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the Ophthalmologist

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How makers of chimeras came to understand corneal growth and repair

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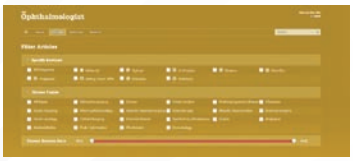

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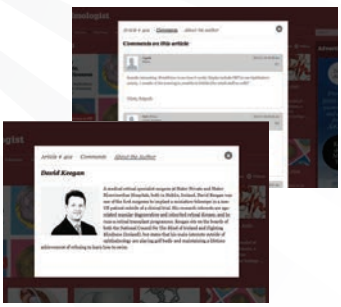

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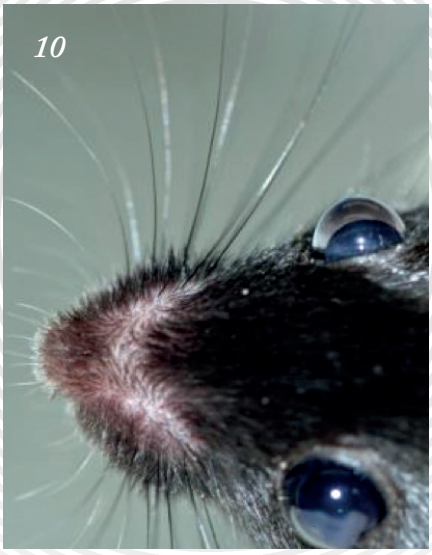
Contents



On The Cover

A stripy and swirly representation of the stripes formed in wild-type/LacZ positive chimeric mice.

Upfront

Feature

In Practice

Next Gen

Profession

Sitting Down With

the Ophthalmologist

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1) Taflotan lowered IOP by 6.9 - 9.7 mmHg in masked, randomized studies 1-4. 1. Uusitalo H et al. Acta Ophthalmol 2010; 88: 12-19 2. Traverso C et al. J Ocul Pharmacol Ther 2010; 26: 97-104 3. Konstas AG et al. Comparison of 24-hour efficacy with Tafluprost compared with Latanoprost in patients with primary open-single glaucoma or ocular hypertension. Abstract 5104/A2458 4. Chabi A et al. Am J Ophthalmol 2012; 153: 1187-1196 **2)** Low risk of hyperaemia among prostaglandins: SPC texts of preservative-free Taflotan.

Santen

September 2014

Equanimity About Equality

Why are most of the speakers at congresses – and the vast majority of industry leaders – men?

Last month, during the ESCRS congress in London, I was invited to an "OWL roost", which consisted of wine, nibbles… and insightful discussions with twelve eminent people from the ophthalmic industry. All were women; this was a meeting of the Ophthalmic Women Leaders group.

Yes, this Editorial is about gender imbalance in ophthalmology. The exhibitors' booths may have had a fairly equal gender balance, but it was a different story on the podiums. Of the main symposia speakers, just under 13 percent were women. That's exactly the same proportion of women present in The Power List that we published earlier this year. Though the remaining 87 percent deserve to be recognized as ophthalmology greats, they're all men. Why? Three things strike me.

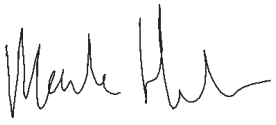
First, the mostly male old professors and CEOs aren't retiring. Fresh opportunities for women to fill these roles will happen – eventually.

Second, there's a deficit of recognition. Tropes about women not speaking up for themselves and hiding from the limelight do have an element of truth – and encouragement and coaching from institutes, organizations, and groups like OWL will help.

Third, family life. Again, the old story is that women are expected – and want – to take a career break to "bring up the kids"; men, typically, aren't. Career breaks occur and can delay or diminish career progression. The reality isn't quite so black and white. Some women do want to spend time with their young families – or to prioritize a better work-life balance – and if that compromises their career, so be it. I also think some – if not many – men would prefer to make the same choices.

It strikes me that gender ratios on the podiums or boards of directors can be thought of as an equilibrium. History, deficits in opportunity and recognition, and childcare expectations have pushed the ratio towards men, but as these are addressed, the equilibrium will shift. It may be that the natural equilibrium will ever be 50:50 – actual gender differences in approaches to things like childcare may play a role – but I do think to get the best possible person to fill a given position, a culture of equal opportunity is needed. I hope that's becoming the case. Time will tell.

Mark Hillen
Editor



John West

John West is a reader at the University of Edinburgh, in Scotland. His principal research interest is understanding how stem cells maintain the corneal epithelium of mice, and he and his research team achieve this through the fusion of wild-type and transgenic mouse embryos in order to create mouse chimeras. John's interests outside of work include hillwalking, real ale, and the occasional bout of waterskiing.

J. Martin Collinson

A professor in the University of Aberdeen's Institute of Medical Sciences, Martin leads a research group with interests in the development and evolution of eyes (including those of the Iberian mole), and the genetic control of axon guidance and epithelial cell migration. Martin serves on the editorial board of *BMC Research Notes*, *The Open Ophthalmology Journal*, and as a keen birder, *British Birds*.

On page 16, John and Martin explain how they came to understand how corneal stem cells act to build and maintain the cornea – by forming stripes.

José Cunha-Vaz

José Cunha-Vaz is emeritus professor of ophthalmology of the University of Coimbra, Portugal and president of the Association for Innovation and Biomedical Research on Light and Image. A pioneer of the characterization of the blood-retinal barrier and its role in retinal disease early in his career, today Cunha-Vaz remains a world leader in diabetic retinopathy research.

Read José's review of the current treatment options for patients with diabetic macular edema on page 26.

Gerd Auffarth

Gerd Auffarth is the director of the David J. Apple International Laboratory of Ocular Pathology and International Vision Correction Research Centre as well as Chairman of the Department of Ophthalmology, Ruprecht-Karls-University of Heidelberg, Germany. Auffarth's research interests include cataract surgery; intraocular lenses; implants; viscoelastic, refractive laser technology and surgery, diagnostic tools, and the cornea.

On page 31, Gerd and his colleague Florian Kretz ask, in terms of IOL design, is better is the enemy of good?

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Upfront

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

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Can we regrow Schlemm's Canal?

Transgenic mouse studies have revealed a signaling pathway that's central to Schlemm's canal formation

Perhaps you wouldn't normally associate lymphangiogenesis with glaucoma – so why, in mice, would the deletion of genes encoding transcription factors involved in the formation of lymphatic vessels and the cardiovasculature, result in a very glaucoma-like phenotype?

A team of researchers from Illinois, Los Angeles, New York, Toronto and Uppsala were using transgenic mouse models in order to understand what role the of angiopoietin/TIE2 signaling pathway had in developing the mouse vasculature. Their model: conditional knockout mice that either have both the genes encoding angiopoetin-1 and -2 (*ANGPT1* and *ANGPT2*) deleted after 16.5 days embryonic gestation – or the gene encoding for their receptor, *TIE2* at postnatal day 0. For their first three weeks of postnatal life, all of these transgenic mice appeared normal – indistinguishable from their wild-type littermates. But then something started to happen to their eyes. The transgenic mice started to develop elevated intraocular pressure (IOP), buphthalmos (Figure 1), and glaucoma-like features, such as retinal ganglion degeneration and vision loss – and their Schlemm's canal was absent.

"Our finding was serendipitous," explains one of the study's authors, Susan Quaggin. "We were studying the angiopoietin-TIE signaling pathway, which is important for normal vascular development, and we expected to find a major effect in blood vessels. However, our studies demonstrated a key role in lymphatic vessels and particularly in the specialized lymphatic-like vessel present in the anterior chamber of the eye – Schlemm's canal." According to Quaggin, the disorder observed in the mice most closely resembled pediatric congenital glaucoma (PCG).

The mouse model could be a new foothold into the causative mechanisms

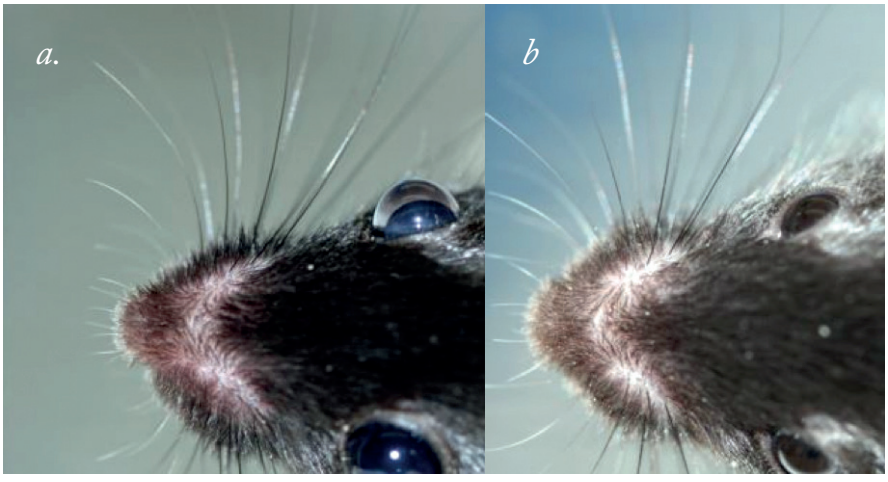

Figure 1. Images of the eyes of 8-week old mice that are (a) conditional dual *ANGPT1/ANGPT2* knockouts, or (b), wild-type controls.

of high IOP in glaucoma by providing the opportunity to develop and test new treatments to improve drainage of aqueous humor and prevent vision loss.

On the basis of their discovery, the researchers are now looking at developing therapies that promote lymphangiogenesis – such as angiopoietin analogs, TIE2 agonists, and even VEGF-C. "Once we identify an active drug, we need to develop a way to enhance its penetration into the anterior chamber of the eye," says Quaggin – which suggests nanoparticle formulations.

Preclinical testing of two candidate molecules is underway, with the objective of promoting the growth of more lymphatic vessels (or enlarging existing ones) to improve drainage in the glaucomatous eye. *RM.*

Reference

1. *B.R. Thomson, S. Heinen, M. Jeansson, et al., "A lymphatic defect causes ocular hypertension and glaucoma in mice", J. Clin. Invest., Epub ahead of print (2014).*

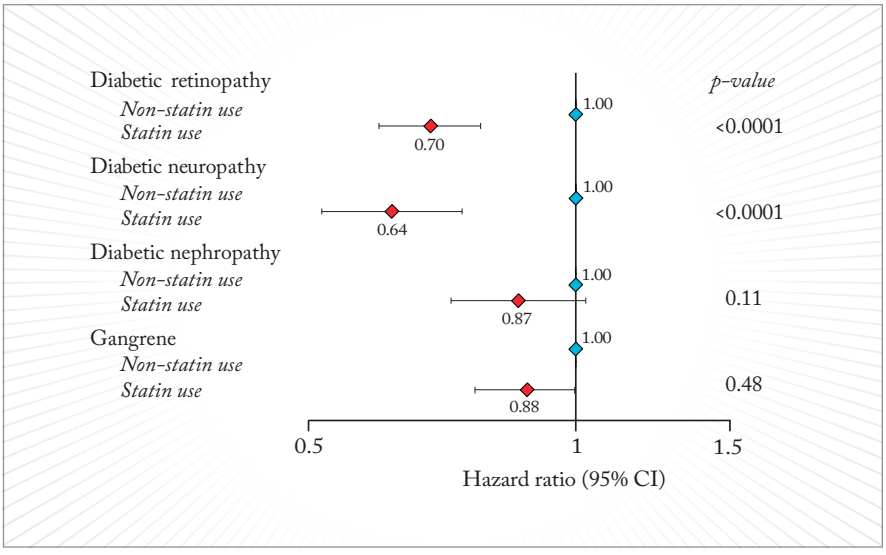

Figure 1. Statin use protected against the development of diabetic retinopathy and diabetic neuropathy.

A Glut of Glucose? Gibberish!

Statins may interfere with glucose metabolism, and their use might be damaging the diabetic eye. Or perhaps not...

In cardiovascular disease, statins are a wonderful class of drugs. Many tens of millions of people receive them, and they prevent hundreds of thousands of vascular adverse events like myocardial infarction, stroke and cardiovascular death each year. A certain patient group – those with diabetes – benefit greatly from them to prevent just these events. But there is some doubt about it all being good news for diabetics. Hypothetically, statins may interfere with glucose metabolism, resulting in elevating levels of a highly reactive, micro- (and macro-) vasculature-damaging aldehyde, known as… glucose. Is there a new dark side to statins? Might they induce microvasculature disease like diabetic retinopathy?

Until recently, nobody was certain. Thanks to a study performed by two Copenhagen-based researchers, Sune Nielsen and Børge Nordestgaard, we're beginning to understand the truth of the situation (1). Denmark has some impressively comprehensive healthcare records, and this enabled the pair to identify all patients in the country who were aged 40 years or older, and who were diagnosed with incident diabetes over the years between 1996 and 2009. At random, they selected 15,679 people who had been statin users until their time of diabetes diagnosis, and matched them in a 1:3 ratio with 47,037 people who hadn't. They then determined the cumulative incidence of diabetic retinopathy, diabetic neuropathy, diabetic nephropathy and gangrene. Median follow-up was 2.7 years, and adjustments were made to account for certain biases between both populations – for example, there was a reason certain people were taking statins, and this made them more likely to visit a physician and obtain earlier diagnoses of diabetes than non-statin users.

So have statins been damaging the retinas of Danish patients with incident diabetes? The answer appears to be no – statin use conferred a highly significant, 30 percent reduction in the risk of diabetic retinopathy (Figure 1), and an even greater 34 percent reduction of diabetic neuropathy in general. Interestingly, there were no significant differences in the incidence of either diabetic nephropathy or gangrene between statin users and non-users. So, based on this evidence, it would appear that statins are likely to be protective against microvascular disease. How or why are yet to be determined. *MH.*

Reference

1. *S.F. Nielsen, B.G. Nordestgaard, "Statin use before diabetes diagnosis and risk of microvascular disease: a nationwide nested matched study", Lancet Diabetes. Endocrinol., Epub ahead of print (2014).*

My Retina, My Rules

Ophthalmologists would change recommendations if treating themselves

When it comes to treating wet age-related macular degeneration (AMD), ophthalmologists are more likely to choose more expensive anti-VGEF agents and less likely to choose treat-and-extend dosing regimens for themselves, compared with what they might prescribe for patients (1).

Researchers based at the Rutgers-Robert Wood Johnson Medical School in New Jersey, performed a survey of 200 retina specialists in the USA. They were split in to two groups – the first was presented with a hypothetical 70-year old patient, the second group was told that they were that patient. The symptoms were wet AMD with 20/100 visual acuity in the left eye, choroidal neovascularization, subretinal fluid, cystoid macular edema, and high-risk drusen in the right eye. Respondents then gave their recommendations on dosing regimen and on which anti-VEGF treatment they would use: aflibercept, bevacizumab, or ranibizumab.

So what choices did they make? When it came to the hypothetical patient, just over half of the specialists recommended using bevacizumab. Those treating themselves had less of a preference for bevacizumab, being split equally across the three drugs – demonstrating a slight, but significant preference for the costlier compounds. Dosing regimen choice differed between the groups too – 73 percent said they would treat and extend in the patient, but only 63 percent would do the same if they were the patient.

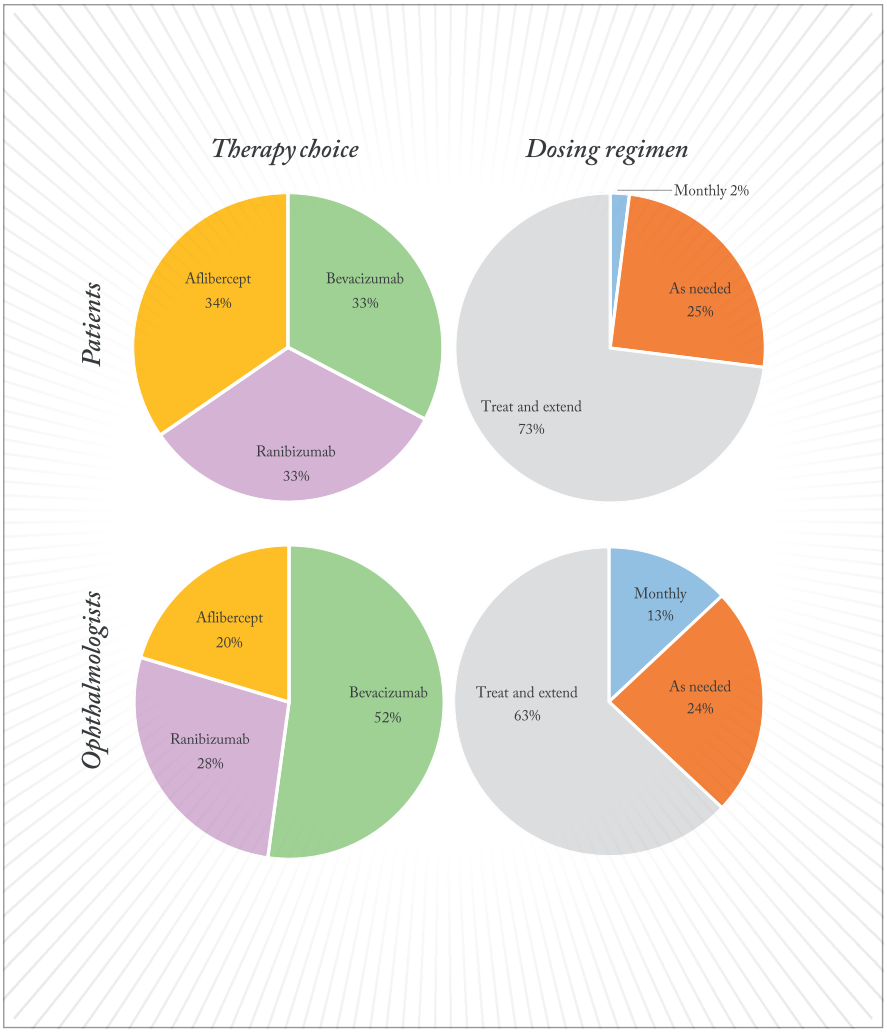

Figure 1. Prescribed therapy and dosing regimen chosen by US-based ophthalmologists for administration to either themselves (if they had wet AMD) or a hypothetical 70-year old patient (with the same symptoms).

