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Image of the Month

Seeing by Touch

This image shows sensory artwork of a red blood cell from the Moorfields Eye Hospital BlindArt Collection. Mariya Moosajee, consultant ophthalmologist and researcher at Moorfields, incorporated pieces from the collection into her recent "Science of Sight" exhibition at the Science Museum in London, UK. Moosajee said: "Art shouldn't just be something people can experience only through vision, but also through touch and smell." More information on Science of Sight can be viewed here: http://bit.ly/ScienceOfSight

Credit: Moorfields Eye Hospital BlindArt Collection

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

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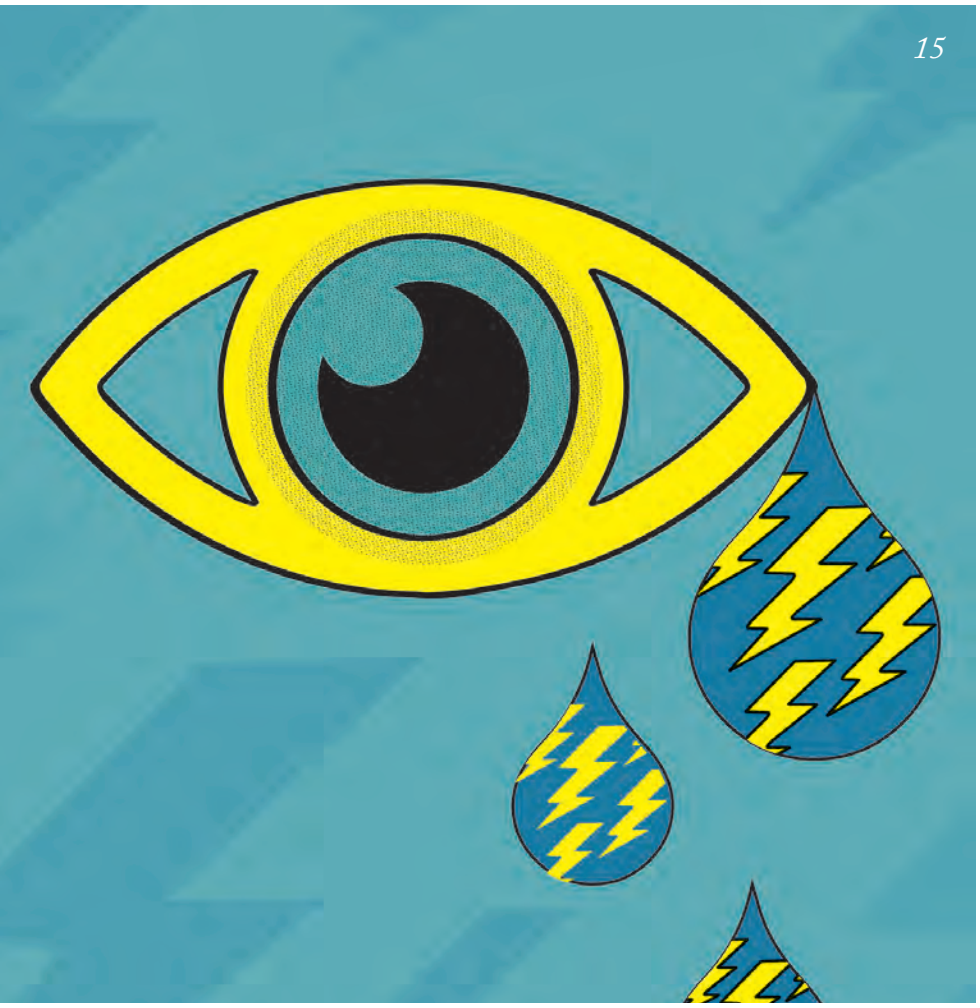

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17 **Roy Rubinfeld**, who is actively developing a methodology for transepithelial CXL, explains why it's time drop the epi-off versus epi-on CXL debate.

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In late September, in a restaurant called Botafumeiro, Adnan Tufail, David Johnston and Javier Zarranz-Ventura gathered together to talk about the life and work of one man: the late Rob Johnston. The information age of ophthalmology has come sooner thanks to Rob's vision and insight – but there's more to the man than Medisoft alone.

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"Cataract Surgery: Telling It Like It Is" is a highly successful and informative meeting for cataract surgeons. Robert Osher, the man behind the meeting, shares his story on how – and why – he started the meeting, and what's needed to attract attendees.

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C. Andrés Benatti tackles the dogma of 'brain drain,' arguing that the worldwide movement of doctors and researchers is no longer one-way, and the bidirectional circulation of knowledge and experience improves medicine.

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Founder and Medical Director of Matossian Eye Associates, Mercer County, New Jersey, and Bucks County, Pennsylvania, USA.

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Our Rob

Rob Johnston made a real difference in his lifetime – and his story is well worth telling.

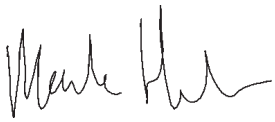
It's rare that I record a dinner conversation and turn it into an article. For one thing, restaurants are usually busy and noisy – especially when there's an ophthalmology conference. But on the first day of this year's EURETINA, I nevertheless found myself in the glorious (and fully-booked) Botafumeiro seafood restaurant in Barcelona, interviewing Adnan Tufail, Javier Zarranz-Ventura and David Johnston. I was hoping to relive a slightly more lubricated conversation I'd had with Javier and Adnan in the Baltimore Marriott Inner Harbor during ARVO in May, but this time, "on the record." In short, we were there to talk about the late Rob Johnston.

I never met Rob, but I was well aware of Medisoft (the EMR company he'd started with his brother, David) and the value of the data and insight it provides. But in the Marriott bar (in between trying to use my graduate NUS Extra card to try and obtain a student discount on an eyewateringly expensive round of drinks, and consuming said drinks) I found myself learning more from two surgeons who knew him well – and clearly loved the man. I learned about his personality, his professionalism and what his work over the years has done (and will continue to do) for ophthalmology.

Adnan explained that Rob had built something that has laid the foundations of functional, valuable big data in ophthalmology. Unlike many other EMRs, Medisoft was designed not for billing but for quality outcome audits, so the quality and structure of the data within was ideal for training artificial intelligence algorithms. Meanwhile, Javier told me about the man himself: kind, warm, generous, and intelligent. He also spoke of the impact of Rob's death after a long on–off battle with cancer – both on him personally and the ophthalmology community in general.

Rob's story is definitely worth sharing – you'll find the result of our restaurant conversation and more from page 20. In both Baltimore and Barcelona, we raised our glasses to toast his life and work. I hope after reading his story, you may feel the need to do the same.

Mark Hillen
Editor



Upfront

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

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

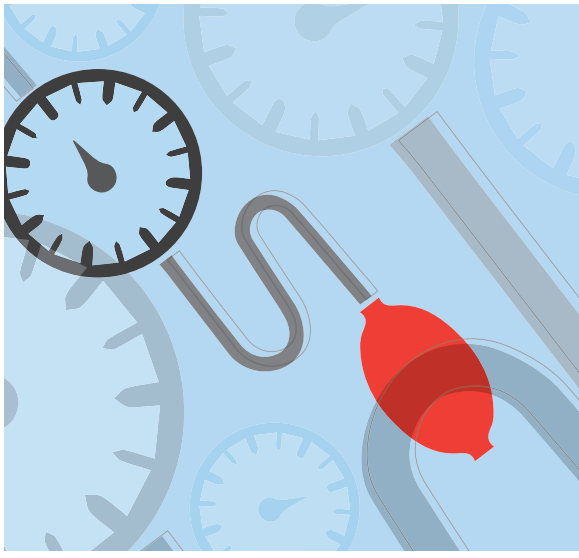
Feeling the Pressure

Is a low-cost pressure-sensing contact lens the key to 24-hour IOP measurements?

