows for an IOL surface profile that can be manufactured more precisely thus reducing light scatter inherent in other IOLs. As a consequence, a smaller fraction of the incident light is misdirected, and accordingly, minimizes visual side effects. Not only does the AT LARA 829MP represent an innovation in optics – it's also an innovation in manufacturing.

With AT LARA 829MP, ophthalmic surgeons can decrease spectacle dependence for a broader group of patients and address the growing need for improved intermediate vision performance, which is important for activities such as working at a computer. ZEISS AT LARA EDoF IOL enhances the range of vision for patients by creating an elongated focus range. Now, doctors have a new option to provide superior visual outcomes for cataract patients for whom multifocal IOLs might not be the optimal choice because of sensitivity to visual side effects, such as halo and glare at night.

Balasubramaniam Ilango, Medical Director of OPTIMAX clinics, U.K.

"My patients are delighted and very happy with AT LARA 829MP. Their visual acuity is excellent over a wide range of distances and so far they do not report about any visual side effects."

DOUBLING UP ON INNOVATION

Glaukos' iStent inject® device allows two micro-stents to be implanted via a single corneal entry point

ELIGIBLE PATIENTS

Mild to moderate POAG, pseudoexfoliative glaucoma or pigmentary glaucoma

- C/D ratio ≤0.8
- pre-op IOP up to 30 mmHg (medicated)
- target post-op IOP to 15 mmHg

Phakic patients or pseudophakic patients with PC-IOLs
Patients with medication issues, such as side-effects or poor compliance
Normal angle anatomy as per gonioscopy, Schaeffer grade 3–4
No peripheral anterior synechiae, rubeosis or other angle abnormalities that could impair iStent placement

Glaukos has been at the forefront of glaucoma management since 1998, and has built an unparalleled reputation for innovations that are progressively transforming the treatment of this most problematic disease. Now, the company that pioneered MIGS by introducing the iStent® – previously the smallest medical implant in standard use – has further enhanced its revolutionary product by developing the iStent *inject*® device, which is smaller still.

The original iStent's advantages are well-known; the creation of a permanent trabecular micro-bypass allows the resumption of fluid flow out of the eye, thereby reducing IOP and bringing potential benefits to patients such as delayed disease progression and avoiding the need for complex, invasive surgery. In addition, the IOP reduction achieved is often sufficient for iStent® recipients to reduce or entirely eliminate the use of eye-drops. And given glaucoma medication issues – namely, uncomfortable side-effects, poor compliance and cost – this represents a real benefit of the iStent® system.

So what's new about the iStent *inject*® system? iStent *inject*® features heparin-coated titanium microstents with a central inlet and four outlets to optimize flow and collector channel access – like iStent®, only smaller. The delivery device comprises a neat, hand-held injector – a cam-driven, single-use sterile unit, with a window in the insertion tube to optimize visualization of stent delivery during implantation. Furthermore, the iStent *inject*® device is preloaded with not one but two stents, and the innovative design of the injector delivers both stents into the trabecular meshwork. Therefore, as well as providing a convenient and cost-effective means of stent insertion, the iStent *inject*® system allows the surgeon to place two stents into trabecular meshwork in a single procedure – that is, via a single corneal entry point. The result? Further pressure reduction for minimal trauma: the safety profile is similar to that of cataract surgery alone (1), and the burden of patient follow-up after the iStent *inject*® procedure is no different from the follow-up associated with standard cataract procedures. Furthermore, and very encouragingly, the iStent *inject*® -associated reduction in medication needs is excellent; 72 percent of patients treated with iStent *inject*® no longer require glaucoma medication 12 months after the procedure (2). Finally, mindful of the real-life needs of ophthalmic surgeons, Glaukos has made the device applicable both in combination with cataract surgery and in standalone procedures.

What next? The iStent® was already known as not only the first MIGS system but also as one of the 'true' ab interno MIGS systems. Now, by coupling two stents with the simple and novel iStent *inject*® implantation system, Glaukos is set to further increase uptake of the iStent *inject*® throughout the EU (acceptance is already impressive – over 300,000 patients have now received the iStent® or iStent *inject*®implants). The iStent *inject*® device is the latest example of how Glaukos is disrupting the traditional glaucoma management paradigm and revolutionizing treatment in this field – but it won't be the last. The company has a suite of other products and indications in the pipeline (over 20 company-sponsored clinical trials in progress), and has ambitious plans for the new iDose™ device (a forthcoming product for continuous intra-ocular elution of medication over extended periods). In the meantime, surgeons caring for the extensive group of patients likely to benefit from the iStent® (see 'eligible patients'), now have an additional tool in the form of the iStent *inject*®, which allows them to offer patients more therapeutic impact from a single procedure.

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BRINGING AMD OUT OF THE DARK

The MacuLogix AdaptDx diagnostic system illuminates age-related macular degeneration (AMD)

AMD remains the leading cause of adult blindness – a result not only of limited treatment options but also diagnostic failings. Even experienced ophthalmologists miss 25 percent of AMD cases (1), meaning that diagnosis often is made only after irreversible visual acuity loss. Indeed, 78 percent of patients exhibit substantial vision loss at first treatment, and 37 percent are effectively blind in one eye. How can we address the problem?

The obvious solution is to improve our diagnostic capabilities. Identifying AMD in its early stages would allow treatment of AMD before it causes irreversible damage. For example, AREDS2 nutritional supplements can reduce disease progression by 30 percent. This early diagnosis–proactive treatment paradigm is the logic behind MacuLogix' AdaptDx system. AdaptDx is a novel automated dark adaptometer, similar in operation to visual field analyzers used in glaucoma. Without any need for pre-adaptation or dilation, the device induces photobleaching by a brief, non-irritating flash; immediately afterwards, it measures the Rod Intercept (RI) – the time for the eye to adapt from bright light to darkness at a standard threshold stimulus. "RI is 90 percent AMD-specific and sensitive," states Gregory Jackson, PhD (Chief Technology Officer). AdaptDx enables AMD diagnosis at least three years before it becomes apparent in structural exams, which, in turn, allows monitoring and early treatment to delay disease progression and preserve vision.

With FDA clearance, Canadian clearance and CE marking for use in the EU, AdaptDx is now broadly available for clinical use. Ideally, it should be used to screen all patients over age 50, especially those with night vision complaints. Such screening would both uncover the true prevalence and – as more patients are diagnosed at earlier stages – provide motivation to develop better treatments for early and intermediate AMD. As William McPhee (CEO) summarizes: "Our goal is to eliminate blindness caused by AMD by changing the trajectory of AMD diagnosis, management and treatment with the AdaptDx."

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DISRUPTING 25 YEARS OF CCC

Precision Pulse Capsulotomy and the birth of a better device

Capsulotomy is the heart of cataract surgery – get it right and the rest follows. For the last 25 years, the standard of care has been continuous curvilinear capsulorhexis (CCC). Though developments in femtosecond laser technology have aimed to replace the manual rhexis procedure, there are cost factors and difficulties associated with the procedure.

Mynosys co-founders David Sretavan and Chris Keller realized that the world did not need another capsulotomy device, it needed a better one – a device that would enhance patient outcomes with premium IOLs. The goal led to their Precision Pulse Capsulotomy concept – and the Zepto Automated Capsulotomy Device was born. The innovative and disruptive device creates anterior capsulotomies precisely on the patient's visual axis: a 360 degree capsulotomy can be created in 4 milliseconds, and the resulting edges are stronger than those created by CCC or femtosecond laser.

One of the key milestones in the company's history was finding the perfect blend of suction, energy pulse and nitinol for the capsule suction tip. With a CE mark, FDA clearance and a successful FDA clinical trial under its belt, what's next for Zepto? Mynosys plan to continue innovating in capsulotomy by developing devices of different sizes and for new uses, such as pediatrics.

This device has a CE Mark and FDA clearance.

STABLER PULSES FOR SAFER SLT

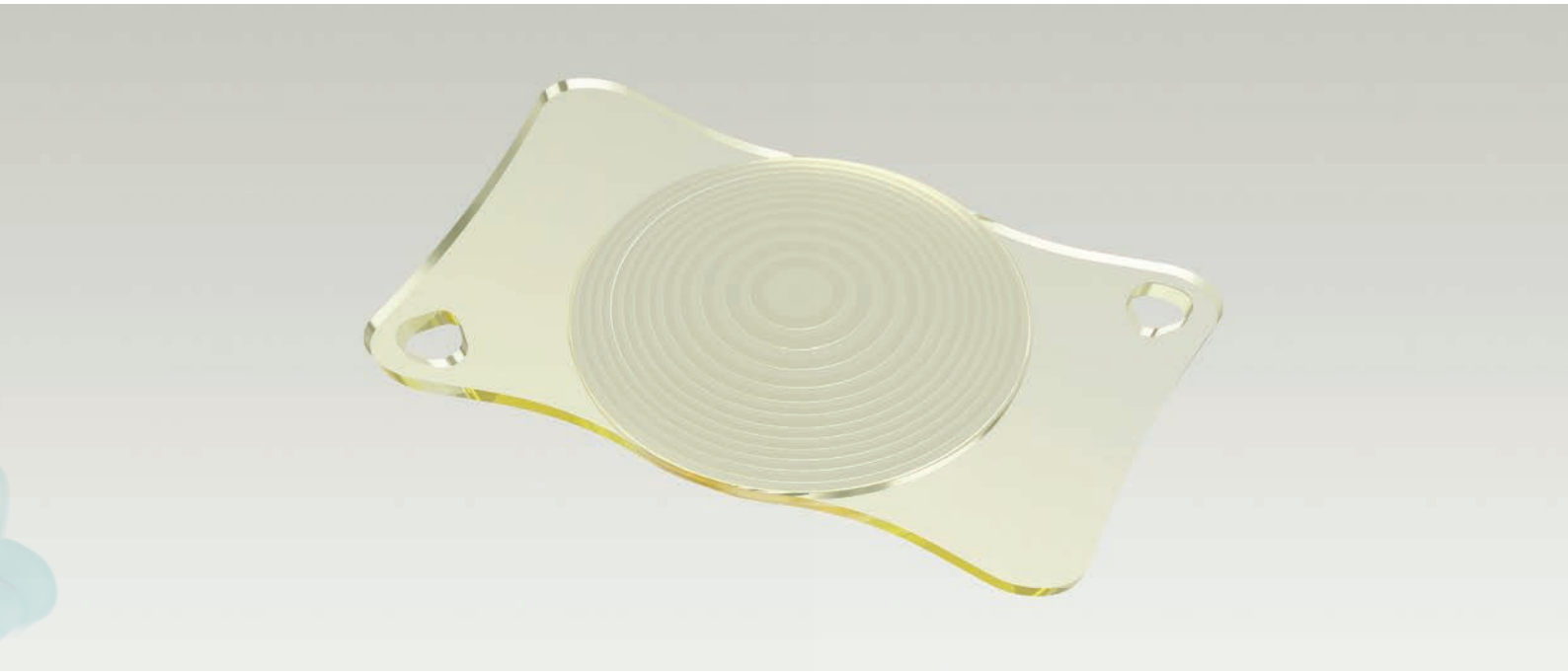
The Optotek OptoSLT nano SLT laser shakes up the selective laser trabeculoplasty market

Selective laser trabeculoplasty (SLT) is a standard option for reducing intraocular pressure in glaucoma patients. But this decades-old technique has been transformed by a device that promises safer and faster procedures: OptoSLT nano, the first diode-pumped solid-state laser for SLT. Why the excitement?