It's a small survey (so take the results with a pinch of salt), but the results tell an interesting story: generally, it's cheaper drugs for the patient, with the longest possible intervals (understandable in a country with expensive health insurance and co-pays for premium medications), and more expensive and potentially more effective drugs for the eyecare professionals, that are more likely to be administered to a regimen that minimizes the risk of visual acuity loss (at the cost of more injections).

If you had AMD, would you follow the regimen you recommend to your patients? If not, why not? *RM.*

Reference

1. *K.W. Jeng, J. Wilgucki, S. Halperin, et al., "Retina specialists treating age-related macular degeneration recommend different approaches for patients than they would choose for themselves", Retina, 34, 1796–1801 (2014). doi: 10.1097/IAE.0000000000000182.*

GPs, Don't Fear the Retina (or the Lens, or the Cornea…)

Survey shows UK-based GPs lack confidence in their ability to diagnose ocular disease

A survey by the Royal College of General Practitioners (RCGP) in collaboration with the UK Vision Strategy Programme has uncovered a significant issue – many GPs do not feel confident in their own abilities to spot the early signs of major ocular disease (1).

Two hundred and five GPs completed a web-based survey – and the numbers were revealing (Figure 1). Of the GPs surveyed, just over a third (34.1 percent) were confident in diagnosing age-related macular degeneration, and around half were confident in diagnosing diabetic retinopathy (48.8 percent), glaucoma (51.2 percent) and refractive error (49.3 percent). More happily, 89.8 percent felt comfortable in their ability to spot the early signs and symptoms of cataracts.

Only a quarter of the GPs reported that they had been offering training and guidance to support their partially sighted and blind patients, and fewer than half said that their practice made information – such as booking and appointment information – available in accessible formats.

It's crucial that general practitioners can confidently diagnose ocular disease as early as possible – meaning that timely referral to ophthalmologists occurs, intervention occurs earlier, and patients experience not just better visual outcomes, but also a better quality of life. GP training and education is key to making this happen. *RM.*

Reference

1. *The Royal College of General Practitioners "Clinical priority on eye health: summary analysis of UK data", http://www.vision2020uk.org.uk/ukvisionstrategy/page.asp?section=390&sectionTitle=RCGP+Survey+Report. Accessed October 1, 2014.*

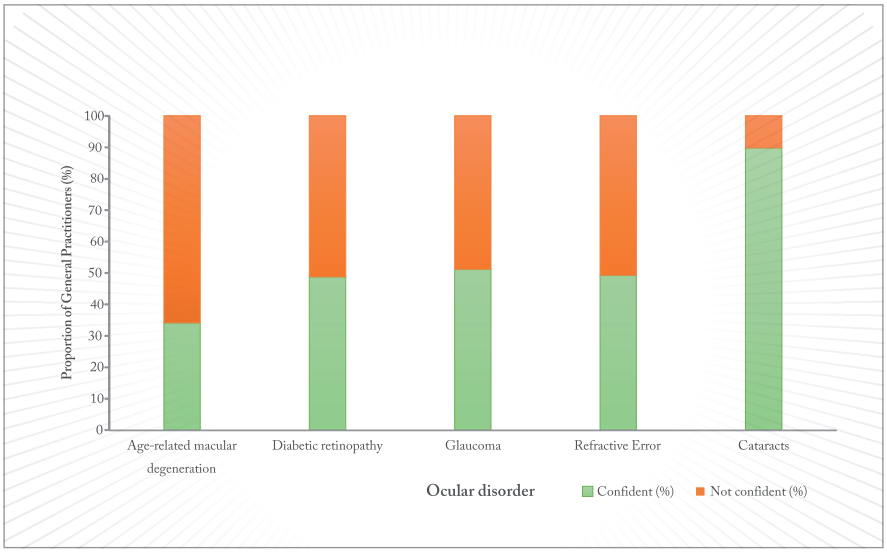

Figure 1. UK-based General Practitioner's confidence in their own ability to diagnose the early signs and symptoms of ocular disease.

This Month in Business

Alimera and Allergan benefit from new FDA approvals, Allergan continues to battle Valeant, and Oculentis sues Lenstec over IOL patent infringement

- The FDA approves Alimera's Iluvien (fluocinolone acetonide intravitreal implant) for the treatment of diabetic macular edema (DME) in patients previously treated with corticosteroids who did not have a significant increase in IOP.
- Allergan's Ozurdex (dexamethasone intravitreal implant) has had its DME indication expanded by the FDA. Formerly approved for the treatment of DME in pseudophakic adult patients or patients who were scheduled for cataract surgery, Ozurdex is now approved for the general patient population being treated for DME.
- Allergan continues to resist Valeant's US$54 billion takeover offer. It was in talks to buy specialist pharmaceutical company, Salix, for US$11 billion, wiping out Allergan's net cash proportion that was so attractive to Valeant, but these talks have ended for now.
- Oculentis is suing Lenstec for infringement of its UK patent for an IOL implant with an enhanced optical blending zone. It is alleged that Lenstec infringed the patent by importing and selling SBL-3 dual-topic IOLs. Oculentis is seeking an injunction against the company, as well as damages and control of the offending products.

The Top 5 Lessons from Ophthalmology Futures 2014

The world's top clinicians and captains of industry came together in London last month to discuss the future of ophthalmology. Here's what we learned

#1. There's no consensus on the best way to invest in innovation

Some, like Ralf Kuschnereit from Carl Zeiss Meditec, believe that you need a balanced research and development portfolio. "Bets" can be small and quick (like improvements to a device) or long-term and big – for something truly disruptive. Calvin Roberts (Bausch + Lomb): "Mid-sized companies need to be agile and clever." He also said, that you should "balance your portfolio by risk, rather than by speed." Murthy Simhambhatla's (Abbott Medical Optics) view was that "Things have changed, now there's no reward for incremental innovation."

#2. Femtosecond lasers are almost certainly the future of cataract surgery

From the surgeon's perspective, Sheraz Daya (Centre for Sight) stated: "Once you go femto for rhexis, you don't go back – as you can lose the feel of the manual rhexis if you're not careful." Julian Stevens (Moorfields) viewed femtosecond lasers as "pretty good", with a great benefit being the ability to do intrastromal incisions. Patients perceive lasers as "good", according to Allan Crandall (Moran Eye Center) and that "US advertising drives patients to clinics with femtosecond lasers."

#3. Reimbursement is the issue that needs to be overcome before femtosecond-laser assisted cataract surgery becomes widespread.

In essence, no play, if insurers won't pay. Matteo Piovella (President of the Italian Ophthalmological Society) explained that "Femto reimbursement is impossible in my country" – politics. Béatrice Cochener (University Hospital, Brest) empathized: the French Ministry of Health trial looks like "it will be hard to demonstrate a robust health-economic benefit of femto-cataract surgery." Soon-Phail Chee (SNEC): put it bluntly: "It's simple – you need to show femto is safer than manual rhexis – and better – before insurers will pay."

#4. Patients age – you're fixing the problem as it is today, not as it will be tomorrow. Manage patients' expectations!

Sheraz Daya: "Current interventions are short-term. But the cornea changes, as do the effect of LRIs. Perhaps we should be thinking of the longer term?" Julian Stevens noted one aspect of presbyopia treatment: "Time passes. People get older. They come back!"

#5. Gene and stem cell therapy are set to transform the outcomes of patients with ophthalmic disease... sooner rather than later.

Majlinda Lako (Newcastle University) looks past the technical aspects: "Growing stem cells – those issues have been overcome. The regulatory hurdles are the next challenge." Interestingly, the biggest advocates of this kind of research aren't necessarily the charities: Sir Peng Khaw (Moorfields) noted that "Patients are often the biggest advocates of getting stem/gene therapy trials funded."

The metrics of success are hard to identify with gene and stem cell therapy – what outcomes should be used? Keith Martin (Cambridge University) explained that the overall impact of the therapy on peoples' lives is what matters. "Many funders now want quality of life measures as efficacy outcomes in their clinical trials of gene and stem cell therapies." Finally, Peng Khaw raised the stakes: "Stem cell regenerative therapy is as disruptive and game-changing as anything Apple or Google do." *MH.*

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The Innovation Awards 2014

Showcasing the greatest ophthalmic advances of the year

Our December issue will showcase the Top 15 greatest innovations of 2014.

Whether transformative technology, game-changing surgical technique, or a benchmark-breaking scientific advance, if the innovation was announced in 2014, it is eligible for the Innovation Award.

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To be considered, please include:

- Name of innovation
- Brief description (~10 words)
- Detailed description (50-150 words)
- The potential impact of the innovation (50-100 words)
- One image (if applicable)

The Ophthalmologist Innovation Awards will be published in the December 2014 issue of The Ophthalmologist, in print, on the iPad app and online.

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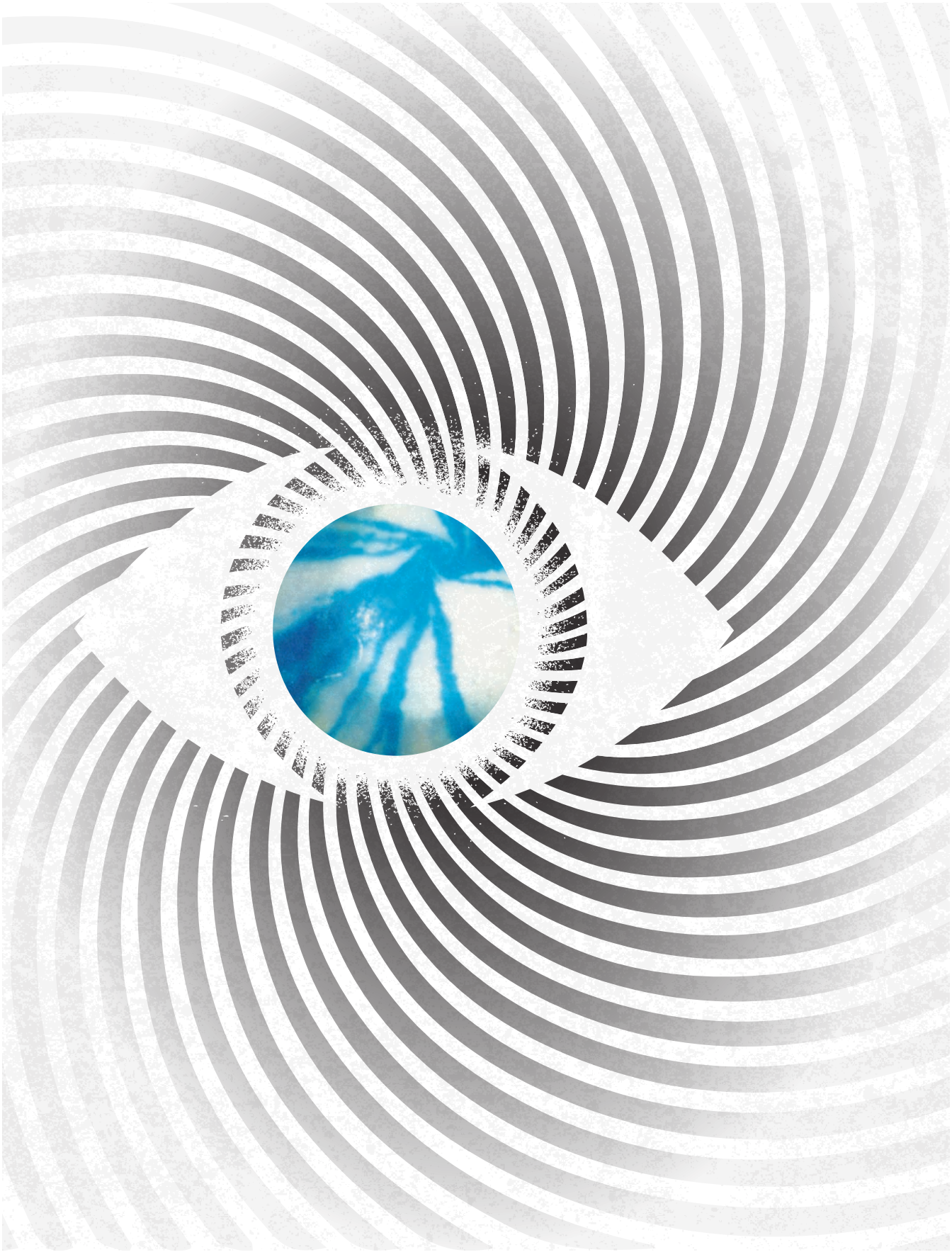

Understanding Corneal Stem Cells Through Stripes

Fusing the embryos of mice, where one contains a marker of its lineage, is a well-established technique in developmental biology research. The stripy corneas were still a surprise, though…

By John West and J. Martin Collinson

At a Glance

- *Despite the fact that hundreds of thousands of corneal interventions are performed each year, our understanding of how the cornea is built and maintained is far from complete.*
- *Mouse chimera studies (where cells from one lineage can be stained blue) revealed mice with stripy corneas!*
- *This suggests that stem cells in the basal layer of the limbal epithelium produce cells that move radially towards the center of the cornea and continue to proliferate as they do so.*
- *A better understanding of corneal cell biology and development will help inform future clinical studies – particularly research involving corneal stem cells.*

With hundreds of thousands of corneal interventions, including transplants, debridements and laser surgery being performed annually, you could be forgiven for thinking that we have a fairly complete understanding of how the ocular surface is maintained and how it responds to injury. It is, in fact, a highly contentious topic that today divides the scientists who work in this area. Given that the integrity of the cornea is essential for vision, resolving the current controversies in the field will impact on clinical practice and could improve the prognosis for those with severe ocular surface injury or disease. Here we describe how we serendipitously stumbled into the world of ocular surface epithelial biology, and what it has meant for our understanding of the roles of corneal stem cells.

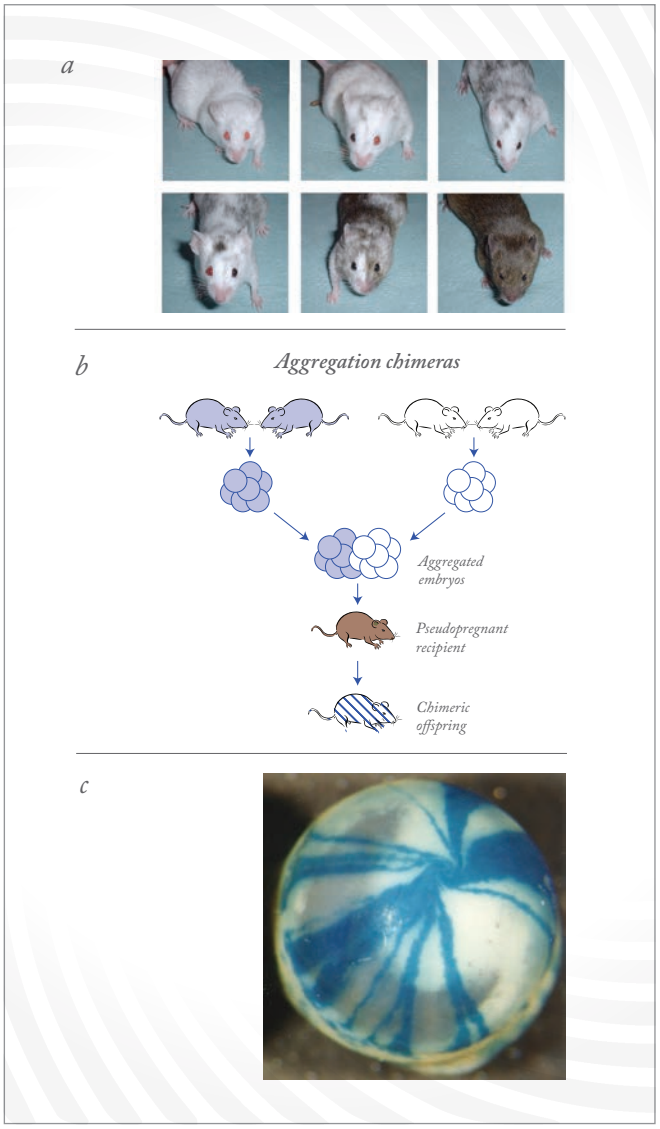

Figure 1. Mouse chimeras and corneal stripes
The top panel (a) shows an albino mouse (top left) and a pigmented mouse (bottom right) plus four mouse chimeras that were produced by combining embryos from albino and pigmented strains. Panel (b) shows the method used for producing such chimeras by aggregating pairs of embryos together at the 8-cell stage. Panel (c) shows an eye from an adult mouse chimera with radial stripes of blue-stained, β-gal-positive corneal epithelial cells and unstained, β-gal-negative corneal epithelial cells that converge at a central spiral.