IOP is known to fluctuate over the course of the day and under different physiological conditions, meaning that single office measurements do not represent the full story. When it comes to patients with glaucoma, a true 24-hour IOP profile could help improve the monitoring of disease status and progression – and even select the most appropriate treatment. But that's easier said than done. Taking up the challenge, a multicenter team from the University of Liverpool and St Paul's Eye Unit, Liverpool, and Moorfield's Eye Hospital, London, UK, have been working on a solution: a low-cost contact lens tonometer (1).

The hydrogel contact lens (Figure 1) contains a patented pressure sensor built into a 'bridge' portion of the contact lens that can factor in mechanical behavior of the cornea and the sclera. It also includes a telemetry system that transmits IOP measurements to an external instrument. The sensor lies on the back portion of the lens, and sits upon the surface of the eye; IOP measurements are collected during reactive deformation in the device, when the subject's eyes are closed during blinking or sleeping (2).

But does it work? In a recent pilot study, 12 volunteers wore the contact lens for one hour rather than 24, during which time the researchers found that the device could track IOP changes whilst causing minimal discomfort (2). Further clinical studies are on the horizon, along with refinement of manufacturing techniques in a bid to commercialize the device.



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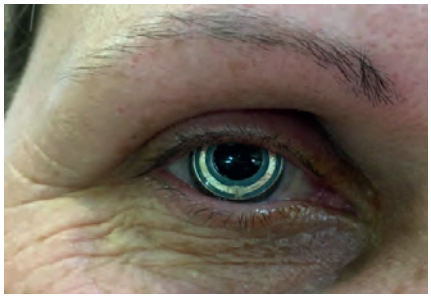

Figure 1. The 24-hour IOP-sensing contact lens device. Credit: University of Liverpool.

Polymers and PCO: the IOL Material Lowdown

When you have a big dataset, what was once suspected can now be confirmed

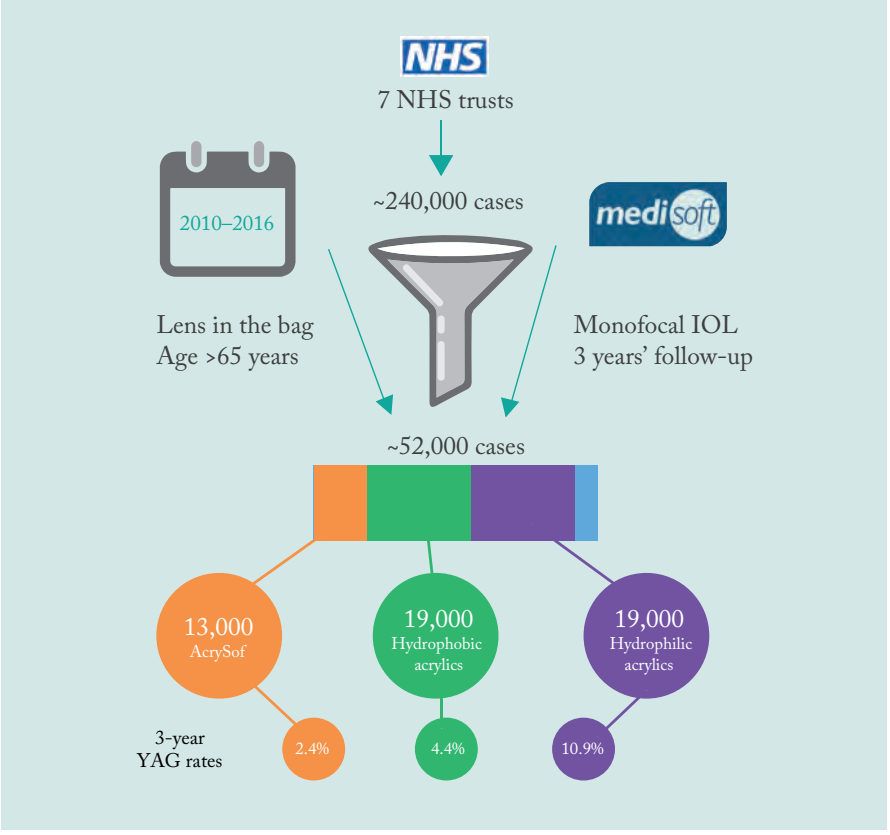

Figure 1. Study design and key results from Ursell et al.'s three-year retrospective database analysis of YAG laser capsulotomy rates for the treatment of PCO following cataract surgery. The main influence on PCO rates was the IOL biomaterial.

Some doctors view electronic medical records (EMR) systems simply as "admin" that gets in the way of interacting with their patient rather than actually helping them. Sometimes it helps to see the value of EMRs by stepping back and looking at the bigger picture. When you have comprehensive, high-quality real-world data available, it enables faint suspicions and "hints of a signal" to be tied down and defined as fact or fallacy. And that's exactly what Ursell and colleagues have managed to do with a three-year retrospective database analysis of YAG laser capsulotomy rates for the treatment of posterior capsular opacification (PCO) following cataract surgery that involved seven NHS trusts in the UK (1).

"PCO is something that happens a few years after surgery and it's thought to be related to the IOL polymer. We wanted to see whether this was the case with real-world data," explains consultant ophthalmic surgeon and first author of the study, Paul Ursell. "[The Medisoft database] is a comprehensive patient record of everything that happens at biometry, vision, surgery, IOL. When the patient comes back to the clinic again, the same data is recorded – and it also records when they had a YAG laser to treat PCO."

"One of the problems with retrospective analysis of databases has been whether the patient actually did come back to you (and didn't go somewhere else for the YAG laser procedure) – and whether it was recorded," says Ursell. The group got around this problem by looking for UK hospitals that 1) used the Medisoft database, and 2) were the only people in the region with a YAG laser – "If a patient did develop PCO, they came back to the same hospital for treatment, rather than leaking out to other units." The team found seven units in the UK and obtained all of their data from 2010 to 2016 – 240,000 thousand cases in all. The cases examined were restricted to monofocal IOLs placed in the bag with three years' worth of follow-up in patients aged over 65 years, i.e. 2010–2013 data. "That whittled it down to 52,000 cases. Of that, we had 13,000 AcrySof, 19,000 hydrophilic acrylic, and about 19,000 hydrophobic acrylic IOLs in there." But what did they find?

"When we looked at three years' worth of data, patients receiving AcrySof lenses had a 2.4 percent chance of a YAG laser capsulotomy, hydrophobic acrylics had a 4.4 percent chance, and hydrophilic acrylics, a 10.9 percent chance. This shows that the overwhelming factor influencing whether a patient having YAG after surgery is the IOL biomaterial." Ursell adds, "There were some other incidental findings: complications during surgery increases the chance of undergoing YAG laser capsulotomy (but in very low numbers). We removed patients under the age of 65 years – but age hardly had any effect at all, which I was very surprised about." The take-home message? "The main thing affecting PCO after cataract surgery is the IOL polymer biomaterial and AcrySof seems to perform better than hydrophobic acrylics and certain hydrophilic acrylics," concludes Ursell.