First, the OptoSLT nano provides significantly lower pulse variability (± 2.5%) than existing laser devices. One consequence of this is increased pulse speed (up to 5 Hz); another is enhanced safety. Both follow from the highly repeatable pulse energy delivered during treatment – as Andrej Vrečko (Optotek's R&D Manager) says, "OptoSLT pulse energies are an order of magnitude more stable than competing systems."

Second, the OptoSLT nano is highly convenient: it is small, portable and can be used either as a complete device – with its own lifting mechanism and slit lamp – or can be used to upgrade most Zeiss and Haag Streit-type slit lamps. Adopting the OptoSLT nano does not require disruptive changes to the clinic.

Finally, multiple studies have confirmed the clinical effectiveness of one nanosecond laser SLT. The Optotek device is now CE-approved, so ophthalmologists keen to prevent vision loss in their patients now have a faster, safer and more convenient option. "OptoSLT nano will make SLT the first-choice procedure for primary open angle glaucoma cases," concludes Vrečko.



NEAR, MIDDLE, FAR – AND EVERYTHING IN BETWEEN

Acriva^{UD} Trinova: creating better visual outcomes with a sinusoidal approach to trifocality

Not all multifocal IOLs are equal. A crucial part of the conversation between a patient who wants a multifocal IOL and the surgeon is finding out the patient's ideal near and intermediate distances are – and then the multifocal IOL that would most closely match their preferences is selected. But the point is, vision isn't just about near, intermediate and distance – it's everything in between too.

Let's examine conventional trifocal IOLs that achieve multifocality through multiple diffractive rings with sharp edges. The sharp edges enable diffraction – they abrupt change in the path of light, after all – but they also lead to unwanted light scattering, which patients typically experience as glare and halo. Further, this light dispersion leads to light loss of up to 15 percent, which decreases patients' contrast sensitivity too. Then there's the elephant in the room: these lenses might offer patients near, intermediate and distance vision – but everything's blurred in between.

The answer is VSY Biotechnology's patent-pending Sinusoidal Seamless Vision Technology (SVT). Unlike traditional trifocals, the only SVT trifocal IOL, the Acriva^{UD} Trinova has twelve unique sinusoidal stepless ridges. The smoothly varying surface profiles give rise not only to the highest levels of light transmission to the retina in the market (92 percent), but also optimum light distribution through all optical diameters. The result? Excellent modulation transfer function (MTF) at all distances, even in mesopic conditions, as well as excellent contrast sensitivity, reduced glare and halo, and outstanding dynamic visual performance – After all, the lens provides the widest depth of focus of all the currently available trifocal IOLs thanks to its EDOF feature. Furthermore, SVT also allows the Acriva^{UD} Trinova to compensate for minor post-op refractive errors and slight tilts.

Ophthalmologists absolutely want to eliminate light loss (and the resulting loss in contrast sensitivity), glare, halo, and post-op refractive errors.

The Acriva^{UD} Trinova lens has been commercially available since October 2017 and has been helping patients see better: near, intermediate and far – and everything in between, too.

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Be confident with SPECTRALIS®, a future-proof platform

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HEIDELBERG ENGINEERING

NextGen

Research advances
Experimental treatments
Drug/device pipelines

Treating OSD Then and Now

Combating the modern dry eye epidemic

By Elizabeth Yeu

Even though we now have a greater knowledge of the etiology of ocular surface disease (OSD), as well as better diagnostics and a growing array of therapeutics than ever before, there still seems to be a tendency to try to pigeonhole this disease into one of two specific categories – evaporative dry eye or aqueous-deficient dry eye. We need to stop trying to post these problems into one box or the other. We need to start thinking about the patient. Ask: what symptoms are present? What risk factors are creating or exacerbating the problem? The patient's medical history, medications, habits, profession, diet, and lifestyle will all affect what happens on the ocular surface. Ultimately, it doesn't matter if the patient's particular case of dry eye is evaporative or aqueous-deficient, or if everything in combination is leading to the breakdown of the lacrimal function unit. The stressor leads to dysfunction and imbalance of tear film, which creates inflammation and perpetuates this cycle (Figure 1) – and that's what needs to be addressed. If the stressors can be reduced or eliminated, the cycle can be controlled, and in certain cases, broken.

At a Glance

- *Modern risk factors are creating dry eye in younger patients*
- *Optimizing the ocular surface to eliminate inflammation increases positive outcomes*
- *Nutraceuticals and healthy diet can regenerate the ocular surface naturally*
- *The modern epidemic of dry eye requires proactive care*

Screen burn

The prevalence of OSD is growing at an alarming rate, and it's affecting increasingly younger people. Why? One of the greatest stressors in today's society: screen time. Twenty years ago, this wasn't an issue for the majority of the population – but interacting with a screen (computer monitor, tablet or phone) is near-ubiquitous today. The use of digital devices puts children at great risk of developing OSD (1) – a risk that only increases with age. American teens typically spend an average of nine hours a day consuming digital media (2) in addition to their school and homework that may also require screen time. Screen time reduces blink rate (3,4) – by as much as 60 percent during computer use (5).

Up until a few years ago, everyone thought about dry eye in terms of aqueous-deficient or evaporative without viewing dry eye disease (DED) as part of ocular surface disease (OSD). What it boils down to is: no matter the cause of the dry eye, there must be a balance. Tear film has to have all the necessary components to do its job correctly. It's a supply and demand issue. Patients may not have an autoimmune issue, such as Sjögren's syndrome, but if they are staring at screens all day and not blinking, it does become a big risk factor that can, by itself, lead to debilitating damage to the ocular surface.

With reduced blink rate comes greater meibomian gland congestion and worsening tear film break up times (TBUT), which can lead to meibomian gland disease (MGD). Additional factors like systemic co-morbidities, contact lens use, cosmetics, cosmetic surgery (such as eyeliner tattoos – which destroy meibomian glands), and medications that cause dry eye (like antihistamines) can all cause OSD. Irrespective of the etiology, what this means is that inflammation is introduced into the picture – and starts the OSD ball rolling.

Deeper into dry eye

A greater understanding of inflammation has been pivotal in triggering essential research into the progression of dry eye. Researcher physicians, such as Stephen Pflugfelder, have spent countless years looking at the markers, mediators, and inflammatory cascade elements that exist in acute or chronic stages of dry eye. As a result, we now have a more qualitative, hard evidence-based approach. Even as recently as 2007, the Tear Film and Ocular Surface Society (TFOS)' Dry Eye Workshop (DEWS) report failed to talk about signs alone as being enough to diagnose dry eye. We'd always been taught to give more credence and weight to staining and would dismiss the diagnosis of dry eye if the patient complained but had no staining. Now, we have a greater understanding, particularly in those patients where such a disconnect existed – typically, younger patients that were very symptomatic but didn't stain, or much older patients who stained remarkably, even to the point of epithelial defects, but were completely asymptomatic.

Now, we look at the different components of a more detailed clinical exam that includes more than going straight to the cornea with fluorescein staining. We understand the prevalence of MGD and are more acutely aware of it during exams. We can now test for the presence of inflammation with matrix metalloprotease (MMP-9) with InflammaDry (Quidel Corporation), perform imaging of the meibomian glands, and gather comprehensive information on the patient through the use of the Ocular Surface Disease Index (OSDI) or Standard Patient Evaluation of Eye Dryness (SPEED) questionnaires. Tear osmolarity is my go-to diagnostic for all of my patients because of the information it provides. If the test outcome is positive in the range of moderate to severe OSD, or even possibly in the normal range but the patient displays clear evidence of OSD, I now have objective evidence that points me in a better direction to build a treatment plan.

Treatment paradigms

Compiling patient-specific information is a good way to determine the best and most effective therapies for that patient. Patients with less severe cases can start out slowly, with more home-based remedies, while more advanced cases will need more rigorous therapies right from the start. The educational process should also not be overlooked: patients need to understand what actors are in play, so that they can be proactive in preventing further damage, like being cognizant of their blinking habits and practicing a full blink. It's amazing how little things can make a big difference!

Artificial tears

Previous generations didn't have a great deal of dry eye treatments at their disposal other than perhaps carboxymethylcellulose artificial tears. Artificial tears are palliative and can be a good starting point for patients who want to start with something that is not a prescription medication. Indeed, the artificial tears that we have available today are improved from past formulas, with various active ingredients, such as hyaluronic acid, and a wide range of different viscosities. Preservative-free options keep tears from exacerbating OSD symptoms and we now have customized tears that can treat lipid deficiency. For patients with occasional symptoms, artificial tears may be sufficient. If patients need the artificial tears daily or multiple times a day, then they are not adequately managing their dryness and you will discuss further therapy.

"Compiling patient-specific information is a good way to determine the best and most effective therapies for that patient."

Nutraceuticals

As with artificial tears, past generations didn't have access to scientifically proven nutraceuticals, and they didn't really understand the need for them. We have, more recently, begun to truly understand the etiology behind dry eye and the connection with diet and nutrition. The average American's diet is full of pro-inflammatory molecules that can not only exacerbate systemic conditions in an inflammatory context like cardiovascular disease (6), but also influence conditions, such as dry eye. Who would have thought that a diet overly rich in meat and dairy could make our eyes worse? But what we eat does matter.

I try to push a healthy diet and nutraceuticals from the beginning. The last thing any patient wants is to be on prescriptions for the rest of his or her life. Adding nutraceuticals from the very beginning is an excellent course of action as it will help with any stage of the disease. Patients appreciate using a nutraceutical that truly has an anti-inflammatory effect and aids in not only rebuilding different components of tear film, but also benefits lids and the way the meibomian glands function, as well as the clarity of meibum that is being egressed and produced (7). We are very fortunate today to have more than one anti-inflammatory nutraceutical on the market, particularly advanced omegas like HydroEye (ScienceBased Health), which will improve and regenerate the ocular surface in a more natural way. We're now starting to learn about the right combinations of fatty acids to truly improve MGD, like the omega-3s eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that are commonly found in fish oil, but also gamma-linolenic acid (GLA). While people have been taking omega-3s for some years to improve a variety of conditions (6, 8–11), omega-6 fatty acids were typically thought to be uniformly bad. However, GLA is an anti-inflammatory omega-6 fatty acid that has been shown in studies to be very effective in combating dry eye (12). The problem is that GLA is only found in plants, such as evening primrose, or borage seed oil and blackcurrant seed oil – not foods commonly consumed by humans (at least not in quantities large enough to make a difference). In order to reap the benefits in dry eye, we must turn to nutraceuticals that combine EPA with GLA to suppress pro-inflammatory mediators while stimulating anti-inflammatories (7, 13–16).

Upping the ante

While diet and supplements can be very effective for those with earlier disease and are of benefit to all patients, more advanced technology is now available for when further measures are needed.