In the beginning, there were chimeras

Our work on mouse models of corneal maintenance began in 1996. John's research group in the University of Edinburgh was making mouse chimeras. At the time, the group's interest was in reproductive and developmental biology, but even then, eyes were on the agenda as John was collaborating with Bob Hill of the MRC Human Genetics Unit on the other side of the city – studying the role of the *Pax6* gene in mouse eye development. Martin joined the research group to strengthen this part of the work.

Formally, a chimera is a composite organism containing two or more lineages of genetically distinct cells that are derived from different zygotes. It may be easier to think of it as being the opposite of identical twins: whereas one zygote splits to produce two separate identical twins, chimeras are the result of cells from two zygotes coming together to form a single embryo. One way of producing mouse chimeras experimentally is to collect 8-cell stage embryos from two different strains of mice (e.g. pigmented and albino), aggregate them in pairs (one from each strain) and culture them overnight (Figure 1b). By the next morning each pair will have amalgamated into a single chimeric embryo, and groups of these chimeric embryos can be surgically transferred to female mice to complete development. If all goes to plan, chimeric pups are born. Amazingly, these chimeras are normal sized, perfectly formed animals. It would be easy to imagine them being twice the size, or having two heads, but early mammalian embryos exhibit a property of regulation, whereby they can recover from sometimes quite significant injuries or manipulations and restore normal development. It is this property of regulation that, for example allows clinical scientists to remove one or two cells from an early human embryo for genetic testing after in vitro fertilization, without danger of harming the baby.

If one of the two embryos in a chimeric aggregate carries a suitable genetic marker, the distribution of the two embryonic lineages can be traced in different tissues of the chimera. The simplest type of marker is pigment. For example, if a chimera is made by aggregating an embryo from a pigmented mouse strain with one from an albino mouse strain, the distributions of pigmented and albino cells in tissues, such as the retinal pigment epithelium (RPE) and the coat, can reveal information about how these tissues grow and patterns of cell migration (Figure 1a). Transgenic markers, such

β-galactosidase (β-gal) from the bacterium *Escherichia coli* and green fluorescent protein (GFP) from the jellyfish *Aequorea victoria*, have allowed the same approach to be used in non-pigmented tissues and this has proved extremely useful for many biological studies with chimeras (1).

Chimeric corneas with stripes

Back in the 1990s we were exploring the use of a β-gal marker in different tissues of fetal and adult mouse chimeras. Basically, cells from this embryo carry the *LacZ* transgene, and go on to express the β-gal enzyme – and these cells can be stained blue. In most tissues, the blue-stained cells formed rather confused patterns of randomly oriented patches, which reflect the chaos of randomly oriented growth and cell division during embryogenesis. It was a totally different story in the eye: the adult cornea produced beautifully clear patterns of radial stripes, often with a tight spiral at the center (Figure 1c) – rather like children's marbles! From that moment we were hooked on the cornea – what could cause these amazing stripes?

We already knew that Lawrence Bodenstein and Richard Sidman at Harvard had published elegant work explaining how pigmented and albino stripes formed in the peripheral RPE of chimeric mice. They showed that during early post-natal development, the dividing cells were mainly at the edge of the growing RPE and this edge-biased growth caused the stripes to extend outwards as the tissue enlarged (2,3). Our first thought was that the stripes in the corneal epithelium must also arise during development and extend outwards as the cornea grew. However, our preliminary work showed that this was not the case and, as we had no other ready explanation, the work was shelved for a few years.

Enter the ophthalmologists

The penny dropped in 2001 when we met two Edinburgh-based ophthalmologists, Baljean Dhillon and Kanna Ramaesh, to discuss our work on *Pax6* mutant mouse eyes. In conversation, they mentioned that it was widely believed that the corneal epithelium was maintained by stem cells at the periphery of the cornea in the corneal limbus. According to this limbal epithelial stem cell (LESC) hypothesis

"You could be forgiven for thinking that we have a fairly complete understanding of how the ocular surface is maintained..."

(Figure 2a,b), the stem cells that maintain the corneal epithelium are all located in the basal layer of the limbal epithelium. They produce transient (or transit) amplifying cells (TACs), which move radially towards the center of the cornea and continue to proliferate as they go, producing the more differentiated cells in the suprabasal cell layers, which are eventually lost from the surface. The LESC hypothesis immediately suggested a new explanation for the radial stripes in the corneas of our mouse chimeras. It seemed likely that β-gal-positive stem cells in the limbus produced clones of β-gal-positive cells that moved into the cornea and continued to move across the corneal radius to the center, thereby forming radial stripes. We then set out to explore the nature of the radial striped pattern in mouse corneas in order to see if it could help us understand how stem cells manage to maintain the corneal epithelium.

Of course, it's not as simple as it sounds. The structure of the limbus differs slightly between humans and mice. The human limbal epithelium is thicker than the corneal epithelium and has a series of folds, called palisades of Vogt. It has been suggested that crypts between, or peripheral to, the palisades may provide the required niche environment for maintaining human LESCs (4,5). In contrast, the mouse limbal epithelium is thinner than the central corneal epithelium and, like many other species, the mouse lacks the palisades and associated crypts. Nevertheless, the basic biology of corneal epithelial maintenance is likely to be similar across mammalian species and given the formidable array of genetic resources now available for studies with mice, they are indispensable models for most biomedical systems, including the cornea.

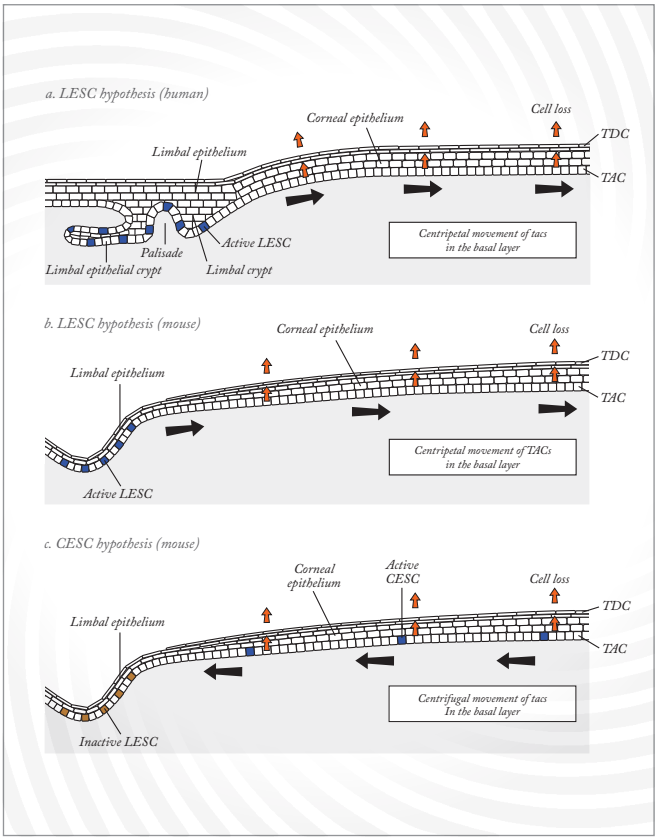

Figure 2. Alternative hypotheses for maintenance of the corneal epithelium. The limbal epithelial stem cell (LESC) hypothesis, shown here for humans (a) and mice (b), proposes that all stem cells (shown as blue squares) that maintain the corneal epithelium are located in the basal layer of the limbal epithelium between the corneal epithelium and conjunctiva. Stem cells produce transient (or transit) amplifying cells (TACs), which continue to divide and move across the corneal epithelium towards the center in the basal layer (black arrows). TACs also produce the more differentiated cells, which move to the suprabasal layers and are displaced towards the surface where terminally differentiated cells (TDCs) are shed (orange arrows). The alternative corneal epithelial stem cell (CESC) hypothesis (13), shown for mice (c), proposes that normally the corneal epithelium is maintained by stem cells (shown as blue squares), scattered throughout the corneal epithelium itself and that LESCs are assumed to be inactive (shown as brown squares) during normal homeostasis and only activated during wound healing. It was also suggested that radial movement of TACs in the corneal epithelium was more likely to be towards the limbus (black arrows).

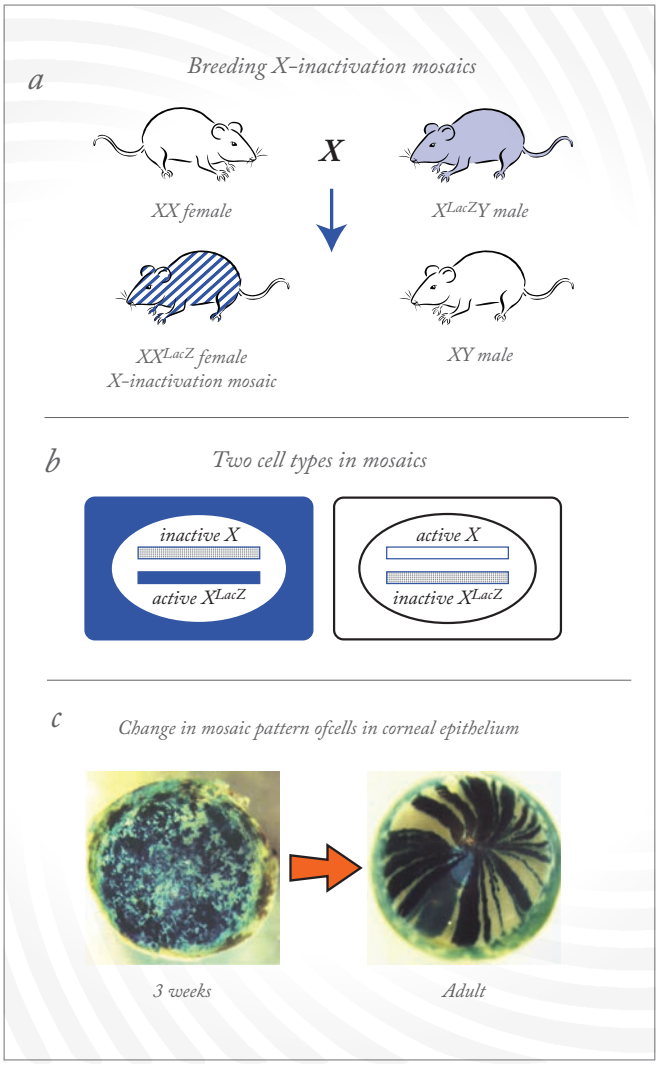

Figure 3. Patches and stripes in the corneas of mosaic mice. Panel (a) shows that X-inactivation mosaics (heterozygous, XX^{LacZ} female mice) are produced simply by crossing an $X^{LacZ}Y$ male mouse, carrying an X-linked *LacZ* transgene, and a wild-type XX female mouse (without the transgene). Panel (b) shows that after X-chromosome inactivation occurs early in development, cells in XX^{LacZ} females will only express genes from one of the two X-chromosomes. Only cells with an active X^{LacZ} chromosome (left) will express *LacZ* and produce β-gal, which can be stained blue. Panel (c) shows the changes from patches to radial stripes in eyes from X-inactivation mosaic mice between 3 weeks (left) and adulthood (right).

Patches are replaced by stripes after stem cells are activated

Having identified radial patterns of stripes in the corneas of adult chimeric mice (Figure 1c), we replicated the observation with a simpler experimental system using female, X-inactivation mosaic mice, which carried a *LacZ* marker transgene (X^{LacZ}) on one X-chromosome (6) (Figure 3a,b). Because, in female mammals, one of the two X-chromosomes is silenced independently in every cell of the early embryo (more or less at random), these mosaic mice are composed of the usual jumble of blue and white cells we saw before with *LacZ* chimeras. Once again, however, the adult corneal epithelium produced a striking pattern of radial stripes. What particularly caught our attention was that before about five weeks of age, the blue-stained, β-gal-positive cells were arranged as a randomly oriented patchwork. However, this pattern changed dramatically from patches to radial stripes over a few weeks (Figure 3c), which implied that LESCs do not become active until several weeks after birth. Assuming that the postnatal pattern of patchy β-gal-positive cells represents the stem cell-free random growth of the corneal epithelium, produced during development, its eventual replacement by radial stripes fitted well with the LESC hypothesis. Once activated, LESCs would produce new TACs that could move radially into the corneal epithelium, so replacing the original population of corneal epithelial cells, as they are lost by abrasion (7). Similar results have now been described in other mouse experimental systems (8–10).

Interestingly, the number of radial stripes declines with age, suggesting aging affects stem cells in some way. Richard Mort, a PhD student in the group, also showed that when the periphery of the corneal epithelium is wounded, the radial stripes divert from the center of the cornea and form a second focus of convergence at the wound (11). Currently we have no information about whether this second center of convergence ever goes away, and whether the patterns of corneal epithelial cell migration ever fully recover from wounding. It will be important in future to resolve this issue to try to understand how the human cornea responds to damage, especially with aging. Intriguingly, Lucy Leiper, a postdoctoral scientist colleague of ours, showed that the radial pattern of stripes and central spiral – that revealed the epithelial cell migration pathway – is mirrored by the distribution of epithelial nerves (12). As ever with research, work still needs to be done – unanswered questions remain. It remains unclear whether both epithelial cell movement and innervation follow some cue that we have yet to identify or if nerves guide epithelial cell movement.

"Interestingly, the number of radial stripes declines with age, suggesting aging affects stem cells in some way."

Controversy: a competing corneal stem cell hypothesis

The emergence of stripes at the periphery of the cornea and their extension across the corneal radius fitted nicely with the prevailing LESC hypothesis – but this narrative was soon challenged. François Majo and his team in Lausanne, Switzerland tested the LESC hypothesis surgically by transplanting β-gal-positive mouse limbal tissue to the limbus of β-gal-negative, immunocompromised mice, the transplanted limbal tissue failed to contribute to the corneal epithelium unless the host corneal epithelium was removed (13). So, although the transplanted limbal tissue contributed to corneal repair, it did not contribute to steady state corneal maintenance during normal tissue homeostasis – as was predicted by the LESC hypothesis. This surprising result prompted the authors to suggest the alternative corneal epithelial stem cell (CESC) hypothesis (Figure 2c), which proposes that the corneal epithelium is normally maintained by stem cells (CESCs) scattered throughout the corneal epithelium itself. This alternative hypothesis also recognizes the existence of LESCs but they are assumed to be active only during wound healing and so would play no role in normal maintenance of the unwounded corneal epithelium.

This new CESC hypothesis caused a storm of controversy in the field and was criticized for not accounting for several

"Identifying the origin of such stripes and the way they change with time after labeling is induced should help resolve the LESC vs. CESC debate in the near future"

previous observations (14), including the evidence from mosaic mice that radial stripes emerge from the limbus and replace the original patchy mosaic cell distribution. On the other hand, the LESC hypothesis has difficulty explaining why cells from transplanted limbal tissue failed to colonize the host corneal epithelium. Perhaps the CESC hypothesis applies to mice but not to humans? The problem is that the LESC evidence also came from mice. So how do you solve the LESC vs. CESC dilemma? From a clinical perspective, does it even matter which hypothesis is correct?

In some respects it doesn't. Both hypotheses agree that stem cells exist in the limbal epithelium – and it's widely recognized that this region is an excellent source of cells for therapeutic use. Indeed limbal tissue transplantation and limbal stem cell therapy have been developed as successful treatments for visual impairment caused by conditions described collectively as limbal stem cell deficiency (15,16). However, to understand the biology of corneal epithelial maintenance, it is critical to know where the stem cells that maintain the tissue during normal homeostasis are located. If corneal epithelial cells really can show stem cell activity, at least under experimental conditions, this would offer new possibilities of therapeutic strategies for injured or diseased corneas.

Resolving the debate: next steps

Despite the controversy, François Majo's limbal transplantation results (13) might be compatible with the LESC hypothesis if their surgical manipulation perturbed normal homeostasis and so affected the outcome. To test this, what we need is a method that can label some of the putative stem cells in the adult ocular surface without disturbing homeostasis. Sophisticated, inducible lineage tracing methods using transgenic mice are now available that can be used to throw a genetic switch to label individual stem cells present in either the limbus or cornea with a fluorescent or histochemical marker that will identify them and all their mitotic progeny. The labeled stem cells would then produce clones of labeled daughter TACs and it should be possible to identify whether they arise in the limbal epithelium and move centripetally to the cornea or if they arise in the corneal epithelium itself. Such methods have already been used to trace stem cell lineages in other tissues, including the intestinal epithelium (17).