View the interview video with Paul Ursell online at: top.txp.to/issues/1117/202

Reference

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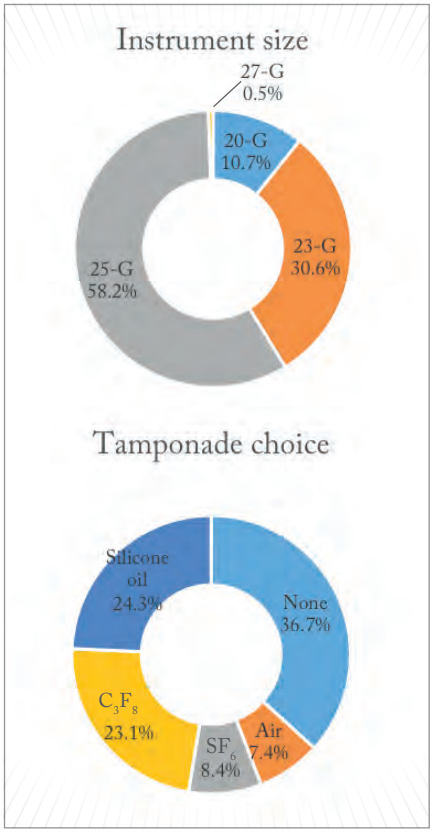

Figure 1. Vitrectomy instrument size (a) and tamponade choice (b) made by the 14 surgeons involved in the study.

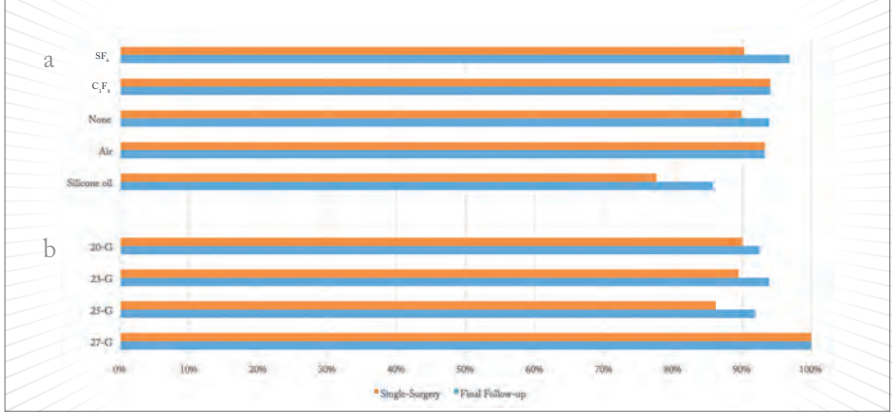

Figure 2. Anatomical success (retinal reattachment) by tamponade choice (a) and instrument gauge (b).

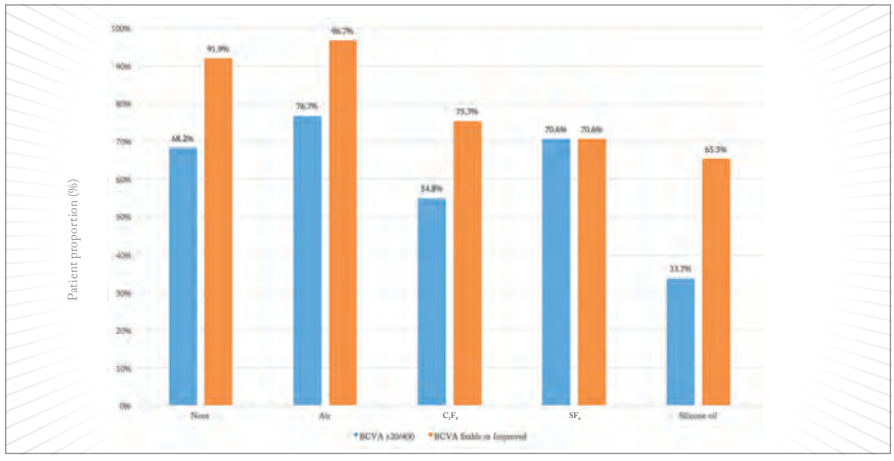

Figure 3. Visual outcomes by tamponade choice

Does Size Really Matter?

A (much) closer look at vitrectomy instrument size

Diabetic retinopathy (DR) can be treated: the introduction of panretinal photocoagulation and anti-VEGF therapy over the last few years have transformed patients' visual outcomes. But many people with DR still go on to experience vision loss and blindness, partly because of complications such as tractional retinal detachment (TRD). The treatment for TRD is pars plana vitrectomy (PPV) – perhaps one of the most complex vitreoretinal surgical procedures. Fortunate then that vitrectomy systems have undergone a great deal of development over the last decade – better fluidics, faster cut rates, modified tips and ever-smaller gauge instrumentation: 20-G gave way to 23-G; 23-G gave way to 25-G, and we now have 27-G instruments. As the gauge increases (and the instruments get smaller in diameter), in theory, so does retinal stability and the ease of manipulation of the instruments. But there's been no direct comparisons of visual and anatomical outcomes of PPV for TRD repair using different gauge instruments – until now (1).

The study used an outpatient chart and operative record review from a large public eye center – the Los Angeles + University of Southern California (LA + USC) Medical Center – over a five-year period. In total, 403 eyes (from 359 patients) with diabetic TRD were included in the analysis. All patients had vitrectomy performed by either an Alcon Accurus (n=27) or an Alcon Constellation (n=376) machine, but surgical approach and choice of tamponade were based on the surgeon's preference at the time of surgery. Baseline visual, demographic and hemoglobin A1C levels were all collected, and follow-up ranged from 0.1 to 66.9 months, averaging out at 17.5 months. The spread of instrument size and tamponade agent used during surgery is detailed in Figure 1.

The outcomes? Retinal reattachment rates were good, with the vast majority of patients experiencing either improved (56.3 percent) or stable (23.8 percent) vision following surgery. Did gauge girth make a difference to the success rates? Not really. The study authors wrote: "Smaller gauge vitrectomy systems were found to have similar outcomes (p=0.73) to 20-G instrumentation" (Figure 2a).

What did make a difference was the tamponade used. Patients who received silicone oil had significantly lower reattachments rates (p=0.013, Figure 2b) and significantly higher rates of vision loss (p<0.0001; Figure 3) – although these cases tended to be more challenging, as they were more likely to have concurrent rhegmatogenous and macula-involving detachments.

So the answer to the age-old question of does size matter? According to this study, not as much as what you choose to do with it – "it" being the tamponade choice.

Reference

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Evidence for CME Prevention

As the full PREMED study results are released, do surgeons now have an answer on how best to prevent cystoid macular edema after cataract surgery?