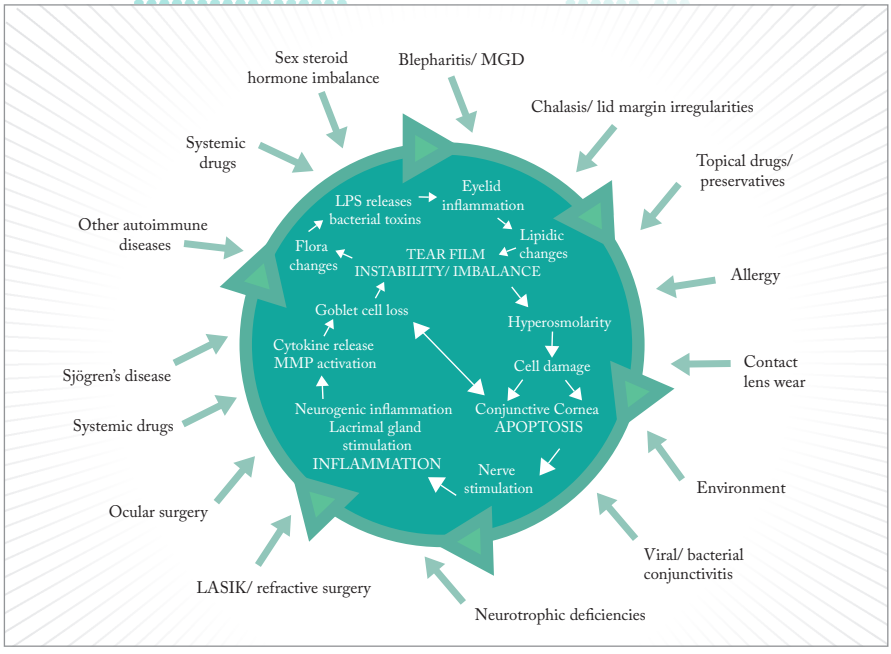

Figure 1. The vicious cycle theory of dry eye disease – one that inflammation is central to the development and continued degradation of the ocular surface.
LASIK, laser-assisted in-situ keratomileusis; LPS, lipopolysaccharide; MGD, meibomian gland disease; MMP, matrix metalloproteinase. Adapted from (20).

Daily warm compresses can be helpful but LipiFlow treatments are more useful from a compliance and quality of life standpoint; a single treatment is much easier and more effective than a daily compress regimen that may not always be followed properly. I will also prescribe other targeted therapies, such as thermal pulsation, as necessary. Another promising new development is neurostimulation with Oculeve TruTear (Allergan), an intranasal neurostimulator that is inserted into the nasal passage to stimulate the trigeminal nerve, which results in tear production. While more testing is needed, it has been shown to be effective in improving ocular comfort and staining scores (17), as well as increasing the mucin layer and aqueous layer of tear film (18–19).

Punctal occlusion is another option, although if the patient has a more meibomian gland-based dry eye (particularly if inflammation is present), then I will not use plugs; keeping an inflamed tear on the eye will only cause more damage. However, once the eye is quiet, punctal occlusion can be beneficial.

In the pipeline

Several companies are now delving into amniotic cytokine treatment processes. In my experience, these treatments have been phenomenal – and I've even seen significant improvement in as short as a month. Treatments are also available for patients with filamentary keratitis exacerbated with blepherospasms. Beginning treatment with Botox injections to control the spasms is of more benefit than starting with anti-inflammatories right away, as those can take six to twelve weeks to show efficacy.

One new therapy in development is Tavilermide (Mimetogen/Allergan) which induces the natural anti-inflammatory protein, mucin – and there are dozens of different topical medications, including different formulations of cyclosporine 0.1% (Sun Pharmaceuticals), other novel anti-inflammatories, and potentially mucin-producing mimetics that enhance the natural tear film, that will continue to expand topical options for patients. There are also unique thermal meibomian gland interventions that are being devised and in clinical trials to support MGD treatments.

Prepping the Ocular Surface for Surgery

When preparing patients for cataract surgery, accurate diagnostics are first and foremost. Topography and meibography are key images. Infrared meibography (Lipiscan, TearScience/JJV) provides me an instantaneous snapshot of the presence of disease, severity level and gives a sense of chronicity of the ocular surface disease process. Not all patients will have gland drop out, but if they do, it alerts me to the patient's higher risk status and allows me to more appropriately prepare the patient. If the patient has dry eye disease with ocular surface staining, we have a discussion on the presence of OSD, and the treatment options – both acute in preparing the ocular surface for cataract surgery, as well as for chronic maintenance. To rapidly stabilize the ocular surface, a short three-week taper of a topical steroid alongside frequent preservative-free artificial lubrications can quickly improve the cornea to facilitate accurate cataract diagnostics. I prefer a preservative-free dexamethasone, or loteprednol ointment, particularly if the patient is on other topical medications (glaucoma agents) or has a known hypersensitivity to preservatives. I also advocate for an oral nutraceutical and blepharitis management, and schedule a return appointment in 3–4 weeks for repeat measurements.

However, if we are looking for a specific outcome of prolonged improved uncorrected visual acuity after surgery, the patient will likely need to commit to using some medication to control the chronic dry eye disease, and this may be with a daily supplement or daily prescription anti-inflammatory drop(s) to maintain his or her quality of vision.

If the dry eye disease is more reticent and mild, I will be more reserved. With mild dry

eye disease, patients will not have staining, but their OSD can certainly worsen post-operatively, thus patient education is important. These are patients for which oral omegas and palliative artificial lubrication can work effectively.

Those with recalcitrant, more severe dry eye whose corneas do not improve with aggressive lubrication and a short course of topical steroids will undoubtedly need greater therapy, management – and handholding. This patient will unlikely be an appropriate candidate for an extended depth-of-focus or multifocal presbyopia-correcting lens. For patients who have central staining and issues with blinking due to co-morbidities, such as Parkinson's, I recommend using PROKERA (Bio-Tissue) sutureless biologic corneal bandage. The cryopreserved amniotic membrane is placed beneath the upper and lower lids and is very effective in advancing corneal healing, reducing inflammation, and optimizing the ocular surface for a variety of indications, including severe dry eye in patients who haven't responded to other treatments. PROKERA is placed for 5–6 days then removed at the follow-up visit. Diagnostic measurements for cataract surgery can be performed within 24–48 after the treatment has been completed.

A call to action

Knowing that modern life's increased risk factors are going to lead to an epidemic of severe dry eye patients earlier in life with recalcitrant disease, we need to be as proactive as possible. Education and the use of nutraceuticals and a healthy diet is always a good place to start and are beneficial for all patients no matter their level of disease. Dry eye can severely affect patients' quality of life, and improper diagnosis and treatment only leads to more quality of life issues and difficult to manage patients. Taking care of patients earlier with better diagnosis and therapy is ultimately to our benefit as well as the patients,' and allows us to continue to protect them into the future.

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Less Energy, More Impact: How the FEMTO LDV Z8 is Reforming Laser Surgery

Highlights from Ziemer Ophthalmic Systems AG's Satellite Symposium, held on October 7, 2017, at the XXXV ESCRS Congress, Lisbon, Portugal.

DALK Demystified

Theo Seiler, MD, PhD, IROC AG, Zurich, Switzerland

Figure 1. OCT-guided DALK with the FEMTO LDV Z8, available at: www.femtoldv.com/dalk.

We all know deep anterior lamellar keratoplasty (DALK) is better than penetrating keratoplasty (PK) for treating keratoconus because you're avoiding the risk of graft rejection. But when you look at certain national registries, you see that only a third of keratoplasties are DALK – and two-thirds are PK. Why?

"The FEMTO LDV Z8 femtosecond laser can improve anyone's DALK technique."

We believe it's because the big bubble technique used to prepare the DALK graft can be very difficult: the challenge is to make it easier for surgeons to perform. OCT-guided DALK with the FEMTO LDV Z8 is my response to that challenge (Figure 1). Briefly, you can use the Z8's intraoperative OCT to precisely control the laser when making side-cuts and lamellar/stroma cuts, removing anterior stroma, and constructing a guide channel which terminates close to Descemet's. Use the channel to direct the cannula so that it ends up next to Descemet's without penetrating it. Then blow air through the cannula to form a bubble, and complete the procedure per the usual DALK protocol. This isn't 'dumbing down DALK' – the procedure remains challenging – but it is a robust way of improving anyone's DALK technique.

No-Touch Femto-Keratoplasty with a Novel Approach

Gerald Schmidinger, MD, Medical University of Vienna, Austria

The Z8 is a versatile tool for corneal surgery. It can be used to make intracorneal pockets for items like corneal inlays or intracorneal ring segments, and also (of course) for PK and lamellar keratoplasty procedures like DALK. But what I'd like to discuss are the advantages of using a femtosecond laser over the manual method that most people still perform to trephine both donor and recipient corneas.

"Surgeons now can – for the first time – perform non-applanated corneal keratoplasty with a femtosecond laser."

The first advantage is that you should not have an undercut – and in any event, even if you do, you will have the same side-cut geometry in both the recipient and donor corneas, so it will fit well. The second: with the Z8, you can adjust the incision site after docking. The femtosecond laser approach also avoids the risk of tilting the trephine during the laser treatment – something that we know increases postoperative astigmatism greatly. There's another advantage: when you use a femtosecond laser, you have better endothelial cells on the periphery of the donor button (1,2), as well as more accurate cut depth. But until now, there seemed to be no difference in visual outcomes between manual and femtosecond laser approaches. Why? It's probably due to astigmatism – postoperatively, it's more or less the same with both approaches. And this is likely a consequence of applanation – we know that in thin corneas or corneas with very high K readings, applanation leads to distortion which in turn can lead to ovalized cuts of the recipient corneas,

Figure 2. Liquid penetrating keratoplasty with the FEMTO LDV Z8, available at: www.femtoldv.com/liquidpkp.

especially in patients with keratoconus. What we need is an applanation-free femtosecond laser trephination for both donor and recipient. And that's exactly what Ziemer has been working to provide with the Z8 (Figure 2).

The Z8 incorporates a BSS-filled artificial anterior chamber for the donor and new software for OCT-guided trephination. In our experience, this 'no-touch' femtosecond-laser trephination in PK provides donor and recipient cuts which are perfectly matching

and completely free of bridges. To perform this super-accurate excision, the OCT scans in a completely different manner to what you've seen before: it scans in eight meridians and automatically segments the borders of the cornea and adjusts the depth of the cut – and produces a perfectly round cut. We took this back to the lab to look at Descemet's folds and the stress on corneal transplants, with and without applanation. We saw that the stress on the donor buttons was significantly less with the liquid interface – and the side cuts were also more reproducible.

What does this mean? Surgeons now can perform non-applanated, femtosecond laser corneal transplantation. The Z8 liquid interface reduces stress on donor buttons, with significantly less Descemet's folds, and provides cut geometries that are more exactly matching.