We, along with several other research groups, are beginning to use this approach to trace putative stem cell lineages in the mouse ocular surface. The expected endpoint is that transgenic mice will produce a relatively small number of individual, long-lived clones in the form of radial stripes, where each stripe emerges from a single adult stem cell. Identifying the origin of such stripes and the way they change with time after labeling is induced should help resolve the LESC vs. CESC debate in the near future. We are optimistic that the inducible stripes produced by this type of lineage-tracing approach will provide even greater insight into the maintenance of the corneal epithelium than the stripes we observed with the original chimera and mosaic systems.

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STAAR SURGICAL

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SATURDAY, OCTOBER 18

10:00AM-11:00AM
Treating Astigmatism in Phakic IOL Patients
Juan Batlle, M.D., Alaa El-Danasoury M.D., Robert Rivera, M.D.
Moderator: Scott Barnes, M.D.

11:30AM-12:30PM
Continuous Range of Vision and Preloaded Visian ICLs
Robert Ang, M.D., Erik Mertens, M.D.
Moderator: Juan Batlle, M.D.

1:00PM-1:30PM
Methods & Strategies For Treating Astigmatic Cataract Patients
Robert H. Osher, M.D.

SUNDAY, OCTOBER 19

10:00AM-11:00AM
Visian ICL Surgical Pearls And Premium Outcomes
Erik Mertens, M.D., Francis Price, M.D., George Waring, IV, M.D.
Moderator: John Vukich, M.D.

11:30AM-12:30PM
Enhancing The Visian ICL Experience with Bilateral Surgery
Paul Dougherty, M.D., Scott Barnes, M.D.
Moderator: Jason Brinton, M.D.

1:30PM-2:30PM
Treating Astigmatic Cataract Patients With Toric IOLs
Antonio Fea, M.D., Thomas Harvey, M.D., Farrell "Toby" Tyson, M.D.
Moderator: Jeffrey Whitman, M.D.

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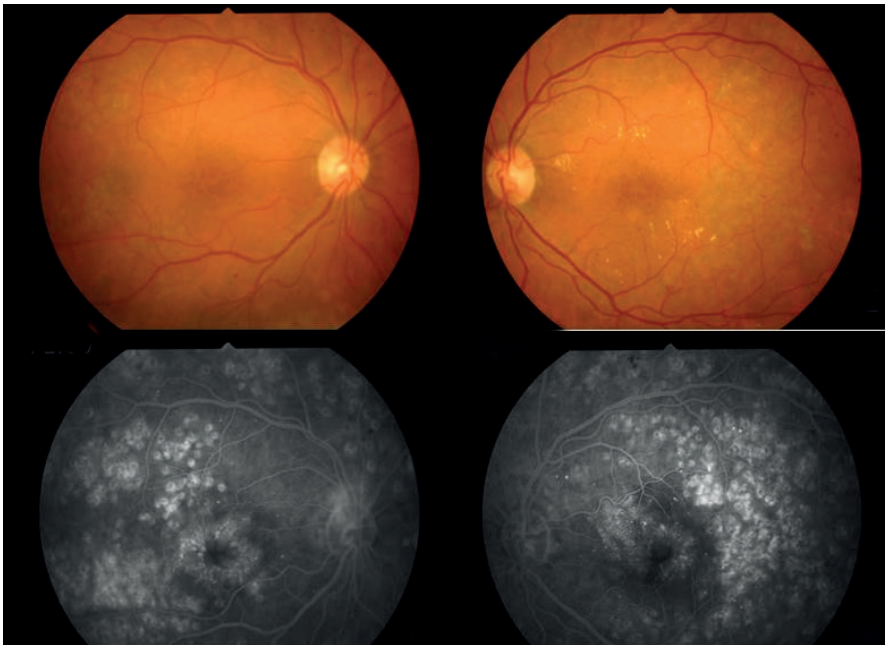
In Practice

Surgical Procedures
Diagnosis
New Drugs

Should Steroids Be Your First Port of Call in the Pseudophakic Eye?

Anti-VEGF agents are effective in treating DME – but not always indefinitely. Steroids work – but accelerate cataract development. If a patient is pseudophakic anyway, how soon do the benefits outweigh the risks?



By José Cunha-Vaz

Most people with diabetes will develop diabetic retinopathy (DR). It's an insidious disease; the early stages are silent, but it progresses relentlessly, and often a patient isn't aware of vision problems until it's fairly advanced.

Diabetic macular edema (DME) is the single biggest cause of visual acuity reduction in people with diabetes. It can affect central vision from the early stages of retinopathy and is the most frequent complication of DR, particularly in older patients with type 2 diabetes.

The role of inflammation in the pathogenesis of DR is now well-established, and the repair processes have been associated with the universal endothelial dysfunction that occurs in diabetes. An emerging focus area of DR research is on the mechanistic link between the activation of subclinical inflammation and neurodegeneration: Müller cells show inflammation-linked responses when exposed to the diabetic milieu, and this environment can lead to activation of microglia and migration of macrophages, both of which may also play an active role in bringing even more inflammatory cytokines into the picture.

The disease processes in DME are mostly extracellular. Edema comes from the ancient Greek for swelling, οίδημα – in this case the swelling comes from the breakdown of the inner blood-retinal barrier, and the increase in tissue volume is due to an expansion of the retinal extracellular space, which is detectable with optical coherence tomography (OCT).

When you have a situation of blood-retinal barrier breakdown, Ernest Starling's observation that "edema occurs in a tissue when the rate of capillary filtration exceeds the rate of fluid removal from the perivascular interstitium" applies (1). With an open blood-retinal barrier, any change in the equilibrium between hydrostatic, oncotic and osmotic pressure gradients across the retinal vessels contribute to further water movements and may result in increased edema. Indeed, any increase in retinal thickness which is not attributable to a neoplasia comes from retinal edema.

DME therapy: now and then

For many years now, the standard of care for patients with DME had been laser photocoagulation. The procedure is not without its benefits – the principal one for most patients being an arrest in the decline in visual acuity loss (2). But only a minority of patients experience (slow) improvements in their edema and

At a Glance

- *DME results from the chronic inflammatory state caused by diabetes*
- *All current treatment modalities have their limitations: photocoagulation (poor efficacy), anti-VEGF (not all patients respond) and steroids (raised IOP and accelerated cataract)*
- *Slow-release corticosteroid formulations have led to a rethinking of their role in DME*
- *The benefit–risk balance may be in favor of steroid implants in those patients who are already pseudophakic*

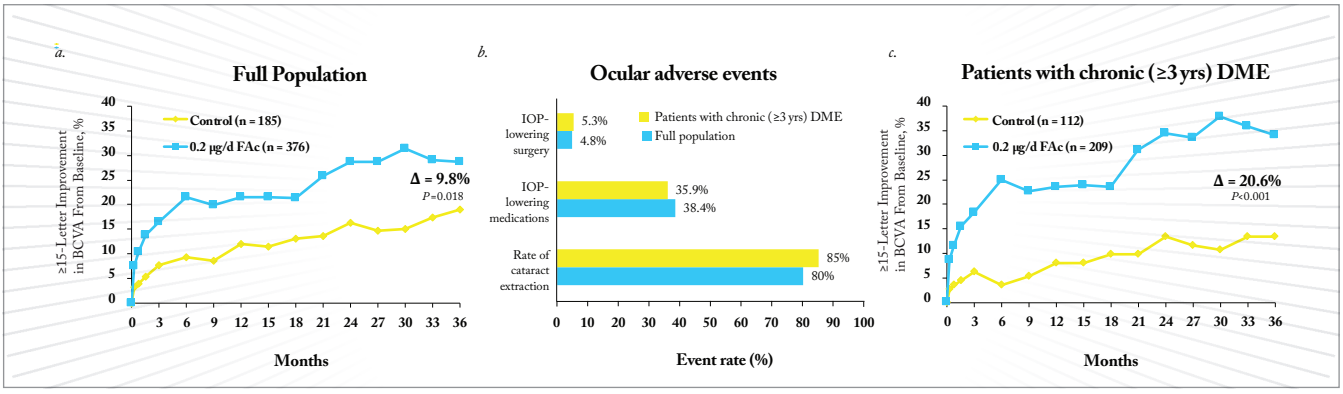


Figure 1. a. The FAME study met its primary endpoint: 0.2 µg/day fluocinolone acetonide (FAc) produced a ≥15 letter response, compared with sham control; b. Adverse event rates pertaining to IOP and cataract formation; c.FAc's effects are more pronounced in patients with chronic DME (≥ 3 years).

visual acuity, and after two years, one in five experience worsening vision once again (3).

For more than a decade now, research has focused on the use of vascular endothelial growth factor (VEGF) antagonists. Intravitreal ranibizumab was approved by the European Medicines Agency (EMA) back in 2011 for DME based on the results of a number of clinical trials – REVEAL, READ-2, RESOLVE, and RESTORE (4–7). The US FDA followed suit, and gave its approval in 2012 based on the results of the Phase III RIDE and RISE studies. In all trials, ranibizumab use was associated with rapid edema reduction, significant visual acuity improvements and retinal thickness reductions, with the READ-2 and RESTORE studies demonstrating ranibizumab's superiority over laser treatment. Very recently, the VEGF and placental growth factor inhibitor, aflibercept, received both FDA and EMA approval based on the Phase III VIVID-DME and VISTA-DME studies, respectively, that compared intravitreally-administered 2 mg doses of aflibercept every four weeks, with conventional macular laser photocoagulation – both studies demonstrated significantly improved visual acuity and significantly reduced central retinal thickness with aflibercept

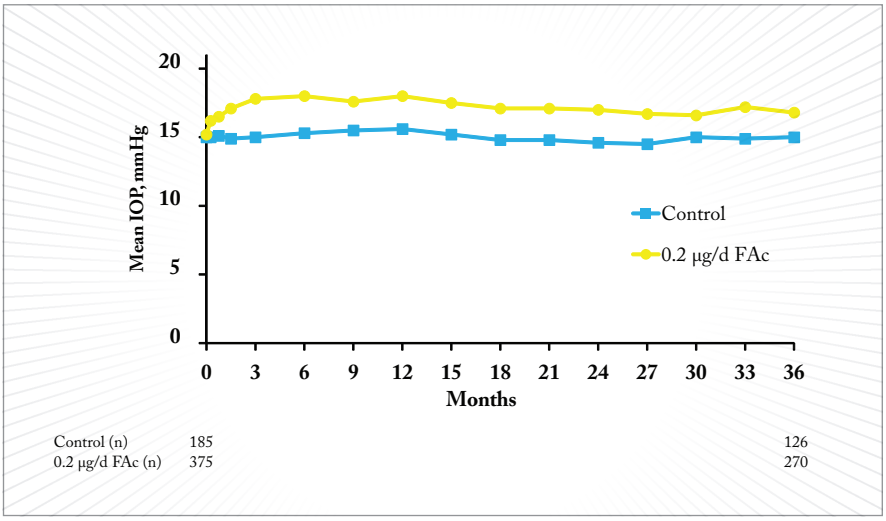


Figure 2. Mean IOP levels for FAc-receiving patients: Full population. 62 percent of patients treated with 0.2 µg/day FAc did not require IOP-lowering therapy. FAc, fluocinolone acetonide.

relative to laser photocoagulation (8).

Although these two agents are currently unparalleled in terms of their safety and efficacy profile, not all DME patients respond and for some, efficacy fades over time. VEGF inhibition also fails to suppress any additional inflammatory mediators and permeability factors (other than VEGF) that are present in the diabetic retina: so patients with DME could benefit from a more comprehensive treatment strategy. This immediately provides a rationale for corticosteroid use. Corticosteroids act at both the biochemical and anatomical levels to exert their therapeutic actions; they reduce the expression of VEGF and other permeability factors in the eye, and they also suppress other inflammatory factors and the influx of leukocytes into the retina (9–11). Their use has, however, not been without risk.

When it was introduced in the 1970s, many ophthalmologists embraced intravitreal injection of triamcinolone acetonide (IVTA) for the treatment of ME because it was effective in reducing macular thickness and improving visual acuity. But its effects were short-lived, which meant that patients needed

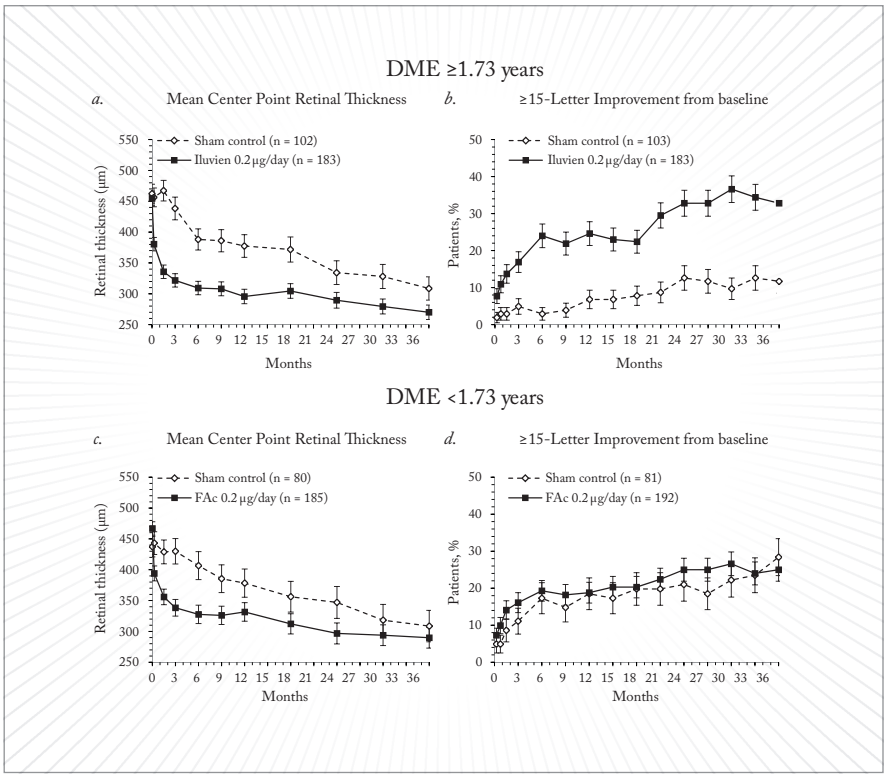


Figure 3. Re-analyzed FAME 36-month efficacy data in patients with DME of greater than (a, b) or less than (c, d) 1.73 years' duration at baseline. FAc, fluocinolone acetonide.

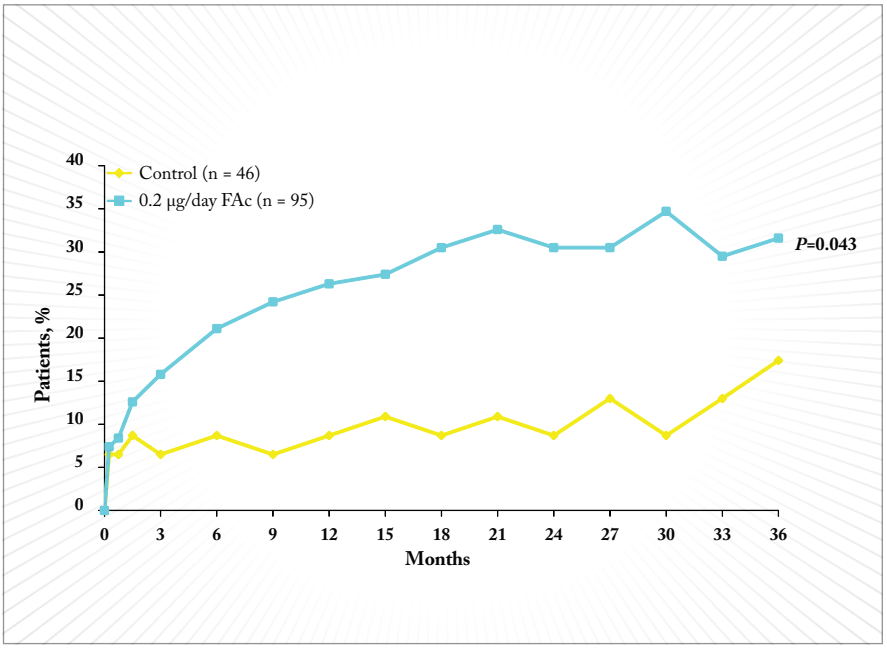


Figure 4. Patients in the FAME study (with DME ≥3 years) who were pseudophakic at baseline, and experienced a ≥ 15-letter response. FAc, fluocinolone acetonide.

frequent injections to maintain the effect (12). Furthermore, its use – as with all corticosteroids – was associated with cataract development and raised IOP.

Intravitreal implants

The short duration of action of IVTA (and other steroids) meant that research turned to developing sustained-release intravitreal implants that would release low doses of steroid over a long period – avoiding the requirement for frequent intravitreal injections and the wide intraocular drug concentration fluctuations that entails (13). Three such intravitreal implants have been developed; one that releases dexamethasone (Ozurdex, Allergan), and two that release fluocinolone acetonide (Iluvien, Alimera Sciences, and Retisert, Bausch + Lomb). Let's look at each one in turn.