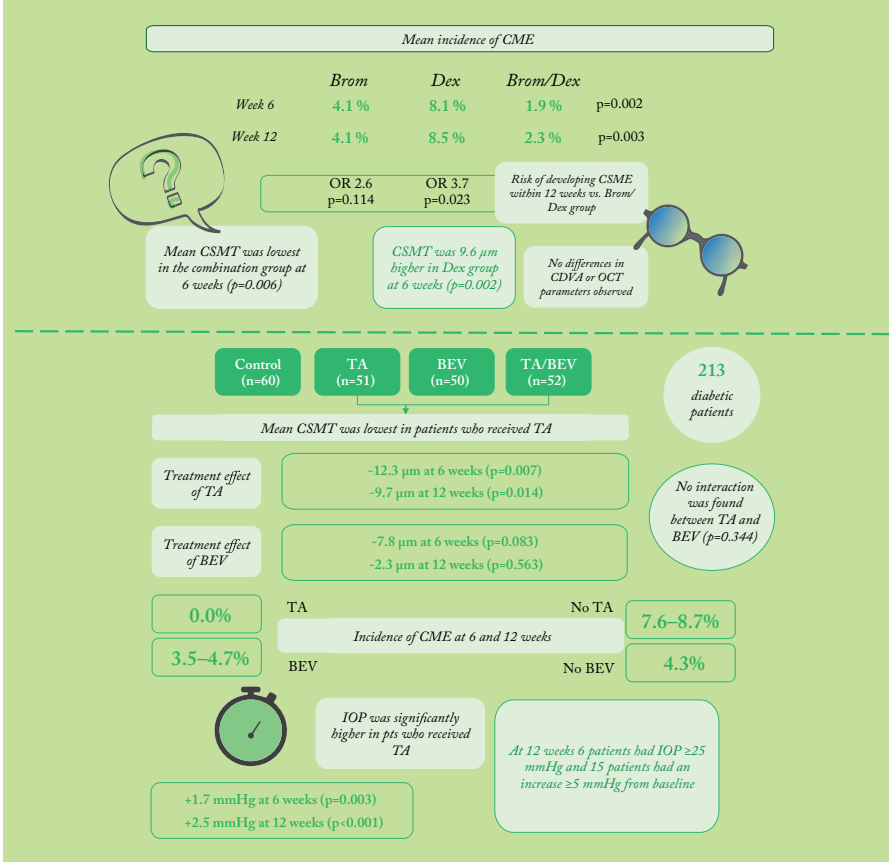
Since 2010, the "prevention of macular edema after cataract surgery" (PREMED) study has been running across 12 European centers to address the lack of consensus on the most effective anti-inflammatory regimen. Even the AAO and the ASCRS have published opposing views on the subject:

- In their 2015 report, the AAO wrote: "There is a lack of level 1 evidence that supports the long-term visual benefit of non-steroidal anti-inflammatory therapy when applied solely or in combination with corticosteroid therapy" (1).
- A 2016 report from the ASCRS Cataract Clinical Committee and the American Glaucoma Society concluded: "Whether used alone, synergistically with steroids, or for specific high-risk eyes, the efficacy of NSAIDs is compelling" (2).

So what is the best approach? On October 8, 2017, full results of the PREMED study – which included over 1,000 patients with and without diabetes who underwent phacoemulsification cataract surgery – were presented at the ESCRS annual meeting in Lisbon, Portugal, by Rudy Nuijts and Laura Wielders of Maastricht University Medical Center in The Netherlands.

Nuijts presented data from 914 patients without diabetes who were randomized to topical bromfenac, topical dexamethasone, or a combination of both. Wielders presented data from 213 patients with diabetes who were randomized to receive intravitreal triamcinolone acetonide, bevacizumab, or a combination of both; all diabetic patients also received topical bromfenac and dexamethasone. Patients were followed up postoperatively at six and 12 weeks. We summarize the studies and key results in the infographic above.

The main conclusions? For non-diabetic patients, a combination regimen of topical bromfenac (0.09%) and dexamethasone (0.1%) was associated with a lower risk of developing CME after cataract surgery (3). In patients with diabetes, both a single 40 mg triamcinolone injection, and the bromfenac and dexamethasone regimen, were found to be effective, with intravitreal bevacizumab having no significant effect (4). However, as IOP was significantly increased in patients who had received triamcinolone, Wielders concluded, "the risk of developing CME should be carefully weighed against the risk of developing an increased IOP" (4). Nuijts commented that the findings from the study offer "the foundation to draw up concrete evidence-based recommendations to prevent the occurrence of CME after cataract surgery in patients with and without diabetes" (3).



BEV, bevacizumab; Brom, bromfenac; CME, cystoid macular edema; CSME, clinically significant macular edema; CSMT, central subfield macular thickness; Dex, dexamethasone; OR, odds ratio; TA, triamcinolone.

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Retinal T-Regimen

Could retinopathies one day be treated by boosting immunosuppressive Treg cells in the retina?

The eye enjoys a certain degree of immune privilege; the efficient blood-retina barrier, which prevents free movement of cells into and out of the eye, and ocular inhibition of immune-competent cells dampen local immune and inflammatory responses, and protect ocular functioning and vision (1). However, this ocular immune privilege is not fully understood, and thoughts are changing on the concept – with mounting evidence suggesting that inflammation may play a critical role in neovascular retinopathies (2–4). Jennifer Wilkinson-Berka of Monash University, Melbourne, wanted to find out more.

"I was interested in how inflammation contributes to the development of neovascular retinopathies, such as retinopathy of prematurity (ROP) and, in particular, if the adaptive immune system influences the innate immune system in the retina," says Wilkinson-Berka. Using a characterized model of ROP in mice – oxygen-induced retinopathy (OIR) – the team set out to examine their hypothesis that Foxp3+ T regulatory cells (Tregs) might be recruited to the retina and that their abundance might decrease with the development of neovascularization (5). And the hypothesis rang true: Tregs were found to penetrate damaged retina in ROP (Figure 1). At postnatal day 13 (P13) – after neonatal mice were exposed to hyperoxia for 12 days – the numbers of Tregs was significantly higher in the inner retina compared with controls ($p<0.001$). By P18 – when there was extensive neovascularization and vascular leakage – the numbers of Tregs had reduced in the inner retina, and were visible within blood vessels. The team also found increased numbers of Tregs in lymphoid organs at P13 in OIR mice and saw a decrease in numbers at P18.

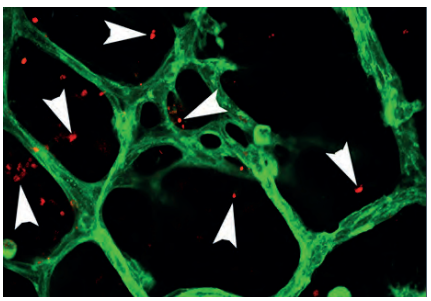

Figure 1. Confocal microscopy image of a flatmount image showing Treg cells (red; located with white arrows) in the inner retina. The mouse model used, Foxp3rfp, was engineered to express red fluorescent protein (RFP) specifically in Tregs under the control of the Fox3p promoter. Isolectin was labeled in green to show the blood vessels.
Credit: J Wilkinson-Berka et al.,

Another key finding was that the team could modulate the Tregs – and help protect against disease. "We found that boosting the number of Tregs – and their immunosuppressive power – reduced severe vascular pathology in the retina," says Wilkinson-Berka. Using a monoclonal antibody against IL-2 and adoptive transfer of Tregs to expand numbers of Tregs in the neonatal OIR mice, they found that retinal vaso-obliteration and neovascularization were reduced at both P12 and P18. Tregs were also shown to alter microglia activation, and in vitro studies confirmed that they reduced the numbers of pro-inflammatory mediators released by microglia.

"It was interesting to find that Tregs are naturally increased in the retina and lymphoid organs in response to acute tissue hypoxia in ROP, and then dramatically reduced when retinal neovascularization is established," says Wilkinson-Berka. "It turned out to be a key piece of information for the treatment strategies we used, as it was important to prevent the decline in Treg numbers to reduce damage to the retinal microvasculature as well as the activation of retinal microglia."