Low Energy Femtolaser Cataract Surgery: Real-Life Stories

Bojan Pajic, MD, PhD, ORASIS AG, Reinach, Switzerland

One of the misconceptions about femtosecond laser system use in cataract surgery is that it will slow patient workflow. My response is: not if you're doing it right. We have used the Z8 for over three years and we have found it to offer benefits including (3): less phaco time; repeatable outcomes; and better visual acuity on post-operative day 1. Furthermore, the Z8's OCT imaging system permits customized treatment, which is a huge advantage. But what about workflow?

When we started, FLACS procedures with the Z8 did take significantly longer than manual cataract surgery – but we eliminated that difference by making simple changes to our workflow. First, the nurse prepares the laser for the next patient while the surgeon concludes the current procedure; this alone reduced the time for preparing the laser from 3.2 minutes to ~2.1 minutes (a ~30 percent reduction). Second, we get the next patient in the operating room within 30 to 50 seconds of the previous patient leaving. Our current Z8 FLACS turnaround time is in the region of 7–8 minutes per patient, which translates to five to six procedures per hour. So the Z8 gives you all of the advantages of FLACS, like optimal capsulotomy placement and improved OCT-based surgical planning with no added time.

Energy is Key

Jod Mehta, MD, Head of the Corneal and External Eye Disease Service of the Singapore National Eye Center

The Z8 contains a number of superb technical innovations: a liquid-optic interface, nanojoule energy, high-frequency pulses and the option of both vertical firing (for lens fragmentation) and rotational firing (for capsulotomies). But do these features give patients better outcomes?

Let's start with capsulotomy strength. Many studies have shown equivalent results to manual capsulorhexis – but most have been performed in pig eyes, some with the lens in, some with the lens out, and there's been great variation between the femtosecond laser platforms used to create the capsulotomy.

We compared Z8 capsulotomies with manual capsulorhexes in porcine and human eyes (4). Interestingly, we found that the rhexis got stronger with increasing capsulotomy size – a 5.5 mm rhexis is stronger than a 5 mm rhexis. Furthermore, compared to the Victus and Catalys systems, the Z8's rotational firing created a very smooth edge, similar to manual capsulorhexes. The vertical firing patterns of high energy lasers, however, score the tissue; this may cause tags, capsular tears, and capsular distortion following IOL implantation. But pig eyes are obviously different to human eyes – and their capsular bag is very elastic, almost like pediatric eyes. Further, the stretch ratio is better in human than pig eyes, which is important when you're looking at capsulotomy strength. But what's interesting is the scanning electron microscope comparison of the cuts made with the Z8 and other femtosecond lasers: the nanojoule pulse Z8-cut surface is smooth, like a manual rhexis, whereas higher energy lasers like the Victus and Catalys cause ridges (Figure 3).We believe this is why some people experience tags with the latter systems that can lead to runaway anterior capsular ruptures.

"With the Z8, cell death rates were basically the same irrespective of whether 90 or 150 percent energy was used, completely different from other femtosecond laser systems."

But what about eyes with thicker corneas – like those that have undergone a prior DALK procedure? To understand the principles of lasering in eyes with thick corneas, we went back to study pig eyes with corneas in the range of 650–1,000 µm and pushed the laser to the limits. Regular laser energy use (90 percent) sometimes resulted in nice capsulotomies, but often didn't – sometimes you saw some very odd laser patterns due to the dispersion

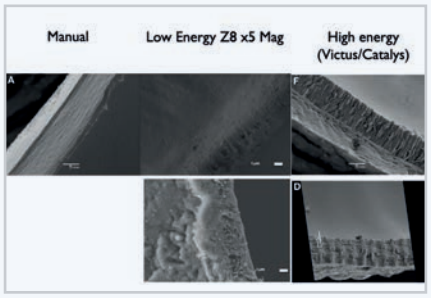

Figure 3. Effect of different laser systems on capsule edge morphology.

of the laser energy through the thickened cornea. When we increased the energy from 90 to 130 or even 150 percent, even with corneal thicknesses of 1,000 µm, we got a perfect capsulotomy every time. But this could raise a potential problem. We know in other laser systems (LenSx and LensAR) that increased energy weakens the capsulotomy, and may even melt the edge! Hence we wanted to study the effect of higher nJ on the lens capsule. We found that with the Z8's nanojoule laser system, the capsulotomy stretch ratios remained the same, irrespective of whether the laser was used at 90, 130 or 150 percentage energy. If we looked at the standard deviation of the stretch ratios, we found there was a much tighter spread with 150 percent energy than with 90 percent. In other words, the Z8's capsulotomy was still strong, even with 150 percent energy and a corneal thickness of 1,000 µm. When we took these settings to patients, we saw the same story, and on removing the capsules and performing a cell death assay in the lab, we found that cell death rates were basically the same, irrespective of whether 90 or 150 percent energy was used – which is a completely different story to that found with other high pulse energy femtosecond laser systems (5).

Lower Energy, Less Stress

Rupert Menapace, MD, University of Vienna Medical School and Vienna General Hospital, Austria

We know that FLACS with other higher energy femtosecond lasers can result in elevated levels of prostaglandins and inflammatory cytokines, a rise in anterior chamber temperature of up to 5°C and a reduction in pH – and these can lead to CME, ocular hypertension and intraoperative miosis (6,7). However, the Z8 employs unique aperture geometry to emit pulses of low energy (nanojoule) and high frequency (in the megahertz range); it delivers only 1.5 percent of the energy per pulse of other manufacturers' femtosecond laser platforms, and this favors the creation of smooth cuts that are free of tears or tissue bridges. But is this reduced energy reflected in lower inflammatory mediator production during cataract pretreatment?

We performed a randomized intra-individual comparison study where aqueous humor samples from Z8-treated eyes taken 5 minutes after laser docking were compared with those from manually-treated partner eyes (40 cataract patients). We found no significant difference in the concentrations of the inflammatory mediators interleukin-6 and -1β.

Simplifying Complex Cataract Cases

Boris Malyugin, MD, S. Fyodorov Eye Microsurgery State Institution, Moscow, Russia

It's becoming increasingly apparent that femtosecond lasers – and in particular the Z8 – are extremely useful when it comes to treating complex cataract cases, like shallow anterior chambers, white (but not intumescent) cataracts, brown nuclei, zonular weakness, low endothelial cell counts, and even pediatric cataracts.

Let's look at pediatric surgery. The Z8 allows us to create the main and side port incisions and perform perfectly sized and well-centered capsulotomies of children's eyes all in a single environment, without ever needing to move the patient. Indeed, a great advantage of the Z8 workflow is that the surgeon is the center of the procedure, and we no longer need to move the patient to the laser. In one case, I found the Z8 to be of great assistance in creating a smooth capsulotomy in a child with a traumatic cataract who had vitreous strands in the anterior chamber. The Z8's OCT imaging system permitted visualization of critical features, enabling capsulotomy even though vitreous was in the anterior chamber.

"A great advantage of the Z8 workflow is that the surgeon is the centre of the procedure, and we no longer need to move the patient to the laser."

Further, the Z8 helps in providing more reproducible posterior capsulotomies, which is specifically useful in pediatric cases when the PCO rates are close to 100 percent. Laser posterior capsulotomy may help to facilitate a bag-in-the-lens approach.

In cases of zonular weakness, the Z8 allows the creation of capsulotomies without stressing the zonules. The Z8's OCT facility is extremely helpful in dealing with cases of ectopic lenses – the surgeon can assess and adjust the

parameters of the femtosecond laser to deal with tilted (or non-tilted) ectopic lenses to produce a superb capsulotomy (Figure 4). The Z8's OCT is also extremely useful when dealing with patients with peripheral corneal scars such as in post-radial keratotomy eyes. The laser may be blocked by the scar tissue, but it can create a perfect partial capsulotomy (aimed with the OCT), such that the surgeon can follow the contour of the cut and easily complete the procedure with forceps. Finally, the Z8 can be useful in bi-lensectomies: it not only creates the capsulotomy but also can be used to chop the phakic intraocular lens so that it can be removed without extending the incision.

So even if the advantages of FLACS over conventional cataract surgery are still being debated, I believe that the Z8 can have a very broad impact in a variety of complex cataract cases.

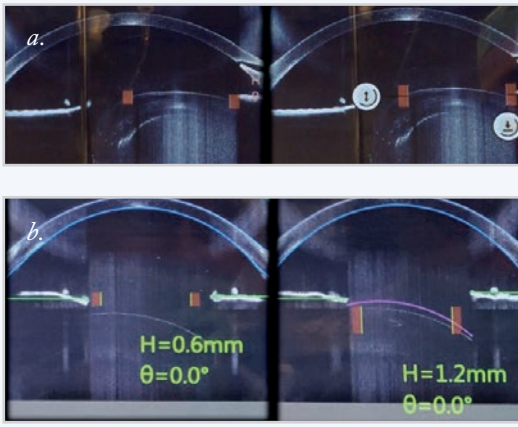

Figure 4. FEMTO LDV Z8 OCT allows prediction of the exact position of anterior capsulotomy in the non-tilted (a) and tilted (b) ectopic lens.

Can LASIK Safety be Improved?

Theo G. Seiler, MD, Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, USA; Universitätsklinik für Augenheilkunde, Inselspital, Bern, Switzerland, IROC AG, Zurich, Switzerland

Can we improve the safety of LASIK? Well, we did a study to find out more.

We used the FEMTO LDV Z6 to create LASIK flaps in rabbit eyes; then we applied riboflavin, reattached the flap to the stromal bed, and performed UV-A irradiation to cross-link. When we do this clinically, we noticed that in some cases re-lifting the LASIK flap is almost impossible.

We performed adhesion measurements on the rabbit cross-linked flap (it's essentially a shear experiment, where we shear the flap against the stromal bed). We optimized the procedure in terms of riboflavin concentration and irradiance exposure, and were able to achieve a bonding of the flap to the stroma that was two times stronger than riboflavin-only (or LASIK flap only) controls.

We then asked what the effect was over time: at three months of follow-up, we attempted the shear experiments again. It was impossible to shear the flap; the flap was stuck to the stroma so strongly that we ended up having to suture the flap on one side, and the stromal bed on the other, then pull them apart (Figure 5a) – the cohesion, instead of being two times stronger than control flaps, was now three times stronger! If you're using LASIK with CXL clinically, be aware that this combination of techniques will mean that patients have slower visual rehabilitation and that you might also induce early post-operative complications like erosions or diffuse lamellar keratitis. Nevertheless, we can conclude that the combination of LASIK and CXL seals the interface between the flap and stromal bed, and looks like it should decrease the risk of central (but not peripheral) iatrogenic corneal ectasias – and improve the safety of an already extremely safe technique even further.