Retisert

Retisert is sutured to the anterior eye wall and releases 0.59 µg of fluocinolone acetonide every day into the anterior part of the vitreous cavity – and is designed to do so for approximately two-and-a-half years. The implant has shown efficacy for the treatment of chronic non-infectious posterior uveitis (14). In DME, a four-year multicenter clinical trial found that Retisert significantly improved visual acuity and diabetic retinopathy severity scores (DRSS) relative to eyes that received standard of care (laser photocoagulation or observation) (15). However, this came at a cost; common adverse effects included cataract progression, elevated IOP and vitreous hemorrhage. Indeed, three years after implantation, 61.4 percent of implanted eyes had IOP elevation of more than 30 mmHg, compared with 5.8 percent of non-Retisert-implanted eyes, and glaucoma filtration surgery was required in 29.1 percent of implanted eyes. Retisert has not been approved

for any indication by the EMA, and received its single FDA approval – for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye – back in 2005.

Ozurdex

Ozurdex is comprised of 700 µm micronized dexamethasone, encapsulated in a biodegradable copolymer of lactic and glycolic acids, which slowly dissolves to release the steroid. The FDA had recently (June 2014) approved Ozurdex for the treatment of DME in patients who are "pseudophakic or are phakic and scheduled for cataract surgery", but September 2014 saw the agency expand Ozurdex's indication for the "general patient population being treated for DME." This was also the same month that saw the EMA grant marketing authorization for the use of Ozurdex in "adult patients with visual impairment due to DME who are pseudophakic or who are considered insufficiently responsive to or unsuitable for non-corticosteroid therapy", meaning that Ozurdex should also be available in European countries within the next few months.

The evidence base for the regulatory authorities' decision comes principally from a Phase II trial of the implant in patients (n=315) with persistent ME, secondary to various etiologies, including DME. Patients who received the Ozurdex implant went on to experience improvements in visual acuity, macular thickness and fluorescein leakage – and these benefits were sustained for up to six months (16). A further study that compared Ozurdex with observation in patients with persistent DME (of 90 days' duration or more), showed that – compared with observation – Ozurdex was well-tolerated, and again produced significant improvements in visual acuity, central retinal thickness (CRT) and fluorescein leakage (17). Two randomized, sham-controlled Phase III trials of Ozurdex (containing either 0.35 or 0.7 mg of dexamethasone) were performed in patients (n=1,048) with DME, BCVA of 34–38 letters and CRT of ≥300 µm, followed for three years, with retreatment permitted at ≥6-monthly intervals. Pooled analysis showed both dexamethasone doses produced significant reductions in macular volume, CRT and disc areas of macular thickening on color photographs (all $p<0.001$ versus sham) (18).

"Slow-release corticosteroid formulations have led to a rethinking of their role in patients with DME"

However, one non-randomized study has questioned Ozurdex's claimed six-month duration of action (19). Fifteen patients with chronic DME (of over six months' duration), unresponsive to bevacizumab, received the Ozurdex implant. Statistically significant improvements in central foveal thickness, relative to baseline values, were seen at one, two and three months post-implantation, but not beyond, and improvements in BCVA after implant placement were seen only in months one and two, waning afterwards. As the implant's approved use in this indication is in its infancy, perhaps further study is needed to determine the actual duration of clinical benefit and the optimal time for retreatment in differing patient populations.

Iluvien

The Iluvien intravitreal implant is inserted into the vitreous cavity through a 25-gauge applicator in an outpatient setting, and contains 190 µg of fluocinolone acetonide, encased within an inert non-biodegradable cylindrical tube. Iluvien has very recently been approved by the FDA for use in patients with DME, adding to the EMA's approval back in 2012 for its use in this indication. The approval wordings are different between the continents – the US label permits Iluvien use in patients with DME "who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP", whereas the European approval is specifically for use in patients with DME that was "considered insufficiently responsive to available therapies."

The EMA and FDA approvals were based on the results from the Fluocinolone Acetonide for diabetic Macular Edema (FAME) study (20,21). FAME was comprised of two identically designed Phase III clinical trials that compared two doses of fluocinolone acetonide (0.2 mg/day and 0.5 mg/day) with sham injection over a three-year period – and all patients could receive standard-of-care laser photocoagulation six-weeks after photocoagulation. Both doses significantly improved visual acuity relative to sham, and patients in the treatment groups showed significant reductions in foveal thickness at all-time points over the follow-up period (Figure 1a). The majority (61.6 percent) of patients treated with the 0.2 µg/day implant did not require IOP-lowering medication and fewer than 5 percent required IOP-lowering surgery (Figure 1b, 2). The treatment efficacy of both fluocinolone acetonide doses were similar, but fewer adverse events occurred with the lower steroid dose, so the 0.2 µg/day implant was the one

"The history of corticosteroids in DME is quite a long one..."

chosen to take to market.

Notably, a significant number of patients enrolled into FAME had chronic DME (in this case, three years), as defined as the median duration of DME at trial enrolment. Iluvien's effectiveness in treating DME was far more apparent in the chronic population compared with the overall population, with much greater improvements in both visual acuity Figure 1c) and foveal thickness being achieved (20,21). One issue, however, was the original calculation of median DME duration: it was particularly conservative in its approach. DME duration was calculated as: the year of study entry, minus the year of first diagnosis – plus one year (to ensure no patient with a diagnosis and enrolment in the same year had a DME duration of 0 years). A post-hoc analysis of the data that was based on the exact dates of diagnosis and study entry resulted in a median duration of 1.73 years. The FAME investigators reassessed the trial data using the 1.73-year duration of DME as the definition of "chronic" and compared it with the original study's data (22). It turned out that 93 percent of patients that had DME defined as "chronic" by the old algorithm retained that definition with the new one, and that irrespective of how it was calculated, Iluvien's efficacy was greater in patients with DME greater than the FAME trial's median DME duration (Figure 3). These outcomes occurred despite a high incidence of cataract requiring surgery in Iluvien-receiving patients (81.7 percent after 36 months of follow-up), but even those who required cataract surgery experienced a mean increase in BCVA letter score of seven. A similar BCVA improvement was seen in patients who were pseudophakic at baseline (Figure 4).

Are we missing a trick?

Although at present intravitreal corticosteroid implant use is not recommended as first-line therapy, the impending requirement for cataract surgery in patients with DME may prompt us to reconsider this – if patients have failed to benefit from laser photocoagulation, then there is a solid rationale to consider steroid implants in these patients.

The history of corticosteroids in DME is quite a long one, and interventions like IVTA have been associated with sufficiently high adverse event rates (principally accelerated cataract progression and IOP elevations) to warrant a pause before use. Intravitreal corticosteroid implants have surmounted or mitigated many of these issues, and it's now possible to have an implant, that has a manageable safety profile, that exerts a therapeutic effect on DME for a prolonged period in a large proportion of patients. Considering the difficulties clinicians face in providing monthly anti-VEGF treatment, a single administration that lasts for a number of years is extremely attractive, particularly in pseudophakic eyes.

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Is Better the Enemy of Good?

New intraocular lenses offer extended depth of focus, but this can come at a cost: glares, halos and comets. Can these be designed away?

By Florian Kretz and Gerd Auffarth

One of the consequences of the great advances in cataract surgery and IOL technology over the last two decades is that many of today's patients now expect almost perfect vision from a premium IOL. They demand excellent near, intermediate and distance vision, without any of the potential drawbacks like glares, halos or comets. Such patients require an element of expectation management, but will this always be the case? Have presbyopia-correcting IOL designs improved to a stage where it is a realistic expectation that these demands – in particular, good intermediate vision – can be met?

Presbyopia correction: design trends and trade-offs

IOL manufacturers have taken three central approaches to address this. The first, was the development of multifocal IOLs (mIOLs). These typically employ either diffractive or refractive optics, and can produce multiple, simultaneous focal points, which – depending on the design – can give a patient good near and distance vision. The cost of splitting the light like this is that less light reaches the retina for each desired focal plane. Most current mIOLs rely on diffractive optics, with tight concentric rings that diffract light for near vision, rather than refractive optics with differently-powered zones, but there are also some that combine the two in a hybrid approach.

"The cost of splitting the light is that less light reaches the retina for each desired focal plane"

One current trend with mIOL is to implant "low add" lenses. In these, the near addition at the lens plane is reduced to around +2.75 or +3.25 D, which translates into a near addition of between +1.75 and +2 D at the spectacle plane. This results in greatly enhanced intermediate vision, but enables the patient to retain good binocular reading function (at a distance of approx. 40 to 50 cm from the eye). mIOL manufacturers have even produced multifocal lenses that have near additions of +1.5 D, in order to maximize visual acuity at intermediate distances. The ability to offer this range of post-surgical outcomes to patients is certainly valuable.

The second option is to modify monofocal lenses in a way that generates an extended depth of focus. This can be achieved in various ways, such as changing the asphericity of the lens (as in the case of the Hoya AF-1) or by applying the "micro monovision" principle to cover the entire range from near to distance by inducing anisometropia – one eye receives a near vision IOL, the other a distance vision IOL. This is common practice with contact lens prescriptions, and the potential visual side effects are similar and well-known too, principally blur, fog, glares, halos and reduced night-time vision – and even transient diplopia. Can we do better?

In contrast…

A newer IOL design, termed "Echelette" has further refined and improved what presbyopia-correcting IOLs can offer. Unlike mIOLs that create a fixed number of focal points, the first Echelette-design, the Tecnis Symfony IOL (Abbott Medical Optics), generates a wide focal range, which results in the patient experiencing continuous sharp vision from distance to near over a 1.5 D range as well as a visual acuity of 20/40 (decimal 0.5) or better over a range of even 2.5 D (Figure 1). Mean visual acuity was above 20/20 (decimal 1.0) for far and intermediate distances and 20/30 (decimal 0.67) for near distance, as seen in a recent clinical study (Figure 2).

An extended depth of focus might satisfy some of the expectations from today's most demanding patients, but they won't be happy if the visual side-effects are many and noticeable. The Echelette-design provides an almost full chromatic aberration correction, which translates into a good optical quality and excellent Modulation Transfer Function – in other words, contrast is well preserved by this lens. As the Tecnis Symfony is essentially an extended depth of focus evolution of the original monofocal Tecnis IOL, it's reassuring to see that there is no difference in patient-reported symptoms that are

At a Glance

- *People purchasing pricey premium IOLs expect perfect vision*
- *Multifocal IOLs (mIOLs) offer excellent near, intermediate and distance vision, but optical compromises have had to be made to achieve this*
- *These compromises can bring about optical adverse events (OAEs) – leaving some patients unhappy with their vision*
- *Presbyopia-correcting design continues to evolve. Can newer optical design approaches minimize OAEs, avoid pupil dependence and fulfil patients' expectations?*

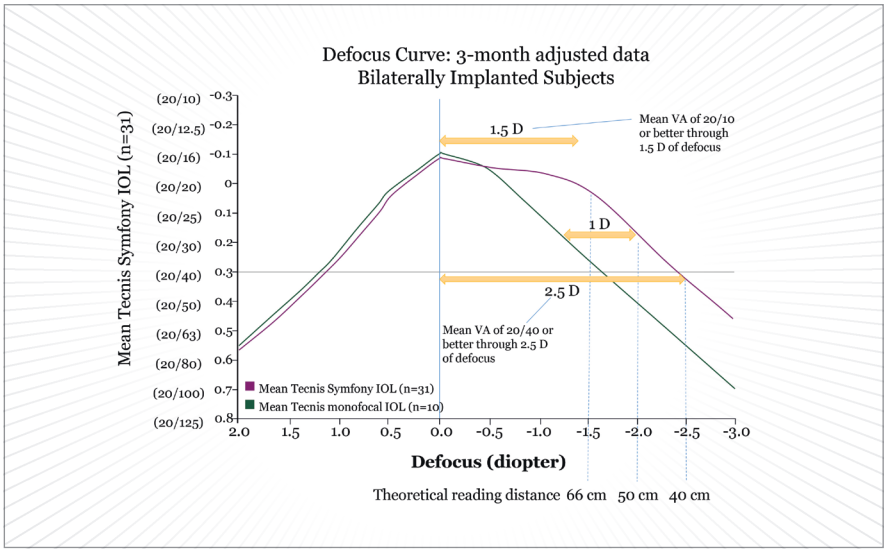

Figure 1. Defocus curve of the Tecnis Symfony IOL compared to the monofocal Tecnis IOL.

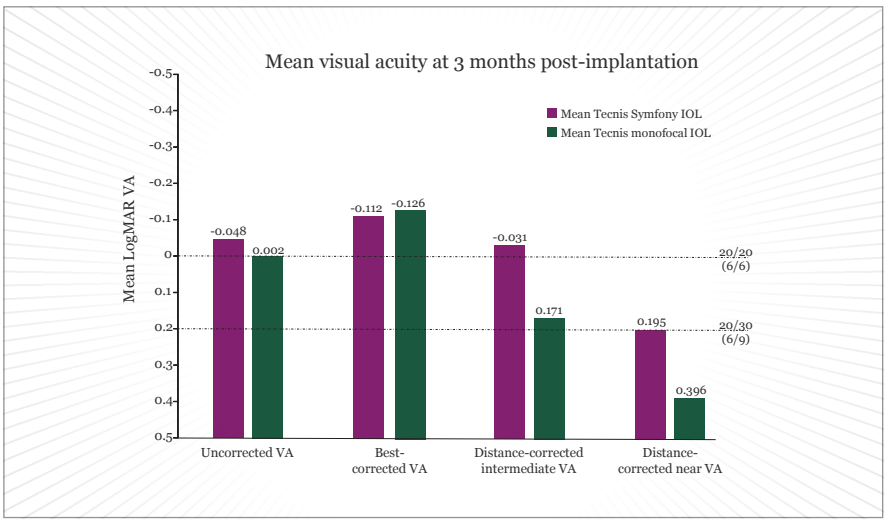

Figure 2. Visual acuity at three months post-implantation: comparison of the Tecnis Symfony Extended Range of Vision IOL versus the Tecnis Monofocal.

typically associated with mIOLs – like halo and glare.

Dim light and expanding pupils

Presbyopia-correcting IOLs also vary considerably in their dependence on pupil size to function at near distances, and this must be taken into account when deciding which lens is best suited to a given patient. Pupil dependence is a complex issue. While it is a function of optic design, each broad category of optic design contains examples that are pupil-independent and others that are pupil-dependent. Tecnis lenses – both the traditional multifocal and the Echelette extended depth-of-focus design, are pupil-independent, so the quality of near and intermediate vision doesn't change as the pupil expands in dim light. The Zeiss trifocal lens is also pupil-independent, having both central and peripheral trifocal elements, meaning that it can extend near function with a wide pupil. Apodized lenses, including the ReStor and the MicroF, however, don't function as well in low light because they direct less light to near vision as the pupil widens. Most patients expect to maintain near function in low light, and pupil-independence is especially important for those who drive a lot at night or whose work or hobbies take place in poorly lit environments. This is another reason why a detailed understanding of a patient's lifestyle and optical requirements is crucial in choosing the most appropriate lens for them.

Today's patients are more demanding than ever before, with a strong desire for a spectacle-free life. Procedures like LASIK have raised their expectations of having great post-surgical outcomes and becoming spectacle-free afterwards. Historically, it's been hard for IOLs to fully bridge the gap between near and distant vision – the compromise was always intermediate vision. But there has been a clear trend towards surgical refractive interventions that close that gap and provide better intermediate vision. The new generation of presbyopia-correcting IOLs that offer an extended depth of focus represent a new opportunity to provide an excellent visual quality of vision at all distances, with a greatly reduced incidence of the optical adverse events that have historically been associated with mIOLs. Patients have been demanding it for years; only now are we really in a position to deliver it.