Wilkinson-Berka hopes that their research will lead to an awareness of the contribution of the adaptive immune system to neovascular retinopathies. Could a new treatment approach be on the horizon? Wilkinson-Berka is hopeful: "Our next step is to develop immunotherapies that are safe, well-tolerated and effective in patients with neovascular retinopathies. My laboratory is very excited about the potential of our work to reduce the health burden of these sight-threatening retinal diseases."

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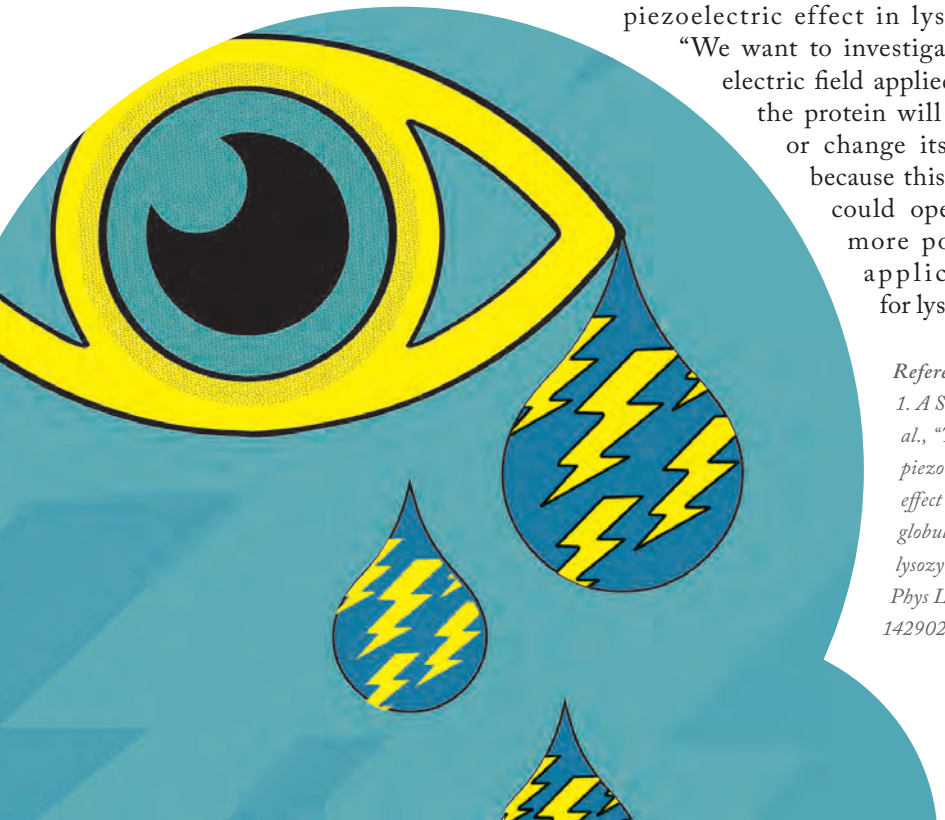
Electric Tears?

The piezoelectric effect of teardrop protein

"We've known since the 1950's that some biological materials, such as bone and wood, are piezoelectric – meaning they generate an electrical charge when pressed," says Aimee Stapleton of the University of Limerick, Ireland. According to Stapleton, bone piezoelectricity is thought to contribute to bone regeneration and healing, but the mechanisms that allow bone and other biological materials to be piezoelectric is not fully understood. Inspired to find an answer, Stapleton and her team were moved to tears…

"In non-biological materials, we know that a certain type of crystal structure is needed for piezoelectricity," says Stapleton. "The protein lysozyme – which is found in tears, saliva and egg whites – can be easily crystallized, so we decided to investigate if it showed piezoelectricity." The team grew crystals of lysozyme and measured their direct piezoelectric effect, finding that they could produce an electric charge when they applied pressure (1). "Although we hypothesized that crystals of lysozyme should be piezoelectric, we were surprised at the magnitude of the response we saw – lysozyme's effect was comparable to that of quartz, a material exclusively used for its piezoelectric properties."

The upshot? As well as the team's findings bridging the gap in understanding piezoelectricity in biological tissues, identifying the magnitude of lysozyme's piezoelectric effect has opened up the potential for its use in a multitude of applications including biomedical devices. The authors also write that "future applications may include controlling the release of drugs in vivo by using lysozyme as a physiologically mediated pump that scavenges energy from its surroundings" (1). Stapleton says that the team are next interested in studying the converse piezoelectric effect in lysozyme. "We want to investigate if an electric field applied across the protein will deform or change its shape, because this finding could open even more potential applications for lysozyme."



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In My View

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

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

Contact the editor at edit@theophthalmologist.com

When Disaster Strikes

What can an ophthalmologist do in times of adversity? A great deal.

By Juan Carlos Serna-Ojeda, Cornea and Refractive Surgeon, Mexico City, Mexico

On September 19th, 2017, 32 years after a massive earthquake in Mexico killed thousands of people and left almost one million homeless, another huge quake hit. At the time of writing, almost 300 were dead, dozens of buildings were destroyed and the earthquake had affected thousands of people's homes – and lives.

In the immediate aftermath, the citizens and government of Mexico worked together to react to the catastrophe, but it wasn't until hours and even days later that the true scale of the disaster became clear. People of all professions volunteered to give support during the chaos, and doctors and paramedics played a fundamental role in attending to the victims in the aftermath. Every health professional played a vital role – in both the disaster zones and in the hospitals – and the skills of all would come in to play; not just those of the emergency physician, but also those of the psychiatrist who could control anxiety crises. It's when I asked myself: what can an ophthalmologist do after a disaster? I remembered the taunts from medical friends in other specialties about the "easy" lifestyle of an ophthalmologist.

Well, ophthalmologists at many clinics, in both public and private practice, gave free-of-charge eye care to those who had suffered because of the disaster. And the eyecare industry donated much-needed medication. My colleagues on the front line reported that ocular trauma, burns and foreign bodies in the ocular surface were the most common emergencies. And that was also my experience. I joined a mobile medical unit – a van armed with both a regular and a portable slit-lamp – sent by the Institute of Ophthalmology Conde de Valenciana (where I completed my training in ophthalmology) – and we set up in one of the most devastated regions of Mexico City.

In those places, our work mostly consisted of treating those people affected by foreign bodies and dust from the building rubble – not just those who had been rescued, but also the rescuers and volunteers, which was crucial because it kept them functional so they could continue to do their jobs. But there were situations where more than eye care was needed (and I am well aware of that part about being a doctor). It was about going back to the basics of our medical training: providing first aid, distributing medication, measuring vital signs, organizing medical kits and so on. It was about going back to the basics of being a human being: working as a team, participating in the human chains that transported supplies, giving support to the sad or tired… I was experiencing the very reason why most of us entered the medical profession in the first place: to help others.

We must remember that every doctor and every specialist is important in a catastrophe – and that every volunteer can contribute in complex situations, such as the aftermath of an earthquake. We still have a lot to do in terms of rebuilding – but living through the disaster has taught me that every person can play an important role, and do far more than they thought possible.

Time to Drop the Debate

It shouldn't be about epi-on or epi-off CXL... The focus should be on what's best for patients

By Roy Rubinfeld, Clinical Associate Professor at MedStar Georgetown University/Washington Hospital Center, and Medical Director of Re:Vision, Rockville, Maryland and Fairfax, Virginia, USA

Back in 2010, during Cornea Day at the AAO annual meeting, I was nearly booed off stage. A few years ago, at a prestigious dinner for cornea specialists, I was accused of malpractice, and of selling "snake oil." Why? Because I was discussing epithelium-on (epi-on) corneal crosslinking (CXL) and presenting results that suggested success.