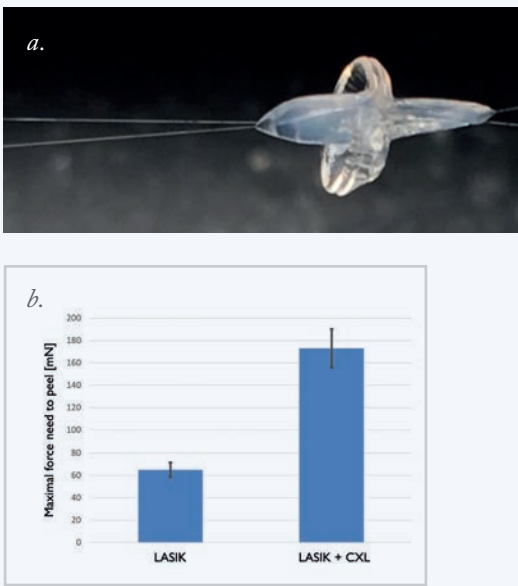

Figure 5. Three months after cross-linking the LASIK flap: a. Shear testing was impossible; peeling had to be performed; b. CXL triples the adhesion of the LASIK flap to the stromal bed.

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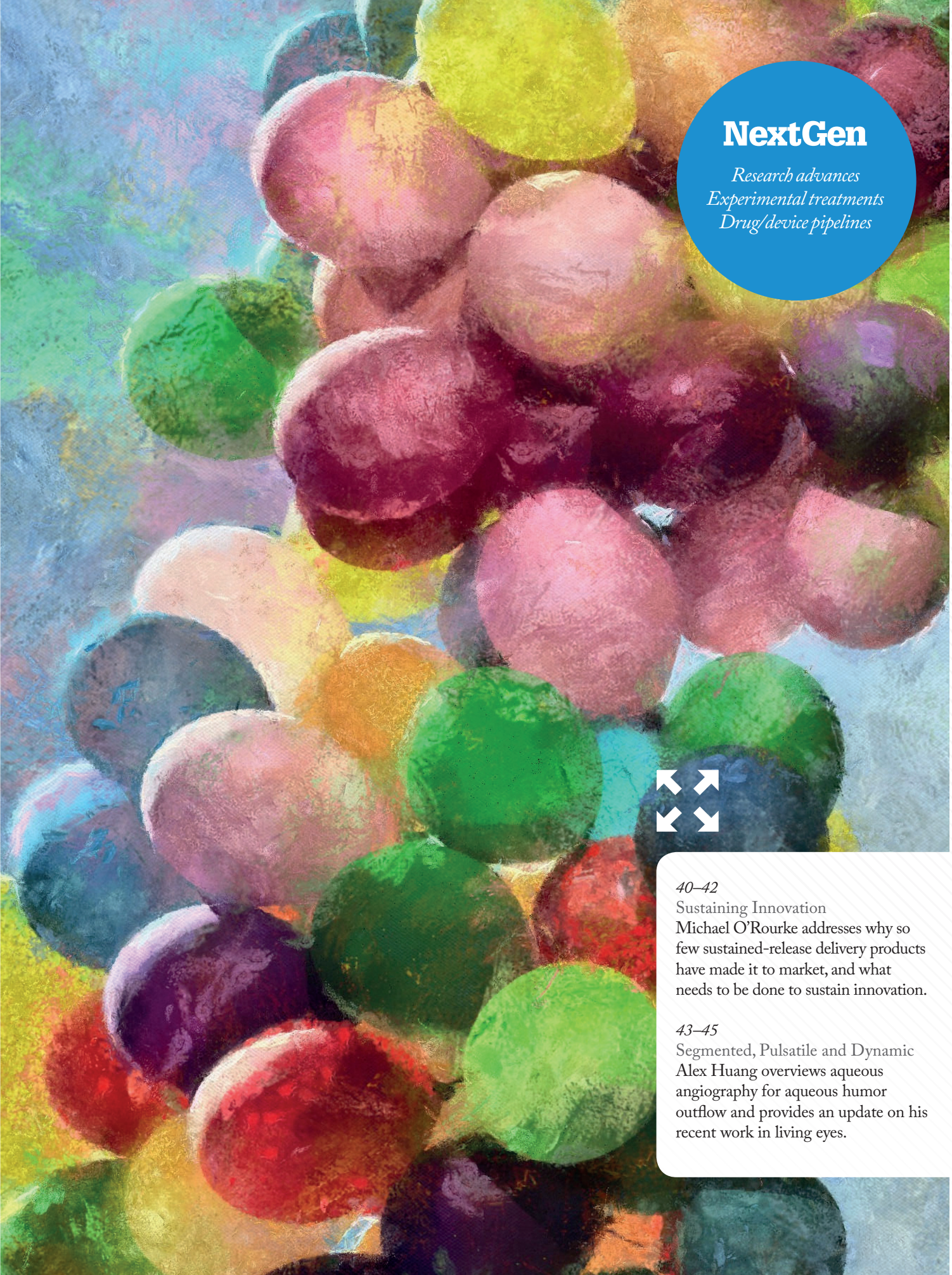
 *Interim 75-eye 24-Month Case Series, data unpublished (Mark J. Gallardo, MD). Data on file. Ellex Medical.



NextGen

Research advances
Experimental treatments
Drug/device pipelines

Sustaining Innovation

The development of sustained-release ocular drug delivery technologies over time, and how innovators should proceed in the future…

By Michael O'Rourke

Currently, more than 10 million people in the United States are affected by the four major posterior segment diseases that cause blindness – age-related macular degeneration (AMD), diabetic retinopathy (DR), diabetic macular edema (DME) and glaucoma (1) – and their incidence is only set to increase as the population ages. But current therapeutic options for these diseases may, at best, manage the condition through slowing further deterioration or halting disease progression. It's why many are looking for new solutions.

Robust sustained-delivery of drugs is a beneficial option for both patients and physicians; long-term delivery of the drug directly to the back of the eye could enhance treatment compliance for patients who have long-term treatment regimens for these chronic diseases. Furthermore, long-term drug delivery could also help improve eyecare in developing countries, as well as address ethical dilemmas; in many developing countries (including China, India and Russia), practitioners often have one chance to address disease morphology because patients are often lost to follow-up. However, significant barriers exist when it comes to successfully developing and commercializing new sustained-release therapies in ophthalmology. Here, I explore the opportunities and obstacles facing developers of ophthalmic drug-delivery systems.

At a Glance

- *In recent years, there have been major advances in the development of new sustained-release ocular drug-delivery systems*
- *Only a small number have achieved both global regulatory approval and commercial success*
- *Despite the challenges, significant market opportunities remain to enhance existing products or develop new technologies that offer improved treatment options for patients suffering from the major vision-impairing eye diseases*
- *In addition to opportunities, there are also obstacles facing developers of ophthalmic drug delivery systems and devices.*

A short history of sustained release

The first polymeric inserts to release an ophthalmic drug over prolonged periods were used in the late 1800s in the UK, where gelatin inserts released cocaine for the purpose of local ocular anesthesia (2). But since the 1970s, only six sustained-release ophthalmic drug delivery products, four of which are intraocular devices, have been successfully brought to market.

The first FDA-approved, sustained-release ocular product was developed in 1975 by California-based Alza Corporation and its innovative founder Alejandro Zaffaroni, following some brief development work in the Soviet Union on soluble ophthalmic drug inserts in the 1960s. Ocusert was an anterior extraocular system for patients with glaucoma that delivered pilocarpine at a near-constant rate; side effects were minimized as absorption peaks were avoided (3). Although Ocusert was a breakthrough innovation from Alza – who were the world's leader in drug-delivery systems at the time – it was a commercial failure. Patient compliance was poor; it had to be inserted in the inferior fornix by the patient and only lasted seven days. However, much was learned from the failure of Ocusert. It became clear that drug delivery systems shouldn't just focus on drug release rates and pharmacokinetics, but should also consider patient compliance and the level of comfort in the eye, as well as have physician endorsement to prescribe the product and support the patient.

In 1981, Merck, Sharp and Dohme launched Lacrisert, a hydroxypropyl cellulose insert for patients with dry eye (4). Inserted in the lower conjunctiva using an applicator, the rod imbibes water and gels, causing the polymer to dissolve and the gel to erode, releasing the drug. Lacrisert remains on the market today (Bausch + Lomb), but with limited commercial success that I believe may be due in part to difficulty of insertion and potential blurring of vision.

1995 saw the launch of the world's first posterior sustained-release intraocular delivery system, Vitrasert, resulting from a collaboration between Chiron Vision and Controlled Delivery Systems (CDS). Each Vitrasert implant contained a ganciclovir tablet coated with polyvinyl alcohol (PVA) and ethylene vinyl acetate (EVA) polymers, which facilitated diffusion of the drug (5). Indicated for cytomegalovirus (CMV) retinitis at the height of the HIV disease epidemic, Vitrasert delivered ganciclovir for approximately 6–8 months. It had initial resounding success in the USA and Europe; however, sales declined after 1998 because there were fewer cases of CMV retinitis (the first protease inhibitor – Fortovase – had become available and offered a greater degree of prevention against declining CD4 cell counts in HIV patients). Vitrasert subsequently exited the market in 2014.

The world's second intraocular posterior delivery product, Retisert, became available in 2005. Another CDS technology launched by Bausch + Lomb, Retisert has an orphan indication of non-infectious posterior uveitis (NIPU), and delivers

fluocinolone acetonide over a period of about 30 months (6). Retisert was also studied for neovascular AMD and DR, but clinical trials failed to meet their endpoints.

The third intraocular sustained-release product was Ozurdex, a dexamethasone intravitreal implant launched by Allergan in 2009, which is used for the treatment of adults with macular edema after branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), noninfectious uveitis and DME (7). An anterior version of Ozurdex, Surodex was also developed by Oculex Pharmaceuticals (who were acquired by Allergan in 2003). Like Ozurdex, it was a bioerodible dexamethasone implant that delivered steroid at a continuous level for 7–10 days. Although intraocular placement of two Surodex implants was demonstrated to be safe and effective in reducing intraocular inflammation after cataract surgery, and superior to eye drops in reducing inflammatory symptoms, Surodex never completed its clinical trials (8,9). The concept of anterior drug-delivery was however widely accepted as a potential breakthrough and remains so today.

The fourth intraocular sustained release product to hit the market was Iluvien – an intravitreal fluocinolone acetonide implant in an applicator from Alimera Sciences that delivers sub-microgram levels of drug up to 36 months after implantation (10). Iluvien gained European approval in 2012 and USA approval in 2014 for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP; it is now approved in 17 European counties, with further approvals and reimbursement expansion expected.

"Since the 1970s, only six sustained-release ophthalmic drug delivery products have been successfully brought to market."

Attribute	*Rationale*
4–12 month delivery*	Obviates frequent office visits
No adverse or minimal side effects	Avoids causing glaucoma and/or cataract
Ability to vary dosage (change of posology)	Customized dosing for patients; perhaps complete withdrawal of a drug if needed
Minimal intraocular debris	Debris from drug delivery can lead to inflammation and floaters
Clearly developed and executed dose-ranging studies	Appropriate dose is identified in Phase II or Phase II/III studies to reduce risk of extended regulatory delays
High patient compliance	Better patient outcomes will trump less compliant regimens
Demonstrated safety and efficacy	Minimum requirement
Cost-effective manufacturing	Manufacturers require acceptable gross margins to participate in this space
Continuous, controlled long-term delivery of small- or large-molecule therapies	Zero order kinetics/steady state delivery (in most cases) will meet patient/physician need for an improved treatment paradigm
Good understanding of the strategic marketing landscape, regulatory and clinical challenges	Plan for long-term development with a competitive product; think outside the box

Table 1: Desirable drug delivery technology attributes
*Many acute and subacute conditions may not even require four months. Two months may be a starting point when the potential for side effects is minimal.