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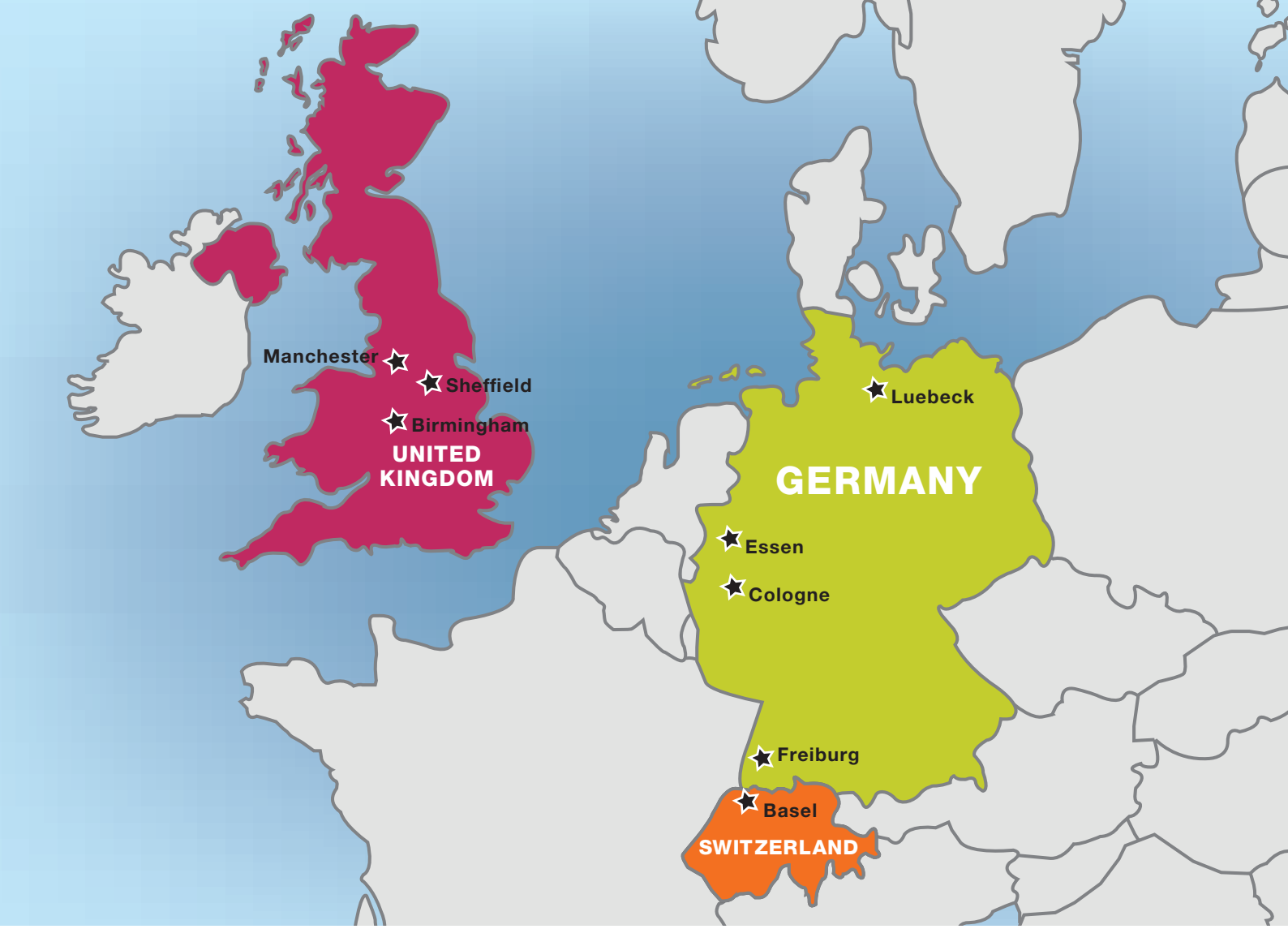

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36–39
Benchmarking Vitreomacular Adhesion
What does analysis of the last five years of literature on vitreomacular adhesion and traction tell us about the priorities of the field and the major contributors to it?

Benchmarking VMA/VMT

What does analysis of the last five years of the literature on vitreomacular traction/ adhesion tell us about the priorities of the field and the major contributors to it?

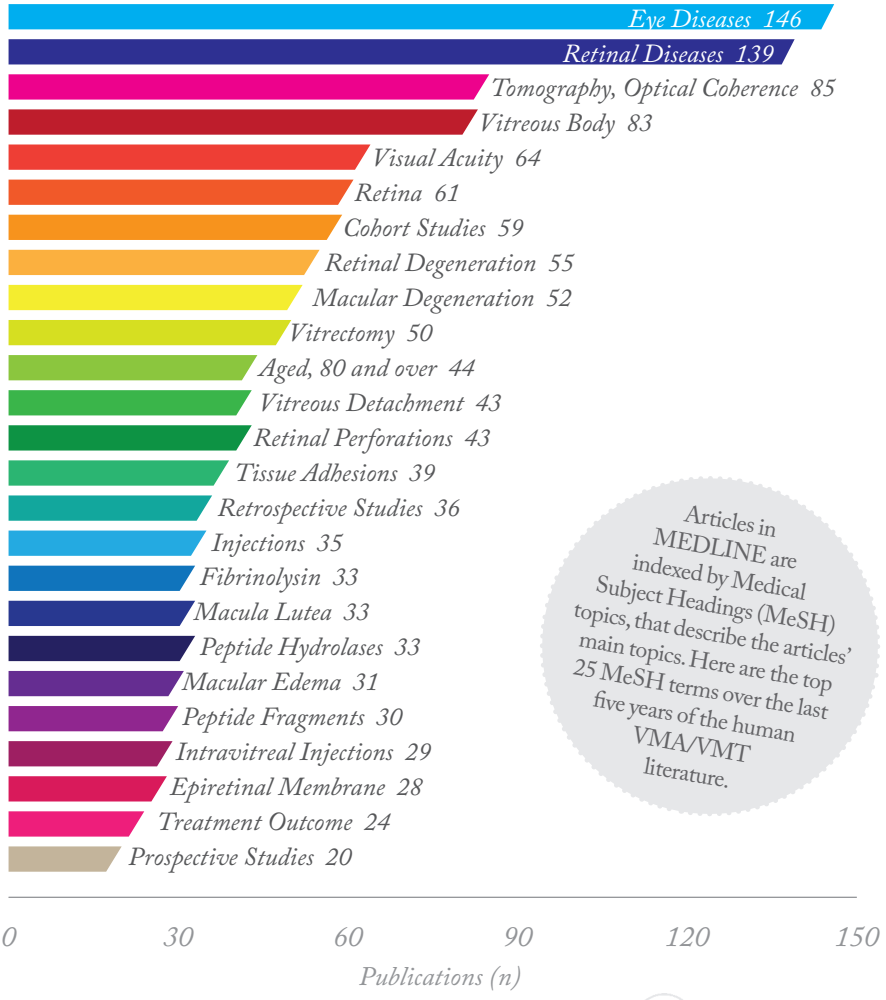
By Mark Hillen

Vitreomacular adhesion (VMA) occurs when the vitreous of the eye adheres to the retina in an atypically strong manner. Usually, the vitreous separates from the retina as part of the normal aging process, but if this separation is not complete – that is, there is still an adhesion – this can create pulling forces on the retina that may result in visual distortion, or even loss. The adhesion may not be dangerous in itself, but the resulting pathological vitreomacular traction (VMT) can cause severe ocular damage. The current standard of care for treating these adhesions is pars plana vitrectomy, but an alternative, an injectable protease called ocriplasmin, has been available for the treatment of VMT since 2013.

To provide insight into the past and predictions for the future of the field, a series of metrics were applied to the last five years of the published literature. We asked: What are the major topics for the field? Which publications have the greatest impact? How is the knowledge available online? Who are the most prolific authors? Has the clinical development of ocriplasmin altered what is published over time?

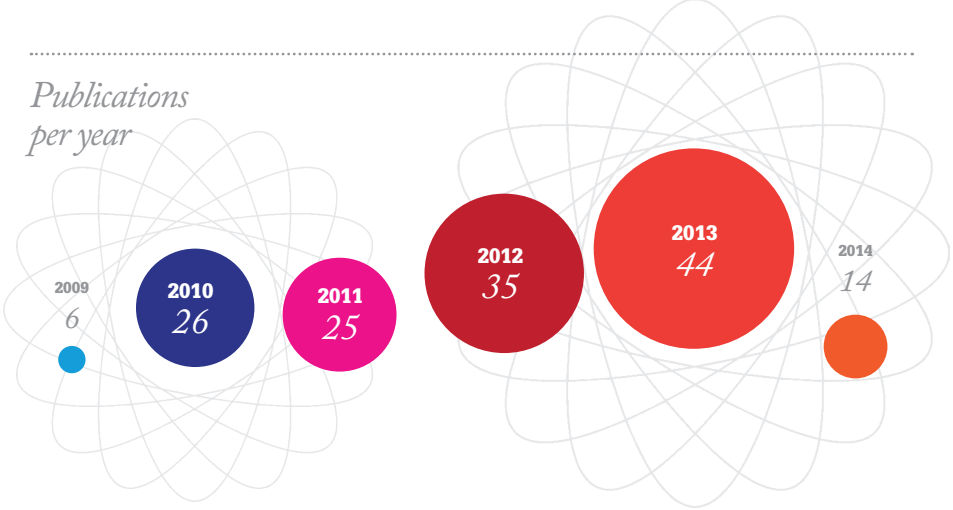
PubMed was searched for: vitreomacular AND (traction OR adhesion), with results limited to the last five years, in humans (for a clinical focus). The data were analyzed in Microsoft Excel 2013.

Most frequent topics on PubMed

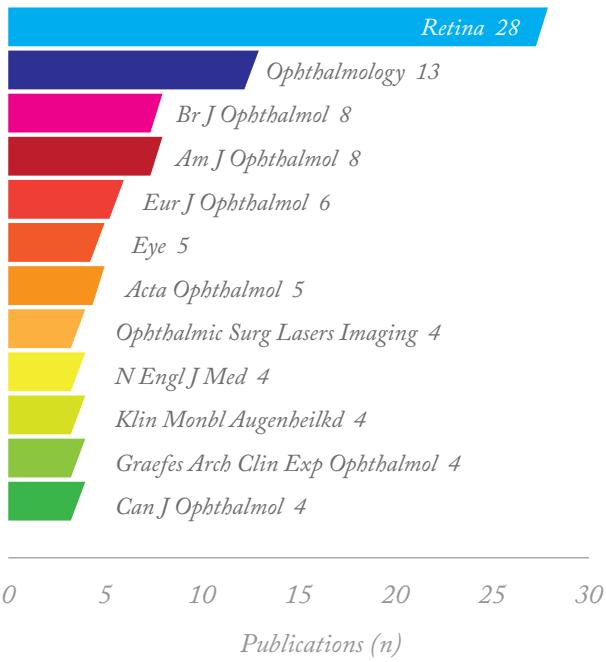


Articles in MEDLINE are indexed by Medical Subject Headings (MeSH) topics, that describe the articles' main topics. Here are the top 25 MeSH terms over the last five years of the human VMA/VMT literature.

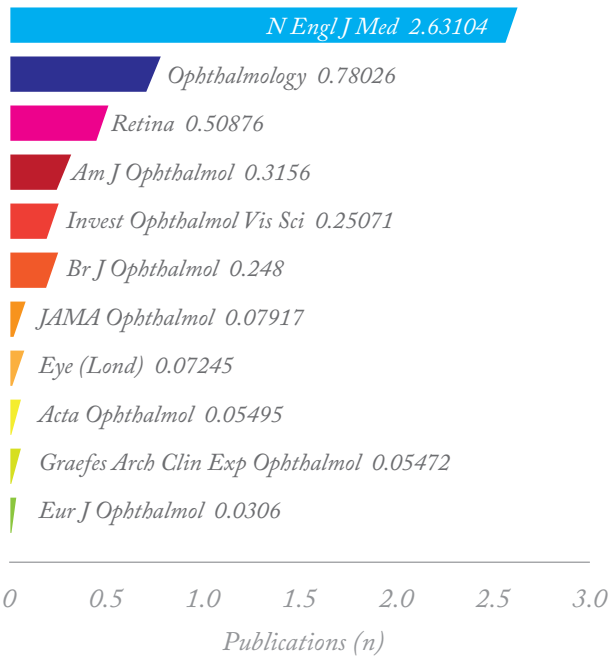
Publications per year



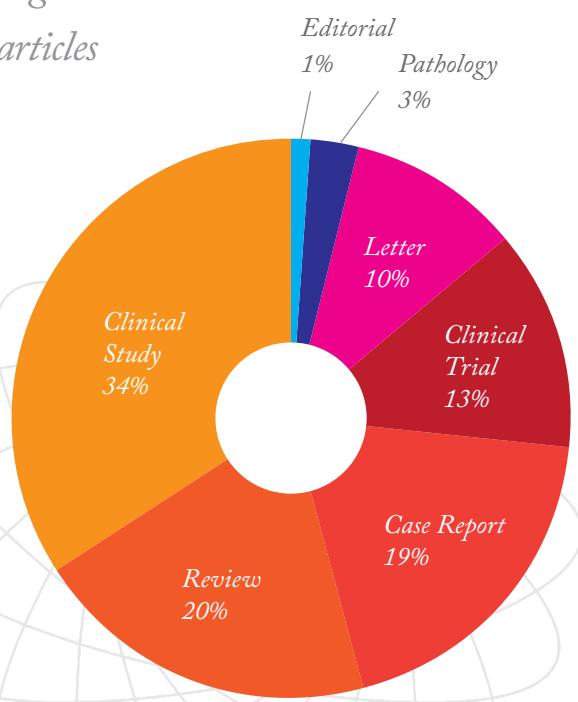
Top 12 journals *(number of publications)*



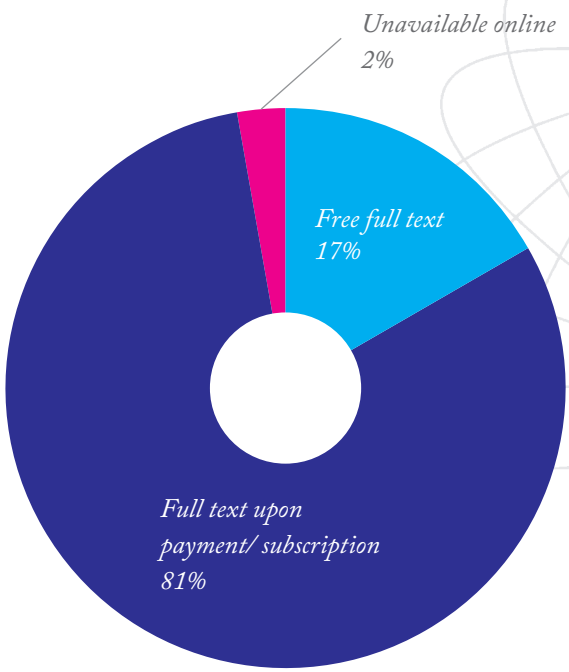
Average journal Eigenfactor score



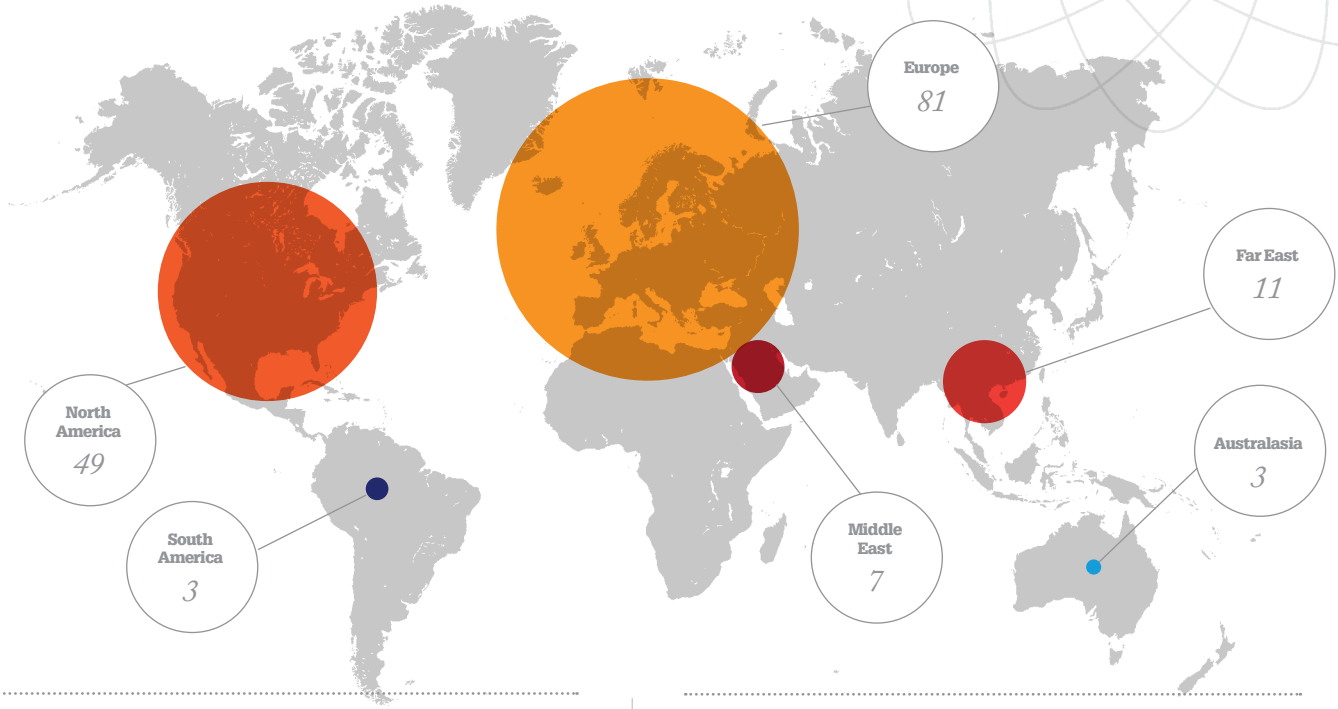
Categorization of articles



Fee or free?