In the CXL space, epi-on CXL (or transepithelial CXL) has been a source of controversy for years – and a healthy amount of skepticism surrounds the approach. This intense skepticism likely stems from the history of CXL, which began back in the late 1990s with Theo Seiler, Michael Mrochen and colleagues at The University of Dresden, Germany. After demonstrating riboflavin-UVA corneal collagen crosslinking in porcine and rabbit eyes after epithelium removal (1, 2), they went on to show promising epi-off results in a pilot study in humans with moderate or advanced progressive keratoconus (3). But why was the epithelium removed? According to personal communications with Michael Mrochen and others, despite a self-evident preference to leave the epithelium intact, making CXL a non-invasive procedure, it was primarily because there was no formulation or technology available to adequately load riboflavin into the stroma through the epithelium. Instead, a technique from photoreactive keratectomy (PRK) was used: they surgically removed the protective epithelium and applied the riboflavin directly to the deeper layers of the cornea... And the rest is history. Epi-off CXL became the "norm."

Traditional epi-off CXL is a typically safe and effective procedure, but there are well-documented complications including corneal edema, infectious keratitis, delayed epithelial healing, corneal haze, stromal scars and even corneal perforation – nearly all of which derive from the surgical removal of the epithelium. Additionally, removal of the epithelium is painful for patients, and re-epithelialization can take at least a week during which they may require opioids for pain management. Recovery of pre-operative vision can take at least one month or longer. Would most patients prefer to have their epithelium removed, suffer worsened vision, be in substantial pain and at risk of complications such as infection, perforation, scarring and haze, and effectively 'out of commission' for weeks per eye – or undergo an equally effective non-invasive procedure that consists essentially of 'eyedrops and sunlight,' returning to work the next day? The advantages of performing CXL with the epithelium intact is clear, so why aren't people more accepting of an epi-on approach?

I believe false promises in the rather stormy history of epi-on CXL are to blame. The procedure wasn't approved in the US by the FDA until 2016, so Europe has largely led the way in CXL – and it's been quite a frustrating experience. I live part time in Europe and have observed CXL's development from the beginning. When the epi-on approach first came around; everyone was excited about it – all the while hoping that a less-disruptive, safer approach might be forthcoming. And indeed, over the years, there have been many attempts to develop an effective epi-on procedure, from various commercial formulations to different devices designed to disrupt the epithelium – and even a "scratching" technique (a "happy" medium between removing the epithelium and leaving it intact). Europe is a wonderful place for innovative technology, and many of its ophthalmic surgeons were excited by the products and systems that they believed would more safely and conveniently strengthen corneas to protect against vision loss – only to find to their great dismay that they didn't. No commercial transepithelial CXL has been definitively proven to work long term. In many cases, exciting six-month data turned into unacceptably high failure rates with many patients progressing and losing vision one to two years after the procedure – it turned out that 24 months post-surgery was the real test (4, 5). Trying epi-on approaches in an effort to better treat their patients, only to see ectatic disease progress under their care must have caused frustration if not also guilt and anger to these pioneering surgeons, so it is easy to understand why epi-on skepticism persists and has even increased.

But when people use the term "epi-on," do they mean the 10 approaches that haven't worked or the one approach with scientifically validated potential? I have heard that Robert Machemer performed almost a dozen failed vitrectomies before he found success. Do people say "vitrectomy doesn't work?" No, because it was the first dozen approaches that

didn't work. And that's why I refer to "epi-on versus epi-off" as the great non-debate; this discussion is a red herring leading nowhere. We should be open to scientifically evaluating any approach that achieves the best outcomes for patients. Previous epi-on approaches may not have worked well, but we have developed a new approach – and we are seeing extremely promising long-term study results.

As a corneal surgeon in 2009, having observed CXL being performed in Europe, I organized a group of innovative surgeons across the US (CXLUSA) to find a way to reduce the number of corneal transplants in their respective states. Back then, we were performing epi-off CXL under Institutional Review Board (IRB) approvals just like everybody else. Why? Because we didn't believe epi-on approaches worked. But that didn't stop us from seeking improved, non-invasive corneal strengthening treatments for our patients. And because our IRB protocols allowed us substantial freedom in terms of iterations, we were able to test different modifications; concentrations, pH, osmolarity, excipients, and more – we performed literally dozens of modifications to the protocol whilst staying in the range of approvals as part of a group effort. Through much communication between our investigators and many procedures, we have developed a new way to perform epi-on CXL: the CXLUSA methodology. The main differences between previously-trialed epi-on methodologies and our approach include the riboflavin formulation itself, a novel non-iontophoretic delivery system and the light diameter. We also use a patented, pulsed UV light cycle, which allows molecular oxygen – the rate-limiting reagent of the crosslinking reaction – to be replenished in the stroma during the dark cycle.

Using our approach, we have found in our multicenter study transepithelial treatments we can consistently load riboflavin into the stroma in 10–20 minutes. In ex vivo rabbit cornea studies (performed by an independent laboratory), adequate riboflavin loading was consistent with that of epi-off stromal concentration (≥15 μg/mg). Loading was observed in as little as 10 minutes through slit lamp examination, and chromatography and mass spectrometry analysis confirmed a four-fold greater concentration of riboflavin with our formulation than commercially-available alternatives (6). Earlier this year at the American Society of Cataract and Refractive Surgeons (ASCRS) annual meeting, we presented results from 592 eyes with keratoconus (n=512) and ectasia (n=80) that received our procedure between October 7, 2013 and April 26, 2016 (7). The results are promising: at 12 and 24 months after surgery, we saw improvements in five parameters (corrected distance visual acuity, uncorrected visual acuity, Kmax, higher order aberrations and coma), and we saw no progression, even among the 48 pediatric eyes (≤18 years) (7). Adverse events of hydrops, scleritis and disciform edema were reported from one eye each, but were not related to the treatment.

In conclusion, we believe that our novel approach works – and we're thrilled with the results we're achieving because it means we're able to perform a safer and more comfortable procedure for our patients. We have submitted our findings for publication, and our next goal is to proceed through the regulatory process so that more patients in the future might be able to benefit from an effective epi-on CXL approach. It hasn't been easy to reach where we are now after eight years of research – there have been many hurdles, not least the ongoing skepticism. However, I believe the tide is slowly turning and that more people in the field are willing to accept the idea of an epi-on CXL approach once they see the scientific in vitro and clinical study data. The fact that there are many other groups investigating transepithelial CXL is testament to this. I think it is time to 'drop the debate,' because it is not about epi-on or epi-off; it is about what is best for our patients and which approach works best with the least discomfort and risks.

Rubinfeld reports that he holds equity in CurveRight, LLC; CXLOphthalmics, LLC; and CXLUSA, LLC.

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Move Out of the Tunnel… and into the Light!

When it comes to glaucoma care, metabolomics could well be the future

By João Barbosa-Breda, Glaucoma Fellow, Ophthalmology Research Group of the KU Leuven (University of Leuven), Belgium

I believe metabolomics has the potential to shed light into the pathophysiology behind glaucomatous damage, as well as providing potential biomarkers for early glaucoma detection.