Barriers, challenges and the Holy Grail

But why have so few sustained delivery devices made it to market? It is primarily because the pathway for developing a new therapeutic is complex, expensive and risky. About 50 percent of new systemic drugs fail because of issues with safety, toxicity and pharmacokinetics (11–13). With only four approved posterior-segment sustained release products by year end 2016, it is clear that there are challenges to the successful development of drug delivery devices. In 2009, a major drug delivery forum identified the following as key barriers to new effective sustained-release treatments and drug delivery technologies (DDTs: 14):

1. Developing an effective product
2. Identifying and implementing the best delivery method
3. Using the appropriate animal model for drug safety and efficacy
4. Identifying an adequate patient sample and developing a clinical trial treatment design or plan to attain a satisfactory endpoint
5. Locating a company to finance the product and guide it into the commercial market.

Despite the challenges facing development, there exists a multi-billion dollar market for new and innovative ocular sustained-release

Examples of DDTs currently under development

- Refillable drug reservoirs.
- Cell-based programs, including stem cells for neovascular AMD and other blinding diseases.
- Photo crosslinking technology with UV light for both small and large molecules.
- Microparticle and nanoparticle systems for neovascular AMD, glaucoma, including neuroprotection and potentially into the anterior segment for dry eye and corneal disease.
- Novel adeno-associated viral variant technology for long-term protein delivery to the eye in DME, neovascular AMD, and other conditions.
- Prostaglandin analog delivery systems for ocular hypertension and open-angle glaucoma.
- Topical semifluorinated alkane delivery, enhancing drug solubility for both posterior and anterior segment applications.
- Proprietary hydrogel technology.
- Suprachoroidal delivery or implants, including injectable suspensions.
- Infrared light-initiated polymer delivery.
- Injectable polymer-based protein delivery systems.
- Topical peptides for neovascular AMD and corneal injuries.
- Contact lens delivery systems.
- Iontophoresis.

products and delivery systems, particularly for the posterior segment. But even though there are significant opportunities – and four currently approved sustained release products for the posterior segment on the market – the Holy Grail has yet to be found. What constitutes the Holy Grail is up for debate, but there are 10 key features that have been identified as being desirable for optimal DDT systems (Table 1; 15).

A sustained-release glaucoma therapy, a slow-release system for geographic atrophy, or any sustained system capable of delivering a biologic for neovascular AMD or DR ideally for 4–6 months at a therapeutic dose, amongst many others, could all be considered strong candidates for this honor. Many new products with potential sustained-release technology are currently in development, ranging from preclinical to Phase III. At the end of 2016, sustained-release development projects in the various disease segments included at least 16 in neovascular AMD and DR/DME, 20 in glaucoma and three in dry eye (16). Some examples of these DDTs are listed in the sidebar (left).

An eye to the future

With increased understandings of diseases and conditions, as well as rapidly evolving technology to deliver agents specifically and effectively to the eye, the next decade promises great strides forwards in therapy for many currently poorly treated or untreatable ocular diseases. However, because of the large number of products in development, new DDTs should ideally be 'disruptive.' They must offer true innovation to both patients and doctors, meet a significant market need, and be clinically feasible and potentially reimbursable.

Michael O'Rourke is the Founder and CEO of Scotia Vision, LLC. He has over 30 years drug delivery experience across ophthalmology, periodontal and pulmonary markets in sales, marketing, product launch, strategy development and global commercialization.

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Segmented, Pulsatile and Dynamic

Aqueous angiography has now been performed in living patients – and holds the promise of truly personalized glaucoma surgery

By Alex Huang

Impaired aqueous humor outflow (AHO) is usually associated with resistance in the trabecular outflow pathways – the trabecular meshwork (TM), Schlemm's canal (SC) and collector channels (CC). So it makes sense (on the face of it) that procedures aiming to bypass or ablate the TM – minimally-invasive glaucoma surgery (MIGS) – are increasingly popular. Big question then: why don't trabecularly-oriented MIGS procedures drop IOP dramatically in every patient? At least part of the problem may be that AHO is not uniform around the limbal circumference. As some segments have better outflow than others, it's almost certain that some are better sites for a MIGS procedure than others.

Clearly, we need a tool that allows detailed visualization of the AHO idiosyncrasies in each individual patient, helping us identify sites of outflow resistance. Such a tool would take the guesswork out of the MIGS game, and might permit truly personalized glaucoma surgery. But what would be the key features of such a tool? The ideal tool would be able to provide real-time, physiologically-relevant and comprehensive information from the patient's eye in situ. In this context, 'comprehensive information' would cover structure and function across all trabecular AHO pathways in their entirety: both linearly (from the anterior chamber [AC] to the episcleral vein) and circumferentially (360° of coverage). But how close are we to this ideal?

Assessing AHO

We've had a tool for the non-invasive structural assessment of AHO architecture in living individuals for some time. Anterior segment OCT (AS-OCT) can image AHO structures; however, the resolution provided by the typical/commercial B scan–B scan distance of ~35 microns) is too coarse to pick up many collector channels, and the number of OCT 'slices' required to collect a full representation of the AHO in a given eye is a challenge. That said, variations on the technique have provided useful insights into AHO biology: phase-based OCT has demonstrated pulsatile AHO flows in live human eyes. Nevertheless, AS-OCT is not equivalent to true functional studies because it doesn't tell us anything about the relationship of structural variations to functional differences in AHO. For example, does an unusually large CC lumen always indicate very active flow versus a cul-de-sac filled with stagnant fluid?

To start, it may be preferable to have a technique that provides true functional assessments of the AHO, which is to say visualization of fluid flow. Previous efforts in this field have included injection of particulate tracers – such as nanoparticles or fluorescent microspheres – into the AC, followed by microscopy of sections of the eye. Of course, this approach is not compatible with live patients. Fortunately, other techniques may permit at least a degree of real-time, functional imaging from intact eyes: episcleral venous waves (described by Ron Fellman, Glaucoma Associates of Texas), canalography (where tracer is introduced into SC) and aqueous angiography (where tracer is introduced into the AC).

Aqueous angiography is the newest functional AHO imaging approach. In our lab, we have developed an ever-refining method that uses indocyanine green (ICG) and/or fluorescein tracers to visualize fluid flow, with images being captured by a Spectralis HRA+OCT (Heidelberg Engineering). It's fair to say that methods development required some out-of-the-box thinking in the early days;

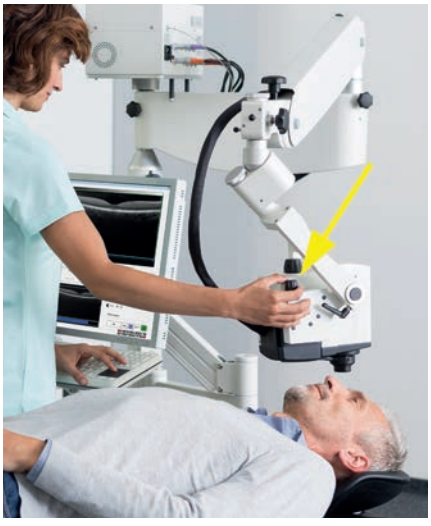

Figure 1: The FLEX module (Heidelberg Engineering) is a fully-functional Spectralis installed upon a surgical boom arm that allows imaging (optical coherence tomography or angiography) in any body position. The micromanipulator substitutes for the standard Spectralis joystick for fine z-axis control.

At a Glance

- *For the first time, aqueous angiography has been applied to living subjects (both humans and non-human primates)*
- *Real-time data from live patients was consistent with previous post-mortem aqueous angiography: outflow is segmentally heterogeneous*
- *Furthermore, live-patient data confirmed a pulsatility to outflow and resulted in the discovery of dynamic features of aqueous outflow – a unique observation*
- *Increasingly, aqueous angiography appears to have the potential to guide surgery to patient-specific regions, thereby enhancing MIGS outcomes.*

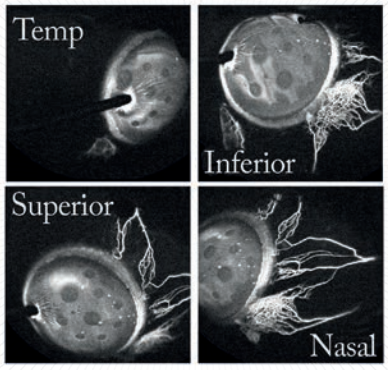

Figure 2: Aqueous angiography show segmental AHO in the intact right eye of a 73-year-old healthy male undergoing cataract surgery. More angiographic outflow is seen nasal compared to temporal (Temp). Superior and inferior are variable.

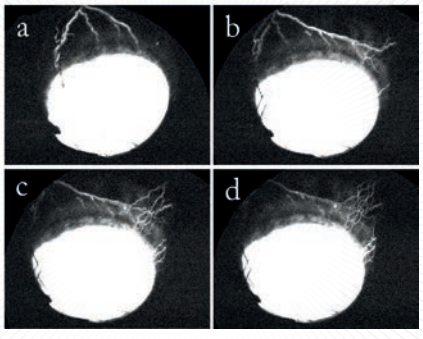

Figure 3: Aqueous angiography shows dynamic AHO. In one NHP eye, over approximately 10 seconds, the post-limbal angiographic signal moves from superior to superior-nasal (A to B to C to D) with disappearance of some angiographic structures simultaneous to appearance of new ones.

for example, our Spectralis HRA+OCT instrument was designed for patients with chins, so it wasn't immediately applicable to the post-mortem pigs and cows we used for our initial studies... The solution? We obtained styrofoam heads from a cosmetics school and placed enucleated eyes into drilled holes. Subsequently, to image in the operating room, the Spectralis FLEX module was developed (Figure 1). These tools allowed us to develop a robust method (See Box, Aqueous angiography method outline), which has yielded encouraging data in a range of settings (post-mortem pig, cow and human eyes; live non-human primates (NHPs); and live humans).

Validating the past, discovering the future

Our initial experiments indicated that aqueous angiography was a valid means of visualizing AHO; in particular, multi-modal imaging confirmed that the angiographic signal corresponded to AHO structures (for example, AS-OCT showed that intrascleral vessel lumens overlapped with angiographically-positive vessels identified by aqueous angiography; and in laboratory experiments, tracers accumulated preferentially in the TM of angiographically-positive regions). Furthermore, segmental variation was seen in all species, confirming that AHO vessel distribution is non-uniform around the circumference. In sum, these data suggested that aqueous angiography could be a useful technique to answer fundamental questions regarding AHO function in diseased and healthy eyes.

The ideal location for trabecular MIGS was one of the first questions we addressed. Should the surgery focus on a low-flow region (because in high-flow regions, the TM may be offering little resistance; therefore, bypassing the TM would be of little benefit); or should the surgeon avoid low-flow areas (because they may be intrinsically poor drainage sites, because of anatomy, for example). Investigating the issue required a two-tracer system to be devised. Briefly, the native state of the eye is first investigated by ICG-based aqueous angiography; subsequently, the effects of trabecular bypass stents are gauged using fluorescein-based aqueous angiography. Using this two-tracer technique, we generated data from post-mortem cow eyes and enucleated human eyes that strongly suggested regions of low flow could be rescued by trabecular bypass surgery (1).