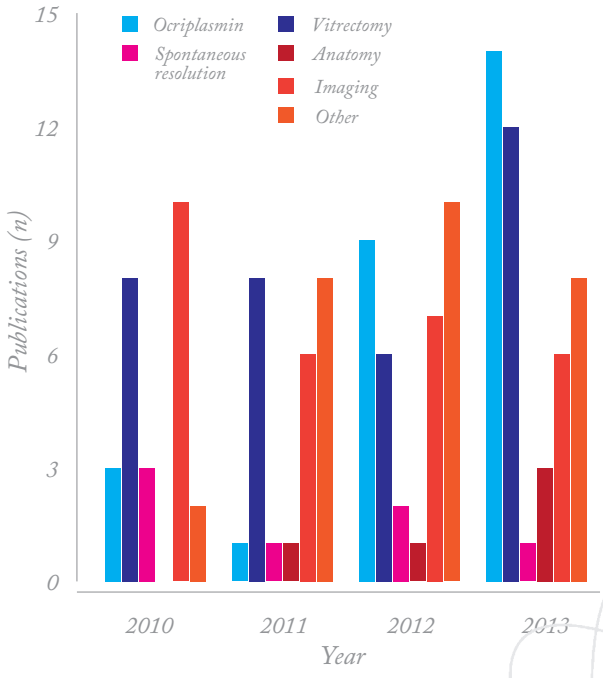


Continents where research was performed (number of publications)



Top 12 authors

Principal focus of article (full year data)



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Managing Expectations

Five tips to ensure patients' expectations of vision following cataract surgery are grounded in reality.

By Shafiq Rehman

Patients' expectations from cataract surgery have changed massively over the last twenty years. Previously, most people would undergo cataract surgery only at the point where their clouded crystalline lenses have seriously impacted their quality of life. Why? People expected a slow recovery after surgery (as was the case at the time) and any improvement in vision was gratefully received. Today, it's a different story. Surgical techniques have advanced; incision sizes are smaller, IOLs can be toric and multifocal. Lasers can automatically and reproducibly produce a 5 mm rhexis every single time. Recovery times are fast, and patient outcomes (and expectations) are substantially different to those of two decades ago – with good reason. The process has advanced so far that not only are people undergoing cataract surgery far sooner than previously, people now undergo clear lens exchange as a purely refractive procedure – cataracts don't enter into the equation.

In my practice many patients now undergo what I term "customized cataract surgery", where special emphasis is placed on achieving some post-operative independence from glasses. Technological advances have also helped. Multi-modal ocular biometry combined with corneal topography), together with scans such as corneal specular microscopy and OCT scanning are now routine parts of our patient assessments. These represent a great step forward in surgical planning, and I consider these steps to be essential in order to deliver the best possible safety and objective outcome metrics.

We now devote considerable time to the art of discussion with our patients. The rationale behind this is simple – we can get everything right, but if it isn't what the patient expected, then we will have failed in our primary objective, which is to achieve patient satisfaction. This is why (as my residents will attest), an often-repeated phrase of mine is, "We don't treat a set of eyes, we must treat the whole person".

We consider managing patient expectations as a five-part process:

1. Understand what the patient wants. First listen to the patient's concerns and aspirations. A patient with cataracts may be perfectly happy just to get rid of the visual impact of the cataract, and the issue of glasses is of low secondary importance. Equally they may nurture a strong motivation to have reduced spectacle dependency. As surgeons, we must have a full understanding of what the patient wants. Beware the patient who harbors such motivations but does not express them! It's our job to ask the right questions. When we have listened fully we move onto the next stage.
2. Reality check:before Can we realistically.... This is where a surgeon must draw on their knowledge and personal experience to asses if we can

At a Glance

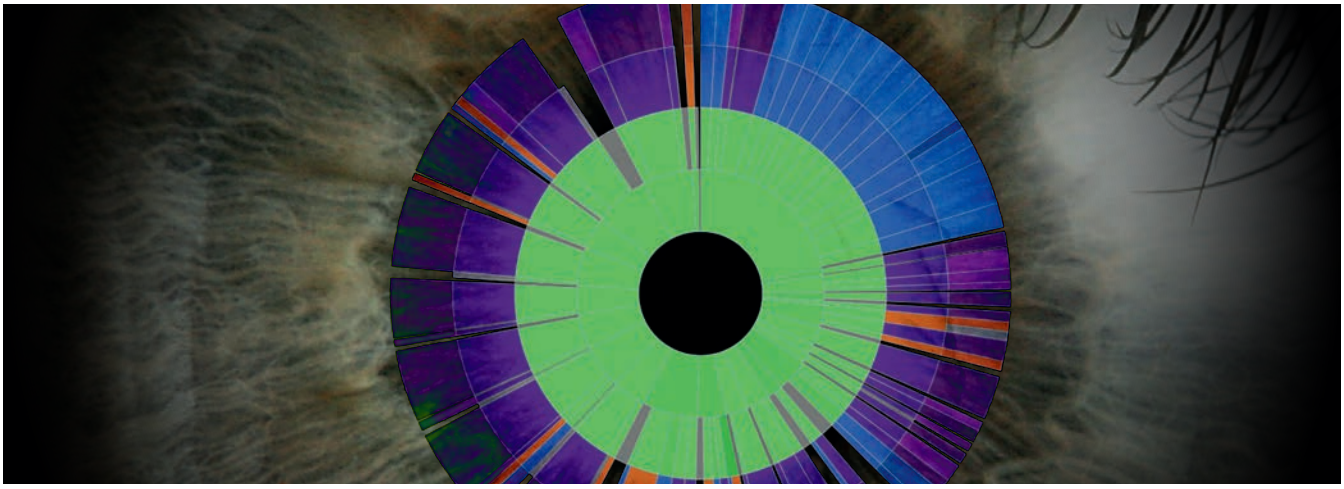
- *Many patients who need cataract excision don't know what they want from the procedure, or what's actually achievable*
- *Understanding what they want is the first step in managing their expectations – either upwards or downwards*
- *Education is paramount; patients need to be on-board with their post-operative vision before surgery*
- *Formalizing what's agreed between patient and surgeon is central to cementing this understanding*

realistically deliver what they want.. The cataract patient who just wants better sight and doesn't mind wearing glasses is clearly more readily satisfied than the patient who wishes for total spectacle freedom. The key word here is 'realistically'. If the patient's desires are unlikely to be met – even if in part – then we must move onto the third stage.

3. Negotiation. The surgeon calls on their own experience to modify the patient objectives if they are unreasonable or just unlikely to be met fully by the treatment(s) available. In my practice, I have found the vast majority of patients are pliant in their initial objectives – after all they don't know what's achievable! It may be that the patient has to accept certain areas of visual compromise – e.g. glasses may still be required for prolonged computer work, if the major desire is for sufficiently good close vision to read comfortably without glasses (or vice versa). There must be dialogue and this will hopefully lead to the fourth stage.
4. Agreement. Most of the time, I have found it possible to reach a clear, bilateral understanding of the objectives that are to be set for the planned treatment. In rare cases you might not be able to reach an agreement, in which case it may be best to advise against the planned treatment.
5. Documentation. If stage four is successful, it's imperative to document the agreement and any caveats reached, and to communicate this formally to the patient in writing. This underscores both the discussion and the eventual conclusion, helping to reinforce the clarity to the benefit of both the patient and the surgeon.

This five-stage approach to managing patient expectations has been applied across a range of scenarios in my practice, but in particular, I have found it helpful in improving patient satisfaction rates for both cataract surgery and elective vision correction treatments.

Shafiq Rehman is the Medical Director of Bettersight Advanced Eye & Vision Consultants, Leeds, UK.



How Much Statistical Expertise Does an Ophthalmologist Really Need?

Peer reviewers should insist that tricky statistical techniques are explained clearly to non-statisticians.

By Adam Jacobs

Renato Lisboa and his co-authors (1) published a paper earlier this year that examined what statistical techniques are employed in the ophthalmology literature. The Ophthalmologist reported on it at the time of publication (2), but briefly, the study authors found that a wide variety of statistical techniques are reported in the ophthalmological literature, and concluded that "readers of clinical journals in ophthalmology need to have substantial knowledge of statistical methodology to understand the results of studies published in the literature".

So just how much statistical knowledge do ophthalmologists need?

As with so many other things in medical statistics, the answer is: it depends. I really don't believe that it is essential for most clinicians to be experts in statistics, but there are certainly times when some statistical knowledge can be handy.

Insist on an adequate explanation

Do you really need to be well-acquainted with all of the statistical techniques used in the paper to understand it, as Lisboa et al. insist? It's reasonable for authors of clinical publications to assume that their audience is familiar with basic statistical tests, such as the t-test or the chi-squared test – if a reader doesn't then their ability to critically appraise most of what they're reading is in doubt.

I dispute the assumption that ophthalmologists need to understand almost all of the statistical techniques used in the literature. They shouldn't have to. I would argue that there is an onus on the authors of any publication to ensure that their papers are understandable for their intended audience. If you are writing a paper for a clinical ophthalmology journal, and you happen to have used a multivariate random parameter logistic regression model to analyze your data, you really ought to know that most of your readers won't be familiar with multivariate random parameter logistic regression models. It is up to the authors of that paper to make sure that the rationales for both the statistical test and the interpretation of its results are clearly explained, in order that a non-statistician can follow what is happening. If the authors do not do that, then it is up to the peer reviewers and journal editors to insist that it is done.

The reality of peer review

Now, of course authors of papers ought to explain complex statistical techniques, but the reality is that this doesn't always happen. Lisboa and his colleagues make the entirely valid point that it's generally not a sensible strategy to assume that a paper that has been peer-reviewed must have impeccable statistical analysis. If you don't understand the statistical methods in a paper, perhaps the peer reviewer doesn't either… and will they admit it? If they don't, then it's likely that flaws will go undetected (3). This presents a real challenge for clinicians who are not expert in statistics when faced with a (hopefully rare) paper that describes a study that employed complex statistical methods and explains them poorly in the methods section.

Of course, you may be the person

performing that research. If, for example, you were performing a mid-scale clinical trial, would you consult a statistician beforehand? This is one case where you really would have to have a statistician's comprehensive understanding of all of the appropriate statistical methods, before you even start performing the trial. Teaming up with a statistician is one of the first steps most people would take. So if you're presented with a paper that contains hard-to-interpret statistics, consider teaming up with a statistician in this context too.

A binocular understanding

One little bit of statistics that I think all ophthalmologists should be familiar with is the concept of independent data points. Many common statistical tests, such as the t-test or the chi-squared test, make the assumption that all of the data points being analyzed are independent of each other – for example, knowing the value of the data for your twentieth data point doesn't tell you anything about what your twenty-first data point might be.

In many ophthalmology studies, that assumption does not hold. In any study in which the eye, rather than the patient, is the unit of analysis, you immediately have non-independent data points if you include both eyes from a single patient. Chances are that whatever you're measuring, be it intraocular pressure or lens opacity, of a given patient's left eye will be quite similar to that of the same patient's right eye. In other words, the measurements from the two eyes are not independent.

If only a single eye is included from each patient, then this isn't a problem. But if you have more eyes than patients in a dataset, then the statistical analysis must take account of the non-independence of eyes. There are various ways to do this, such as random effects regression analysis (sometimes known as repeated measures or mixed models). But the problem of non-independence should not be ignored in the paper, and if it seems that it has been, then the results may not be trustworthy.

There are no short cuts to statistical nirvana

So what do you do if you feel your statistical knowledge could use some improvement? My top tip would be: don't expect to become an expert overnight. Learning statistics is complicated, and it is best done gradually over a long period of time. There are many statistics courses out there, many of which are very good. There are also plenty of excellent textbooks on statistics written for the non-statistician, and of course there is a plethora of information on the web.

However, don't go to a one-day course, or read a textbook with a title that claims that it will rapidly teach you all of statistics, and expect to come away from it as an expert. Read some more papers, try to engage with them, try to understand a bit more than you did before, and figure out what you still don't understand. Then when you go on your next course, or read your next bit of a textbook, try to clarify points you hadn't yet understood. Repeat as necessary.

In summary, it is not necessary for ophthalmologists to be experts in statistics, and much of the ophthalmology literature can be perfectly accessible to clinicians with a reasonably basic training in statistics. Teamwork is an essential feature of the modern research environment, and there will be times when clinicians will need to collaborate with statisticians if they want to make sense of the literature. But for those who wish to take the time to improve their statistical knowledge, there will undoubtedly be rewards in the range of papers that can be easily understood.

Adam Jacobs is Senior Principal Statistician at Premier Research, Wokingham, UK.

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Quick quiz

Which is a statistical test?
a) Chi-square test
b) Logarithms
c) Truth table
d) Slide rule

What is the most commonly used statistical measure of spread in a normally-distributed population?
a) Variance
b) Standard deviation
c) Covariance
d) Z score

In a study, vitreous samples were measured for fibronectin in dogs with vitreomacular traction and in healthy controls. How would you compare the concentrations between these two groups?
a) Chi-square test
b) Independent t-test
c) Paired t-test
d) ANOVA

The goal of a study is to compare interleukin-8 levels between patients with early AMD, advanced AMD and healthy controls. What test should you use?
a) Chi-square test
b) Independent t-test
c) Paired t-test
d) ANOVA

Answers: a, b, b, d.

Tiny Pulses, Big Progress

Mark Latina recounts his story of the invention of selective laser trabeculoplasty (SLT).

What led you into ophthalmology?

I majored in chemistry and decided I would go to medical school. I thought I wanted to become a nephrologist. I traveled widely as a medical student: nephrology in San Diego, hematology at Tufts University, neurology in Guy's Hospital London, and ophthalmology in Massachusetts Eye and Ear Infirmary. At that time, the ophthalmology department included laryngology and dermatology.

Two months into my internship I realized it wasn't for me. I felt like an over-glorified secretary and triage nurse. All I seemed to be doing was writing orders and other administrative work. I liked ophthalmology, I liked technology, and I thought I'd like optics. I decided that it would be more interesting.

Can you tell us about your work with targeting melanin with lasers?

I was at the point when my research grant was ready for renewal, I suggested we target melanin – as it is present throughout the trabecular meshwork. It just so happened that I was working in the department of dermatology at the time, and they were developing lasers for hair removal. It inspired me to consider whether lasers could target melanin within ocular structures; I thought that if we took a pulse laser and shortened the pulse duration to match it to the relaxation time of the melanin granule, we could target the melanin in the cell without affecting any surrounding cells or tissue structures.

How did you put your theory to the test?

We used cell culture to begin with, just to check the technology and to see if we could do it. I created a system where we cultured pigmented trabecular meshwork cells that we incubated with melanin, and mixed them in with non-pigmented cells. We were able to demonstrate that with certain laser pulse durations – ideally with the 532 nm Q-switched laser – you could target the pigmented trabecular meshwork cell, whereas the non-pigmented trabecular meshwork cell right next to it would be totally unaffected. It worked well, and we published several papers based on our studies.

"Companies would be much more interested if I had a glaucoma treatment, rather than a glaucoma model"

So did you immediately seek medical applications?

That went slowly! I went to several companies like Alcon and said, "Look I think I can develop this model that targets the trabecular meshwork and actually creates glaucoma". They weren't interested. It forced me to rethink my approach. I realized that maybe we don't need to coagulate the trabecular meshwork to do trabeculoplasty and reduce the intraocular pressure (IOP). I thought that you might be able target those cells and get the same reduction of IOP by a creating a biological response in the meshwork. Companies would be much more interested if I had a glaucoma treatment, rather than a glaucoma model. So I turned the whole thrust of our research in the opposite direction.

At that stage did you go in vivo?