Metabolomics is the detailed study of metabolites created by the cellular processes in an organism. Influenced by both genetic and environmental factors, the metabolite profile gives us a "fingerprint" of the health status of the organism at the time of sampling. But aside from disease mechanisms and biomarkers, this technology has also been increasingly used for drug target discovery and the prediction of drug effects – and it can help move medical care towards a more personalized approach.

For all of these reasons, metabolomics is becoming widely used across different fields, from cancer research to obstetrics and, of course, ophthalmology – where it keeps proving its value. A recent paper has shown the potential of metabolomics for the diagnosis of age-related macular degeneration (AMD); both the presence and stages of the disease could be distinguished by identifying differences in metabolic profiles in controls and patients with AMD (1). Glaucoma (the leading world cause of irreversible blindness [2]) is also a good candidate for metabolomic analysis, which has the potential to break knowledge barriers, driving us towards new treatments and personalized care. Our research group, led by Ingeborg Stalmans, recently reviewed results that have already been delivered by metabolomics in terms of understanding the pathophysiological processes of glaucoma in a clinical setting (3). Only one metabolome-wide study for glaucoma has been published to date; it identified significant metabolic differences in blood plasma samples from patients with primary open-angle glaucoma (POAG) and samples from healthy controls (4).

We feel that we can push this research a step further, so we are collecting blood, urine and aqueous humor samples from patients with POAG who are undergoing surgery (MISO Study; NCT03098316). All samples will be analyzed using two complementary metabolomics techniques (mass spectrometry and nuclear magnetic resonance spectroscopy) and compared with control samples (from patients with cataract and no other eye disease). As metabolomics provides an overview of whole body metabolism, we are also including a study group of patients with normal-tension glaucoma (NTG), since systemic vascular dysregulation is thought to play an important role in the pathogenesis in this group of patients.

"Metabolomics is becoming widely used across different fields, from cancer research to obstetrics and, of course, ophthalmology – where it keeps proving its value."

In my view, metabolomics will help bring glaucoma care into a new era by reducing the numbers of patients arriving in our office already at an advanced stage of disease, and by revealing new research paths that can be used to develop new drugs and improve ophthalmic care.

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Rob, Remembered

ROBERT L. JOHNSTON (ROB TO HIS MANY FRIENDS) MADE A REAL DIFFERENCE IN HIS LIFETIME. HIS LEGACY? RESHAPING OPHTHALMOLOGY AS WE KNOW IT.

Mark Hillen interviews Javier Zarranz-Ventura, David Johnston and Adnan Tufail

It's not hyperbole to consider Rob Johnston as one of the fathers of big data in eyecare. Along with his brother, David, he founded Medisoft. The structured, clear-minded, clinician-designed electronic medical record (EMR) system that they produced – and the data it holds – is certainly enabling ophthalmologists to gain great insight into the practice of their specialty. But, perhaps more importantly, it's also perfect fodder for machine learning in medicine – a field led by ophthalmology, in large part thanks to Rob. But he wasn't just the Clinical Director of Medisoft: he was a committed and caring vitreoretinal surgeon, an educator, a husband, a father, a manager, a mentor and a friend to many. He died last year, after a 12-year long fight against cancer. A year after his death, his brother, David Johnston, his former fellow Javier Zarranz-Ventura, and former colleague Adnan Tufail came together to discuss Rob, his life and work, and what he meant to them.

THE MAN

Javier Zarranz-Ventura (JZV): I went to Moorfields [from Spain] as a medical retina fellow, but I also wanted to do a vitreoretinal (VR) fellowship. One of my bosses there, Adnan, told me that a friend of his in Cheltenham also did lots of great research. It was Rob. I met him and we immediately got on – an instant link! I spent a year there, but from day one, he looked after me and my wife. My mother used to tell me that it's normal to hear good and bad things about people – but there are a few exceptions, when you only hear good or bad things about somebody. With Rob, people only said good things.

He looked after us so well. My wife, Paula, and I had planned to fly home for Christmas that year – we already had our flights booked – but when she came home with the staff rota, she had to cover Christmas Eve. As she would be in the hospital all day, she said it would be silly for me to stay. I mentioned to Rob during a coffee break how it was going to be kind of sad. He didn't even think for a second about his reply: "Ask her to come over, ask her to come over!" I've worked with many people in many hospitals, and no matter how sociable you are, you connect better with some people than others – but to be in a foreign country and have someone ask your wife to spend Christmas Eve with their family? That's a perfect example of who Rob was. My wife always says that the time spent in Rob's house was the only good part of a terrible day. In hospital, it was a really rough day; people

died, and she ended up finishing really late. When she finally arrived at Rob's house, as he opened the door, his youngest son, Angus, who must have been 2 or 3 years at the time, ran over, said "hello", grabbed her leg, brought her in – it was so lovely, it almost brought her to tears. She then had dinner with Rob and his family and it was such a lovely evening for her! That was Rob. He was generous, caring and he looked after his staff, family and friends.

And it wasn't just me, it was everyone; ask the people in Cheltenham. All the trainees, registrars and fellows were delighted with Rob because they were never left to fend for themselves; he was always there if they needed something – he would never say no to anybody who needed advice. He was always very approachable, he never ignored people or turned anyone down to make his own day easier. He was simply not like that, not even when it was really late and he needed to get home.

The best thing? His style has rubbed off on me. He has influenced how I treat my own residents. If someone comes to me with even the most trivial thing, I'll take a look. Why? At the back of my head, I hear Rob saying, "If you can do something to help someone, don't turn them down."