Nevertheless, a definitive answer to the question required data from subjects that would be better models for actual human patients. Aqueous angiography had never before been used in living subjects, and we found that its application in NHPs and humans required yet more inventiveness. An immediate problem was raised by the Spectralis HRA+OCT design – it is intended for upright patients, but in the operating room, patients are supine. To address this, we modified the system by mounting it on a modified surgical boom arm with multi-pivot joints (Spectralis FLEX module).

When we applied our method to NHPs with Ningli Wang's lab at Tongren Hospital, in Beijing, it was the first ever attempt to use aqueous angiography in living subjects (2). Gratifyingly, data generated from living primates confirmed our earlier findings from post-mortem subjects regarding the segmental (circumferentially heterogeneous) nature of AHO. Similarly, findings from live NHPs also confirmed the pulsatile nature of AHO. Interestingly, the pulsatile flow was evident despite the use of a constant pressure system to effect tracer delivery. Other groups, such as Murray Johnstone from University of Washington, have suggested the pulses are of cardiac origin. We did not specifically investigate this, but we noted that the NHP pulsation rates we observed by aqueous angiography were similar to published average NHP heart rates.

Even more excitingly, we can now report similar data from live humans (3) done with Robert Weinreb at University of California, San Diego. Briefly, aqueous angiography images, using ICG tracer, were taken from eight patients during phacoemulsification. Again, segmentally heterogeneous and pulsatile AHO characteristics were observed (Figure 2). More interesting still, however, was our observation – seen both in NHPs and in human patients – of a dynamic aspect of AHO. It was an entirely novel observation, and was manifest both as the growth of active flow in regions that

previously did not have an angiographic signal, and as the diminishment of flow in regions with a strong initial angiographic signal (Figure 3). The mechanism behind these fluctuations remains unclear.

In summary, these studies demonstrate that aqueous angiography is possible in the eyes of living human subjects, that it is compatible with successful and complication-free phacoemulsification, and that there is a hitherto unsuspected dynamic element to AHO.

What's in the AHO pipeline?

The dynamic aspect of AHO deserves further investigation; establishing the biological mechanism behind altered flow in a given area may point to new ways of pharmacologically or surgically modulating outflow. Furthermore, AHO detection in live patients would allow identification of differences between diseased and normal eyes, and may lead to the answer regarding surgical choice by identifying optimal sites for surgery. Potentially, this might not only improve the predictability of trabecular MIGS procedures, but also increase the magnitude of IOP improvement provided by these interventions. One can also envisage surgeons and scientists learning from both canalograms and aqueous angiograms in a given eye. Since the AHO contribution of TM is equivalent to the canalography result minus the aqueous angiography result, a comparison of the two measurements would allow the surgeon to distinguish between resistance contributions of proximal AHO pathways (which is to say, TM) and distal AHO pathways (post-TM). Access to such a comparison may also have implications on clinical decision-making.

However, if aqueous angiography is to take its rightful place in the ophthalmologist's toolkit, further refinement of the method is required. At present, tracer delivery is invasive and in the AC, as opposed to the sulcus where aqueous normally arises; in addition, the use of a lid speculum when imaging live subjects may alter ocular surface pressure, and antimuscarinic dilation drops (used in subjects undergoing cataract surgery) may change TM capacity. These factors could, in theory, contribute to angiographic artifacts and will need to be addressed in future iterations of aqueous angiography.

Nevertheless, we believe the technique will soon be used to compare AHO in normal and glaucomatous eyes (although careful attention will be required to exclude patients with low pressure glaucoma). In the longer-term, we hope that the method will be made less invasive.

For true non-invasive imaging, it will be required to identify a marker present at much higher levels in aqueous humor than in serum, such that AHO can be distinguished from ocular blood flow without the need for an externally administered tracer agent. In this context, it is exciting that vitamin C is present at 100-fold higher concentrations in aqueous humor as compared with serum; unfortunately, its fluorescence characteristics are not compatible with current clinical imaging technologies – but who knows what the future holds?

Aqueous angiography method outline

- Anterior chamber maintainers are used in preference to standard needles, as their grooved ridges result in less sliding and less leakage at the entry point.
- Constant pressure, gravity-driven tracer delivery is effected by means of a reservoir positioned above the eye.
- Pressures are set at 10 mmHg (enucleated eyes) or 20 mmHg (intact eyes of living subjects).
- Spectralis HRA+OCT system is mounted on a modified surgical boom arm with multi-pivot joints to permit multi-positional imaging of supine primate subjects.
- After establishing a dark pre-tracer background, images are captured with the angiographic function, in either fluorescein capture or ICG capture mode.
- For living subjects, a lid speculum is required. Also, note that eyelids block the post-limbal view in living subjects: for non-human primates, use traction sutures to rotate the eye, and for humans, instruct patients to move eyes as necessary.

Alex Huang is Assistant Professor at the Doheny and Stein Eye Institutes, Department of Ophthalmology, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA. Huang is a glaucoma specialist and advanced cataract surgeon who supports all current and minimally invasive glaucoma surgical procedures. Huang carries his interests regarding angle-based approaches and native outflow pathway improvement into the laboratory as a National Institutes of Health-supported clinician-scientist. His lab explores post-trabecular meshwork outflow resistance as well as real-time aqueous outflow imaging technologies for the development of customized glaucoma surgeries. Huang's clinical practice emphasizes a balance of modern surgical techniques with traditional approaches to ensure optimal glaucoma management. In 2017, Huang was voted #1 on The Ophthalmologist Rising Stars Power List.

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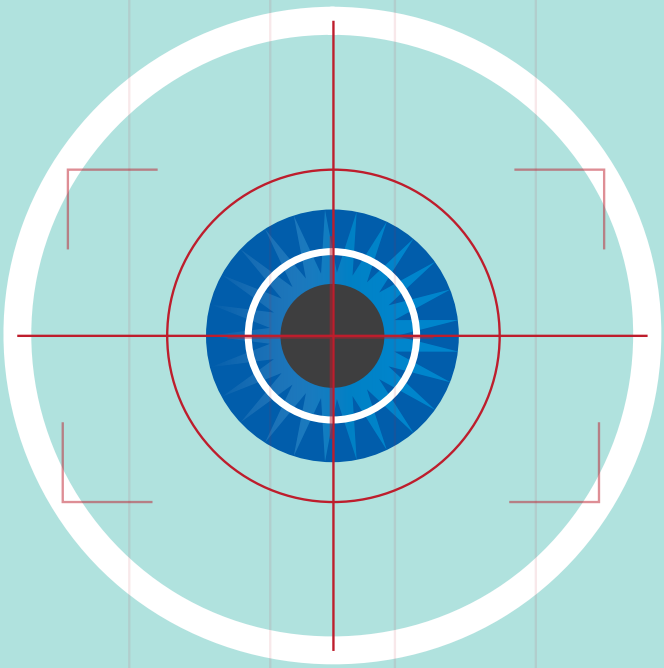

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Recommended Reading for an Optics Refresh

It's difficult to remember all aspects of your training – let alone know how to correctly apply optics principles to the innovative products offered by industry. Have no fear: the Handbook of Visual Optics is here!

By Pablo Artal

Having worked in the field of ophthalmology for many years, it has always struck me as strange that many of my colleagues possess only a poor understanding of the basic principles of optics. And I am afraid that the lack of knowledge extends beyond researchers and technicians to ophthalmologists. All too often, both researchers and clinicians make important mistakes about which they are completely unaware. Now, we have access to a comprehensive reference source that collates all the basic – as well as up-to-date and useful – information in a single work (1). Hopefully, the new resource will greatly reduce the frequency of certain common errors.

At a Glance

- *Many who work in ophthalmology have an imperfect understanding of the basic principles of optics*
- *A lack of optics knowledge can be particularly problematic when introducing new technology, and may lead to sub-optimal clinical decisions*
- *A new resource – the Handbook of Visual Optics – brings together summaries of all key topics, including the most recent research*
- *The two-volume resource aims to be a valuable reference work for clinicians, technicians, scientists and companies working in the field of ophthalmology.*

Forgotten fundamentals

Over the years, I have seen several errors repeatedly being made in the field.

Problem one. Clinicians may report aspects of visual performance, such as contrast sensitivity, without also considering the effect of luminance and patient pupil size in their tests. These two very simple measurements are frequently overlooked – yet the effect of luminance on pupil size can significantly affect test results, especially when measuring near vision in presbyopic eyes. It is unfortunate, then, that many clinicians would not be able to specify the luminance of the charts they use when measuring visual acuity. Furthermore, they usually don't appreciate that the luminance value can change over time – today's value might be only a fraction of that calibrated two years ago. In my experience, poor appreciation of the effects of luminance and pupil size is evident not only in clinical reports but also in research papers – yet it is very simple to check! Similarly, not everybody is comfortable with photometry, but it's important to understand the technology, if you are to accurately measure light levels in your clinic.

Problem two. Another typical oversight occurs in the refractive surgery arena. My impression is that many ophthalmologists have only a superficial understanding of the concept of optical aberrations. Hence, I often see mistakes in this area – even in published papers. For example, an aberration measurement from a patient means nothing on its own, as a given aberration measurement can mean very different things in eyes with 6 mm or 3 mm pupils. Therefore, any aberration measurement should be related to the diameter of the pupil. Failure to do this is a very common source of error.

Problem three. The concepts of scatter and straylight are also poorly understood; people tend to confuse retinal scatter with aberrations and refractive error. I believe that there is significant confusion in this area, particularly regarding measurement methods, and the effect of visual scatter on contrast sensitivity and visual acuity. Though scatter affects contrast sensitivity, it probably affects visual acuity less – something that is not always appreciated.

Problem four. The phenomena of aberrations and refractive error themselves can cause problems for some practitioners. Measurement of refractive error obviously will be affected by aberrations, and this can be confusing when treating presbyopia: for example, when implanting IOLs that increase depth of focus, or when undertaking corneal haze treatments with a small aperture. I often see incorrect figures reported in these circumstances.

> *"I think there is a lack of real understanding of what aberration is and how it is usually reported."*

Problem five. Finally, defining the angles in the eye for refractive surgery is another problematic issue. Clearly, correct procedure in this arena is essential if ophthalmologists are to correctly center corneal interventions, or optimally center IOLs in cataract surgery. In particular, people are often unclear as to the reference points of the different axes:

should one refer to the center of the pupil or to the corneal apex? It can be very confusing, not least because the notation is complicated, and there is no standard nomenclature in the literature.