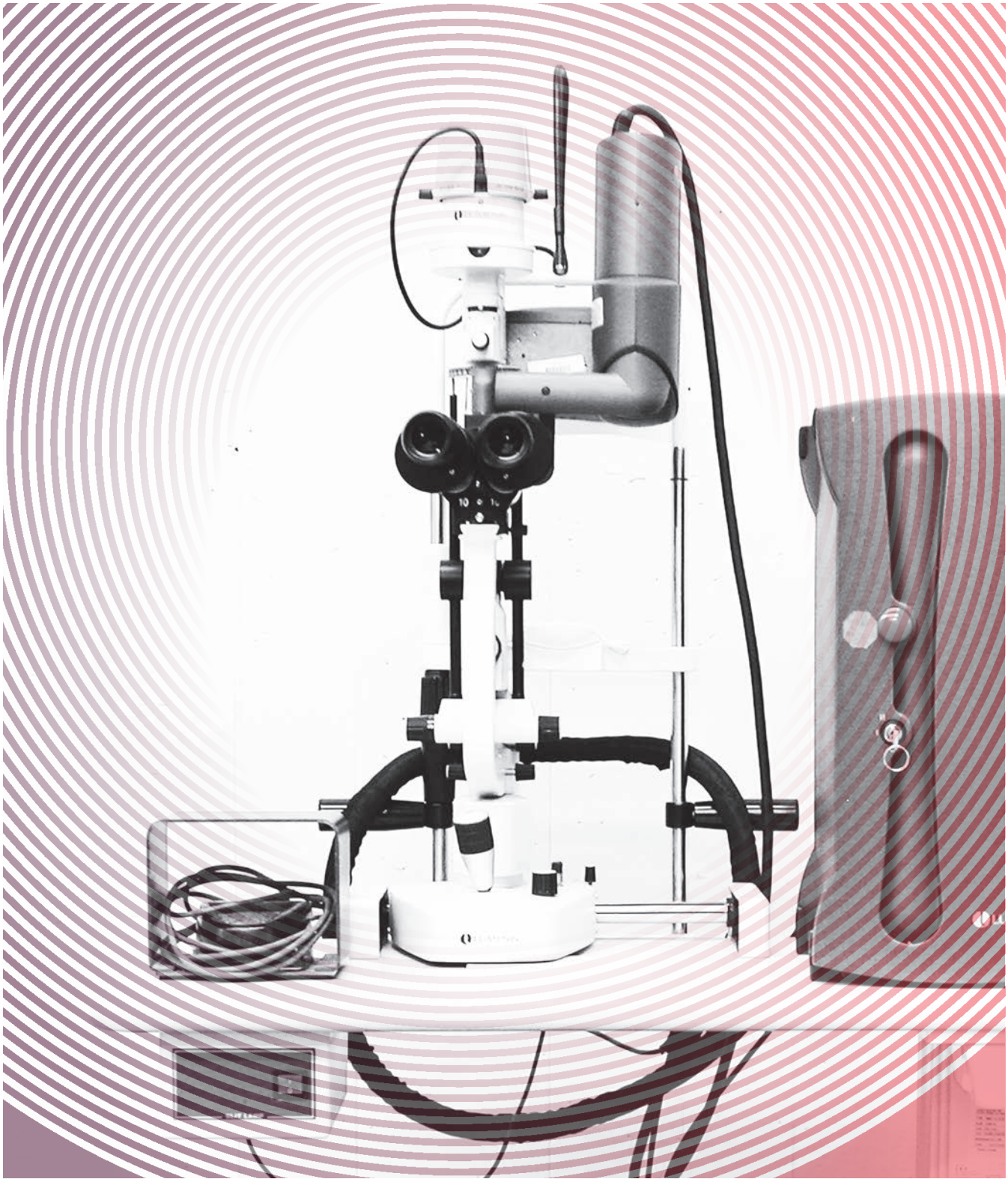
After completing the *in vitro* cell culture studies, we decided to try this approach in monkeys, even though there was no good animal model for glaucoma. We were just about to publish our *in-vitro* results when I realized that it would be better to patent the technology before publishing!

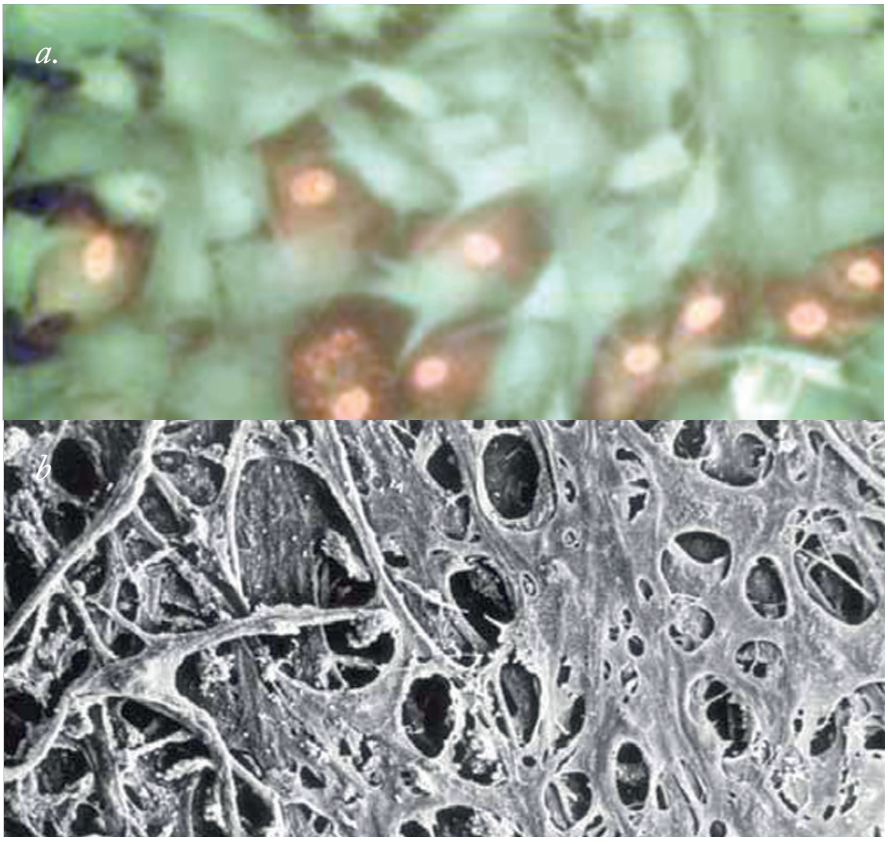
So you though that this cell targeting approach could be a treatment, but you didn't really have any evidence?

We were pretty sure we could target the cells, and we assumed that we didn't need to photocoagulate anything: photocoagulation is like dropping an atomic bomb to kill a fly. I thought that if we could just target the cell and turn on the entire biological response system, we should get a similar pressure reduction without the destructive damage to the trabecular meshwork that photocoagulation produces. Our approach would also show that IOP lowering following laser is not a mechanical response, but a biological one.

How did you commercialize SLT?

I presented our cell culture research to Jim Hobart, who was then the head of Coherent Medical Group. At the time, I had also developed a laser procedure to perform filtration surgery using a technique I invented called laser gonioscopic ab-interno laser sclerostomy. However, for various reasons the technique wasn't successful, and the company that I had developed the laser with had little experience in ophthalmology. I therefore approached Coherent Laser (now Lumenis) which was the largest and most successful ophthalmic laser company in the world; Hobart agreed to fund the project and





Box. a. SLT-mediated selective destruction of melanin-laden trabecular meshwork cells (red). b. Electron micrograph of the post-SLT treatment trabecular meshwork: minimal structural damage is visible.

"Ophthalmologists have finally accepted that it's safe, it's effective – and maybe more effective than argon laser"

we set out to build a prototype laser. He understood the concept; he said yes let's look into it and we'll build you a laser suitable for *in vivo* monkey studies. If it was successful, the company would have rights of first refusal for licensing the technology.

What came next?

We first demonstrated selective targeting in monkeys. I then tried to actually create glaucoma in the monkeys. Argon laser-induced scarring of the trabecular meshwork typically results in significant elevations in IOP – it's called the Gasterland monkey model for glaucoma. But with our laser, we treated, and re-treated and re-treated. Whatever I did, I just couldn't get the monkeys to develop glaucoma. We did the pathology and saw the meshwork looked quite normal; there was some depletion of pigmented cells, but overall it was healthy. That led us to believe it was relatively safe. So we had no choice, we had to build the laser to treat a patient.

Was that done in the US?

No, we took it to Mexico. The first patients we saw all had rather severe open angle glaucoma. I treated their trabecular meshwork in a manner somewhat similar to performing argon laser trabeculoplasty but using the laser parameters that I figured out based on our cell culture results.

What did you expect to see and what did you actually see in the first patient?

We didn't know what to expect; we had just no idea. But we lasered the patients' eyes using low power and we found that the day after treatment, almost all the patients had a 50 percent reduction in pressure.

We thought this was unbelievable. We had patients with pre-treatment pressures of 40 mmHg and they came back after treatment with pressures of 20 mmHg. These were people with bad eyes, some with end stage disease!

Would you have dared hope for those results?

We couldn't have even imagined that result. So, at that point the project took off. I'll never forget when we went to file for an FDA IDE (Investigational Device Exemption) and all the work and studies that followed.

There must have been an incredible amount of trepidation before you treated that first patient?

Yes you're right; we had no idea really how it would turn out. We could make the patient better or we could make the patient worse. Before treating the first patient, based on our monkey studies, I felt that the procedure was likely to be relatively safe.

You knew it was safe but you didn't know if it was going to be effective.

Yes, if there had been a huge pressure elevation or the development of intractable

glaucoma, the whole thing would have collapsed and that would have been the end of it.

So what was the reaction amongst your peers?

People were interested, but our clinical trials were being conducted on eyes that were on maximum tolerated medical therapy, plus the protocol we set up was very conservative. Despite that, we were still getting good – 25 percent – pressure reductions in those patients.

Did you come up against skepticism?

I think there'll always be skeptics. I'll be honest with you, it's taken 10 years because we would constantly hear "What's the difference with what you are achieving, you're still getting equivalent pressure reductions to argon laser trabeculoplasty?" The challenge was convincing them that there was no damage to the meshwork: you'll be able to re-treat them because it's a much gentler procedure, and more biologically specific than the argon laser, as you're not getting its complications – you're not producing peripheral anterior synechiae and you're not scarring the trabecular meshwork.

After a lot of development work with Lumenis, we were ready for the FDA… but they wouldn't let us perform the trial with primary therapy. So we had to go back and do another multi-center clinical trial looking at selective laser trabeculoplasty (SLT) as primary therapy. Now that's its main role Ophthalmologists have finally accepted that it's safe, it's effective – and maybe more effective than argon laser – plus, it doesn't cause any damage to the outflow pathway, the trabecular meshwork. Patients do very well post-operatively, and there's minimal inflammatory response.

Do you think the regulatory process is just a barrier?

I think the FDA's regulatory process plays an important role but they can also be a significant impediment to progress. The FDA's role should be simple – show that a product or medication is relatively safe and has demonstrated efficacy for its intended purpose. Let the markets and physicians decide if the new therapy is going to be successful. There are just too many requirements and unnecessary concern about stuff that's already been demonstrated. Duplication is a huge cost for companies and it's basically holding back improvements in healthcare.

Commercial Adoption of Oraya Therapy Grows as Wet AMD Treatment Option — Second NHS Location Announced

Three-Year Data from INTREPID Study for Oraya Therapeutics Shows Favourable Safety Profile for Non-invasive Wet AMD Therapy — No Significant Difference in Vision Outcomes Compared to Anti-VEGF Injections Alone.

Product Profile

Oraya Therapy uses low-energy, highly targeted X-rays to treat wet AMD and is intended as a one-time procedure with the potential to maintain vision while reducing the required number of anti-VEGF injections into the eye. Full results of the 3-year safety evaluation from Oraya's INTREPID study were presented at EURETINA, with physicians from three countries discussing their clinical experiences. Also announced, two NHS Foundation Trust centres have installed the technology: Royal Hallamshire Trust in Sheffield in July, and Heart of England in Birmingham in September. To date, 100+ patients have been treated with the Oraya Therapy available in eight centres across Germany, Switzerland, and the UK.

Oraya Therapeutics, Inc. develops innovative and non-invasive therapies for diseases of the eye. Founded in 2007, investors include Essex Woodlands Health Ventures, Domain Associates, and Synergy Life Science Partners. For more, visit www.orayainc.com

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Sitting Down With…
Charles McGhee, Director of the New Zealand National Eye Centre, University of Auckland, New Zealand.

Tell us about your move from Dundee, Scotland to Auckland. You took a whole department..?

I moved to New Zealand 15 years ago. Dundee was a progressive university, long well-known for its clinical research and exceptional surgical teaching. About eight people worked with me whilst I was professor in the university department (now expertly headed by Carrie MacEwan) and four of us (plus two colleagues from England) relocated. Unfortunately there wasn't a lot of basic research funding in Scotland at that time. However, I did a lot of refractive surgery in the 1990s and we reinvested all income from that into the department – the laser research unit was, in effect, run as a quasi-public/private setup… but I didn't believe that was a sustainable way of paying for research.

Ultimately, I decided to move to New Zealand for a number of reasons. The university of Auckland offered the dual challenge of setting up a new university department and leading the public clinical ophthalmology service. In support, they offered to: fund six staff; contribute around NZ $2.5 million in start-up funding; create two large laboratories; provide three clinical research areas and several offices. Although the university unit had only two staff at the time, the public hospital's ophthalmology department was well established with 25 consultants. The University's investment enabled us to create a world-class ocular imaging unit, establish laboratory and clinical teams focused on corneal and anterior segment diseases, and support clinical and research fellowships. Initially we didn't need to worry about grants to fund key projects – although we've generated over NZ $20 million for research in intervening years. There's actually less research funding available in New Zealand than in the UK, but as always, there's a fair bit of serendipity, and we have greatly benefitted from New Zealanders' philanthropy!

Quite a journey, though…

It is literally the end of the Earth. A common phrase you hear from New Zealand researchers is the "tyranny of distance"; to get from my home in New Zealand to a hotel in London takes 29 hours. You get used to it. We now have a team of 60 staff and post-graduate students, and have grown from one professor to three professors and five associate professors and a cosmopolitan team representing 16 countries.

"We're trying to construct a whole biological cornea in the lab"

What's the next big thing in ophthalmology?

Two words: stem cells. Many centers, including ours are working on corneal endothelial, stromal and epithelial stem cells, however, Shigeru Kinoshita is the man of the moment in corneal endothelium – he's developed this novel, potentially topical, drug based on a ROCK inhibitor which may allow the corneal endothelium to regenerate in certain circumstances. Others including Donald Tan are working on limbal stem cells and regeneration of the corneal surface.

And this is what you're actively involved in now?

Our research covers everything from ocular imaging, genetics, cell biology, therapeutics, drug development, and clinical areas of: external eye disease, transplantation, cataract surgery, glaucoma and neuro-ophthalmology. Stem-like cells are a strong focus. We culture holoclones from all three corneal cellular layers, and we are increasingly performing *ex-vivo* expansion of limbal cells for human transplantation – two in the last three months – for limbal stem cell failure. We take a tiny biopsy of corneal epithelial "stem" cells from the opposite eye (or a living donor) then culture them in the lab for three weeks on amniotic membrane. Once we remove the superficial corneal scarring, we transplant the donor epithelial cells to resurface the eye. Obviously, patients need to be immunosuppressed if the cells aren't their own. It's still early days – we have only performed nine cases so far – but we already have reasonable success. A couple of patients thought to be permanently blinded by corneal disease are now driving cars!

So stem cells are your research group's future?

It's certainly a key part of it. We're trying to construct a whole biological cornea in the lab – a biomechanical matrix that we can seed with epithelium, keratocytes and endothelium. In our team Dipika Patel is using biological materials to develop a substitute "corneal" matrix, Trevor Sherwin is using induced pluripotent stem cells to regenerate tissue, and Colin Green is using a connexin antisense technique, Nexagon, to modify inflammation and healing in ocular surface damage. In fact Colin's laboratory bench-to-bedside approach has led to a number of spin-off drug patents and US $60 million in investment. Human studies of a manufactured biological cornea are probably 10 years away, but in theory, if the various components work, we might be looking at a healthy replacement for layers of – or the whole – cornea in the foreseeable future.

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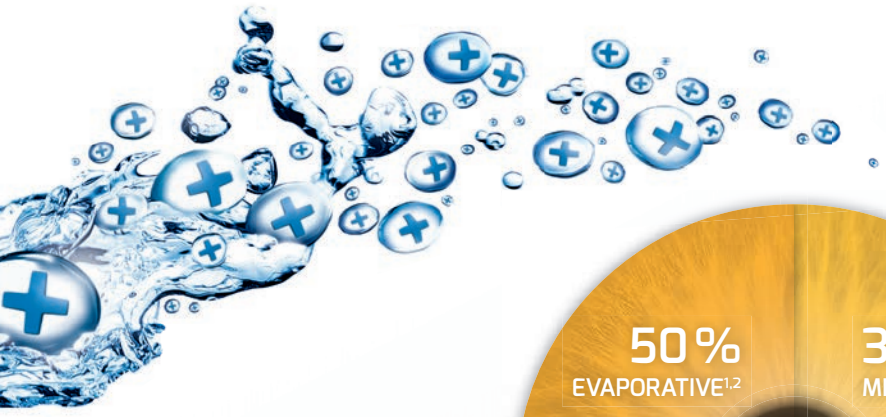
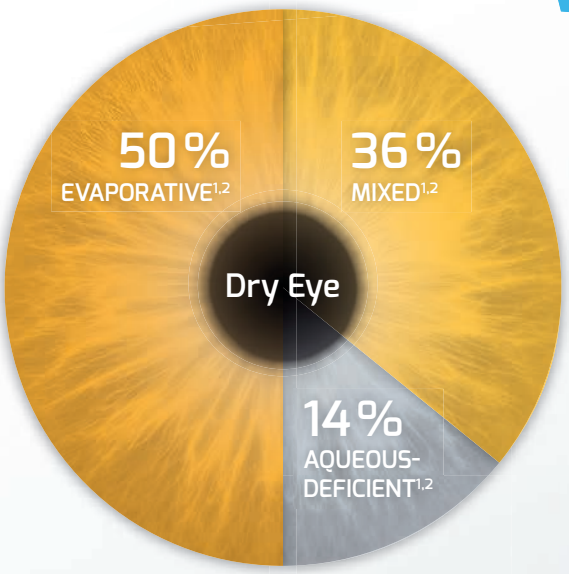


In 86 % of dry eye patients increased evaporation is involved in dry eye symptoms.[1]



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