The good book

Anyone who thought, during training, that ophthalmology would give them an easy life will have been disappointed – but help is now at hand! Putting the Handbook of Visual Optics (Volumes I and II) together required a delicate balance between focusing on the basics and including the very latest research – and I hope we have succeeded. Certainly, I am very pleased with the contents – for example, the first two chapters are authored by a pair of outstanding contributors; in Chapter 1, Gerald Westheimer (University of California, Berkeley, USA) provides a very nice historical perspective on developments in ophthalmology during the twentieth century – he is well into his nineties now, but he is still amazing! And in Chapter 2, David Williams (University of Rochester, New York, USA) gives us his views on the future of physiological optics, which of course is highly relevant to practical ophthalmology. These two chapters are really good reads, and help ensure that the first volume really has something for everyone.

After the introductory chapters, there is a series of 'tutorials' on various topics that are fundamental to ophthalmology, which is why I see ophthalmologists being among the key readers of the handbook. Nevertheless, the information in these chapters – depending on the precise topic – will also benefit those in the research and technical arenas, such as engineers and designers of ophthalmological instruments and devices. Such individuals are technically very capable, but perhaps less familiar with the basics of the visual system in terms of its anatomy and operation. And that's why the Handbook covers not only technological aspects (such as optics, aberrations, photometry, visual stimuli, and basics of optical instruments), but also a good summary of ocular anatomy and embryology, how the visual system works, and visual psychophysical methods. We've included a range of tutorial-type chapters covering the eye as an optical instrument; I believe we address everything of importance with regards to the optical properties of the eye, including the cornea, lens, angles, refractive error, aberrations, customized model, scatter, accommodation, movements, ageing, polarization and more.

Both technology and biophysical aspects are built up logically from the very basics, giving numerous points of access to people with different backgrounds, so I hope the Handbook will be useful to a broad range of readers – not only clinicians, technicians and scientists, but also others in industry. In the latter context, I believe it can help companies better position their products; sometimes the operation of a new product is described as though it were miraculous – but you don't need miracles to explain ophthalmologic devices, you just need to understand the basic principles of optics!

No excuses

I honestly believe that ophthalmologists with a clear understanding of the basic principles will be better able to make important clinical decisions. And I think that it is even more important for clinicians to ensure they have a full and complete understanding of basic principles when they are implementing new technology; for example, premium multifocal IOLs, corneal inlays, or topo-guided LASIK. Unfortunately, I have seen many instances where clinicians attempt to use new technology without a sufficiently clear understanding of the scientific basis for the new device, which is good for neither the patient nor the doctor.

In short, there are no longer any excuses for ophthalmologists to have a poor understanding of the principles behind even the most sophisticated new technology!

Pablo Artal is founder and director of "Laboratorio de Optica" at Universitad de Murcia, Spain. He has published more than 200 reviewed papers that received more than 8000 citations (H-index: 47). He is a fellow of OSA, ARVO, SPIE and EOS. In 2013, he received the prestigious award "Edwin H. Land Medal", in 2014, he was awarded with an Advanced Research grant of the European Research Council and in 2015, he received the "King Jaime I" award in applied research.

Reference

1. *P. Artal, "Handbook of Visual Optics, Vols I and II", CRC Press, April 2017. ISBN 9781482237924.*

Driven by Patient Need

Sitting Down With… Chelvin Sng, Consultant Ophthalmologist, National University Hospital, Singapore

What do you most enjoy about your job?
I enjoy my patient contact the most, because that drives me to look for new treatment options and also to perform more research. I think my patients really drive everything.

What are you researching at the moment?
My research projects are mainly in micro invasive glaucoma surgery (MIGS) and devices. I have a grant funding which has allowed me to initiate the use of MIGS in Asia. The grant funds the cost of these devices for all of my patients, so fortunately they do not have to pay for them; in Asia, the cost of the devices is a major issue. My data have shown that MIGS devices are safe and effective in lowering IOP in Asian patients. However, the post-operative management for subconjunctival MIGS devices (like the duration of steroid use) differs between Asian and Caucasian patients, as Asians have a higher propensity towards scarring.

What can industry do to help support clinician scientists?
I think industry can help by providing funding for some of the research that we do, as well as resources (implants, for example) in surgical studies. It is also important to allow the clinician to design the study and also to publish the data no matter what it shows. Collaborations between the industry and clinicians are crucial in developing new devices which would improve patient care and outcomes.

What led to your career in medicine and ophthalmology?
I've always been inspired by my parents, who are both gynecologists, so that's why I chose medicine. (They also inspired my older brother to become a surgeon!) As to why ophthalmology, it's because I've had a keen interest in the eye ever since I was very young. The eye, despite being a small organ, is so important; it's an extension of the brain and it also reflects a lot of systemic conditions. I find it fascinating! The eye is something that you delve into at great detail without ever getting bored!

How has you career progressed?
I studied medicine at the University of Cambridge in England, but came back to Singapore after graduating for my residency training. I then returned to the UK to complete my fellowship at Moorfields Eye Hospital in London, before ending up back in Singapore where I'm now a consultant in the National University Hospital.

Over that time, I've been very privileged to have wonderful mentors, including Paul Chew at the National University Hospital. I have also worked with Donald Tan, Aung Tin, Jod Mehta and Wong Tien Yin, who have guided me a lot in my research. At Moorfields Eye Hospital, I worked with Keith Barton, Peng Khaw, Nick Strouthidis and Ted Garway-Heath. All these excellent mentors have taught me that I should go where my interests lie, as well as be aware of my strengths and weaknesses so that I can be self-aware when making decisions for my career.

Where do you see yourself in 10 years' time?
Still as a glaucoma surgeon and a glaucoma specialist! But I hope to have developed even better skills in the management of glaucoma, as well as being able to access many more devices and improved methods of drug delivery for my patients.

What advice would you offer to junior ophthalmologists?
I would tell them that they should be very selective in where they choose to invest their energies; their efforts should be directed towards something in which they are not only talented but also interested. Of course, you do initially need to place your eggs in many baskets to find out what most fascinates you, but once you figure that out, you should pursue it vigorously.

You're married to Marcus Ang – what's it like having two rising stars of ophthalmology in the household?!
Marcus has been a great encouragement to me; he's always been very supportive, and I think we're both very fortunate in the sense that we can discuss ophthalmology and gain insight from each other. We have a 14-month old son, so our weekends are for family time; I try to make the most of the weekdays to complete work. Outside of ophthalmology, we go to the cinema and we travel a lot. I really enjoy traveling – I think it opens up your mind. During our year at Moorfields Eye Hospital, we did a lot of traveling around Europe and I think it was one of the best times of my life.

What inspires your philanthropic work?
My philanthropic endeavors have been inspired by Marcus to a great extent. He's very passionate about philanthropy and was recently awarded the President's Award for Philanthropy in Singapore. Marcus is the Director of a non-profit organization, the Global Clinic, and we travel around Asia to less developed countries – such as Myanmar, Cambodia, Indonesia, China, and India – to provide free eye care and perform cataract surgeries. Recently, we've been trying to do more specialty work in these countries as well. I think it's very important to empower local ophthalmologists so that they are better able to help their own population. Because we can't be there all the time, education is a big part of our philanthropic activities; we always partner with local ophthalmologists so that we can teach them how to continue our work within their own communities.

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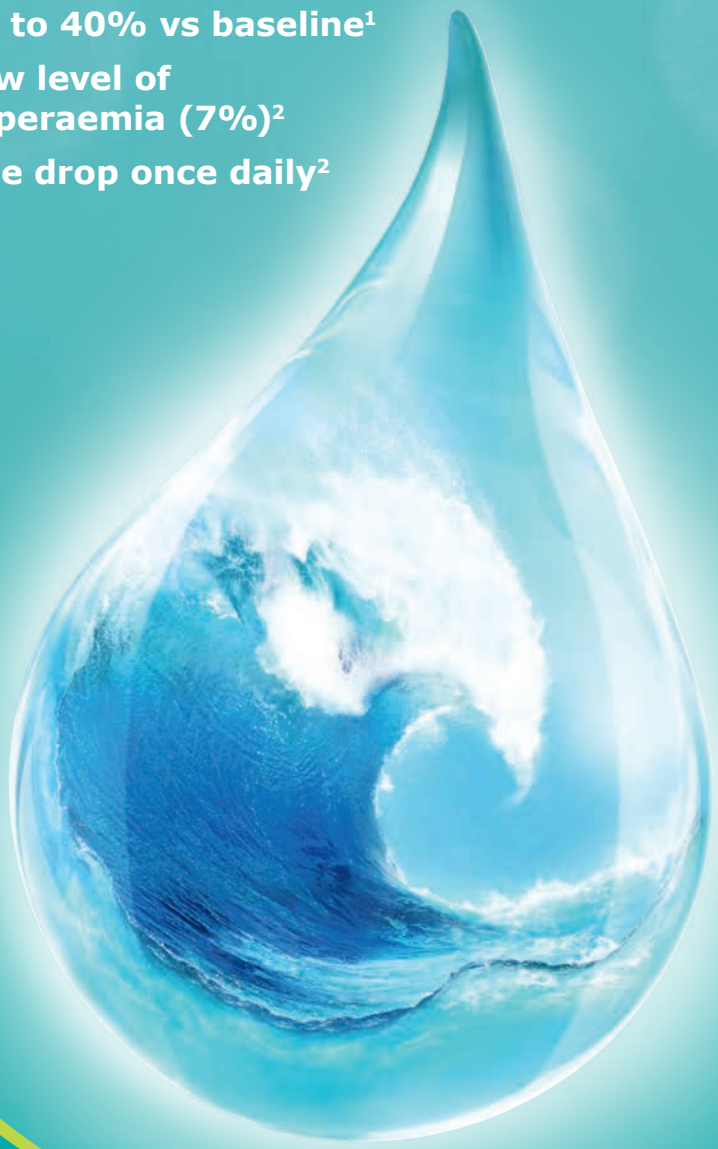

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In renal or hepatic impairment use with caution. To reduce systemic absorption, patients should be advised to use nasolacrimal occlusion or close the eyelids for 2 minutes after instillation. Excess solution should be wiped away to reduce the risk of darkening of eyelid skin. If more than one ophthalmic product is used, fiveminutes should separate their administration. Contact lenses should be removed before instillation. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. Reactive airway disease including bronchial asthma, or a history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, sick sinus syndrome, including sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker. Overt cardiac failure, cardiogenic shock. **Warnings and precautions**: Before initiating treatment, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation related to taflupost. These changes may be permanent, and lead to differences in appearance between the eyes if only one eye is treated. Similar cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-adrenergic blocking agents may occur. The incidence of systemic adverse reactions after topical ophthalmic administration is lower than with systemic administration. Caution should be exercised when prescribing TAPTIQOM® to patients with cardiac or severe peripheral vascular disorders eg Raynaud's disease or syndrome. Use with caution in patients with mild/moderate COPD and in patients subject to spontaneous hypoglycaemia or labile diabetes. 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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Santen UK Limited (Email: medinfo@santen.co.uk or telephone: 0345 075 4863).

References:

1.Holló G et al. Fixed-Dose Combination of Tafluprost and Timolol in the Treatment of Open-Angle Glaucoma and Ocular Hypertension: Comparison with Other Fixed-Combination Products. Adv Ther. 2014; 31: 932-944

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Job code: STN 0918 TAP 00038 Date of preparation: September 2016