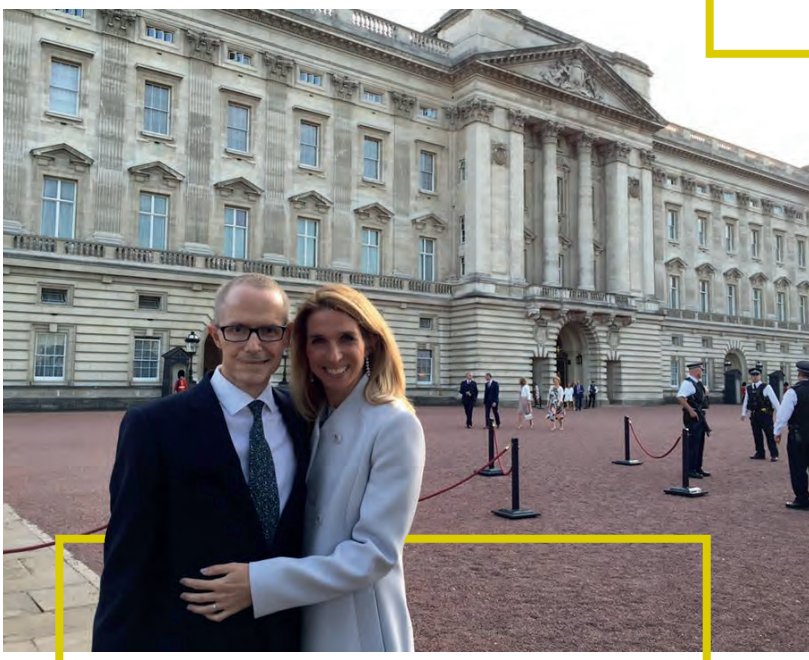
CHELTENHAM

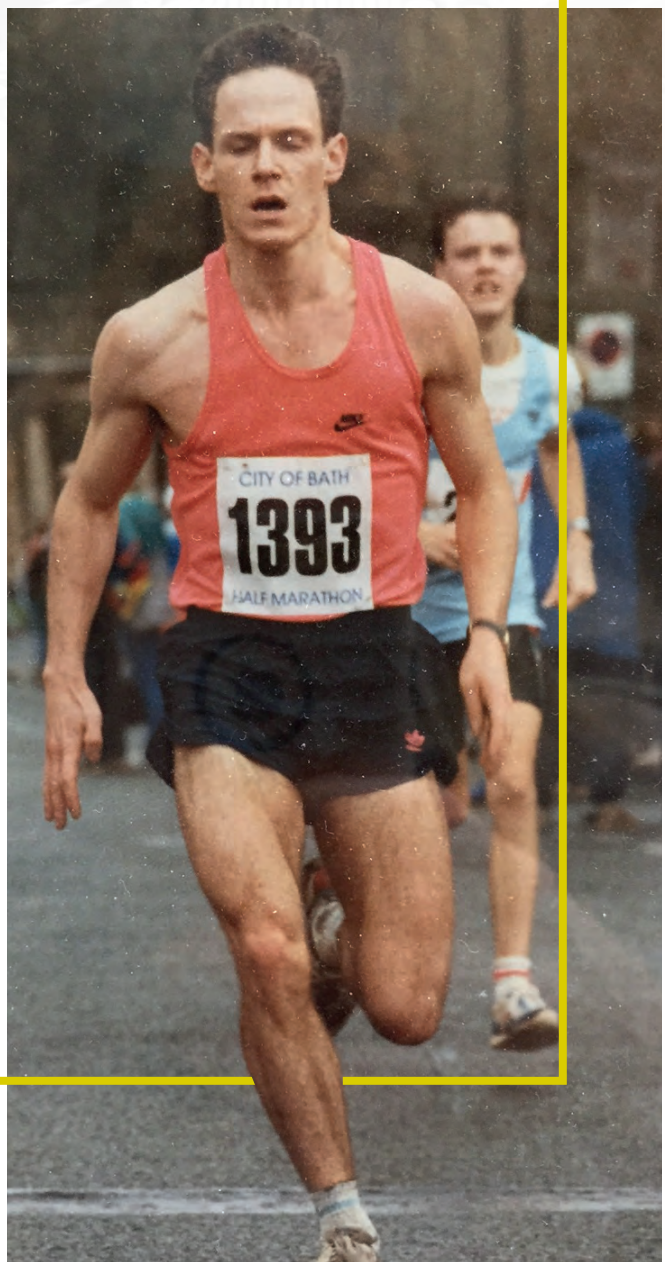
Adnan Tufail (AT): When Rob took the VR Consultant job in Cheltenham, he could have taken any VR job in the country – but he'd worked there before, and everybody knew him. It was already a good department, but Rob definitely gave it a big boost. Cheltenham is a small place – but it's one of the top units in the UK. Cheltenham was also the premier first VR fellowship in the UK for those coming from Australia – Moorfields will only take people who had done it for a year, and the recommended post is Cheltenham. There are huge numbers of Australians coming over here through word-of-mouth recommendations – it is probably the most popular starting fellowship in the country.

JZV: I don't know what the service was before him, but he was definitely one of the driving forces behind the training scheme, which was excellent. I've worked in many places and I have never seen a theatre or an intravitreal therapy unit that worked better than Rob's, either in terms of patient flow or patient clinics. Of course, it's also true that he had an army behind him, especially with the intravitreal therapy unit – but you need the right person to build that up.

AT: It's fair to say that Cheltenham was a good department with some very good senior people before Rob arrived; he wouldn't have taken the job otherwise. Nevertheless, he set up the macular treatment service himself; he knew it would be the next big thing, so he thought quite seriously about how to

"THIS WORK REPRESENTS THE FIRST DEMONSTRATION OF POTENTIAL FOR POOLING THE SURGICAL RESULTS FROM AN ENTIRE REGION OR COUNTRY IN AN ON-LINE DATABASE IN ORDER TO LEARN HOW BEST TO CARE FOR PATIENTS" (3).

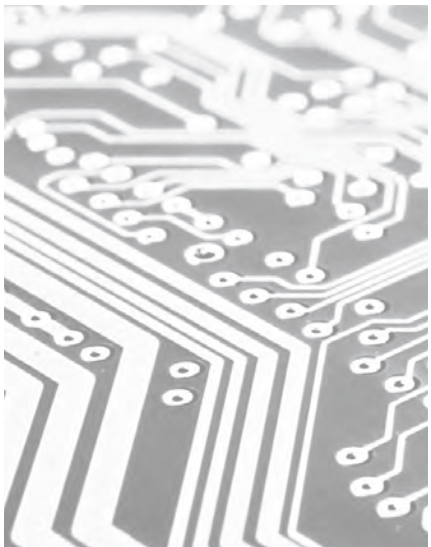




THE FAMILY MAN

AT: When Rob was a trainee in London and looking for his first consultant job, he broke up with his long-term girlfriend. He was single, and so wanted to get a job in London. When the Cheltenham job came up – the first consultant job he ever applied for – he had mixed feelings about it. He certainly wasn't thinking, "'Oh, I must go to Cheltenham' – he thought everyone would be 'very' married; children, a dog, all that kind of stuff. But he got offered the job and took it, while thinking "Oh no!"

However, he had only been in Cheltenham for a short time when he met Alice – a trainee anesthetist. She became his wife and the mother of his three children, so it all worked out really well in the end!



"IT'S NOT JUST ABOUT THE DATA, IT'S ALSO ABOUT UNDERSTANDING HOW THE CLINIC WORKS AND HOW A PATIENT FLOWS THROUGH IT."

make it as efficient as possible. He had optometrists and nurses seeing patients with multiple OCT machines, and so he had a much higher throughput per consultant or per ophthalmologist than most places; the patients got seen every four weeks, and that's important, because if they don't get seen every four weeks their sight can deteriorate.

JZV: How the unit works is amazing… Remember the LUMINOUS study (1), which is directed to assess the use of ranibizumab in routine clinical care? Rob said, "OK, this is a real-life study, let's do this!" Within a week, Cheltenham was one of the highest recruiting centers in the world.

CHICKEN OR EGG?

AT: He had a good mind for process, which must have helped with building Medisoft. You need the data to be right…

David Johnston (DJ): But it's not just about the data, it's also about understanding how the clinic works and how a patient flows through it. When designing the Medisoft ophthalmology EMR, Rob had to think about every step: arriving at reception, seeing a nurse, then having a series of diagnostic tests and then seeing an optometrist or doctor, for example. Rob was forced to think about processes from his experience as a trainee. So designing Medisoft's ophthalmology EMR definitely helped him design an optimal care pathway for the macular treatment service at Cheltenham General Hospital.

THE MEDISOFT STORY

Mark Hillen (MH): How did you go from an EMR system to being involved in the world of big data?

DJ: To be honest, we didn't have big data in mind when we started Medisoft; no one had even heard of the concept. I don't remember the exact date, but it must have been in 1996 when we were both living in London: Rob was a trainee and I worked for a pharma company called Ipsen. I used to market a botulinum toxin product, Dysport, which was prescribed purely for blepharospasm and hemifacial spasm – both of which are treated by ophthalmologists. (This was a long time before this was used to smooth wrinkles!) I'd been doing that for five years, and by then I'd come to know probably half the consultant ophthalmologists in the UK. I'd visited nearly all the units and knew how selling into an NHS organization worked.

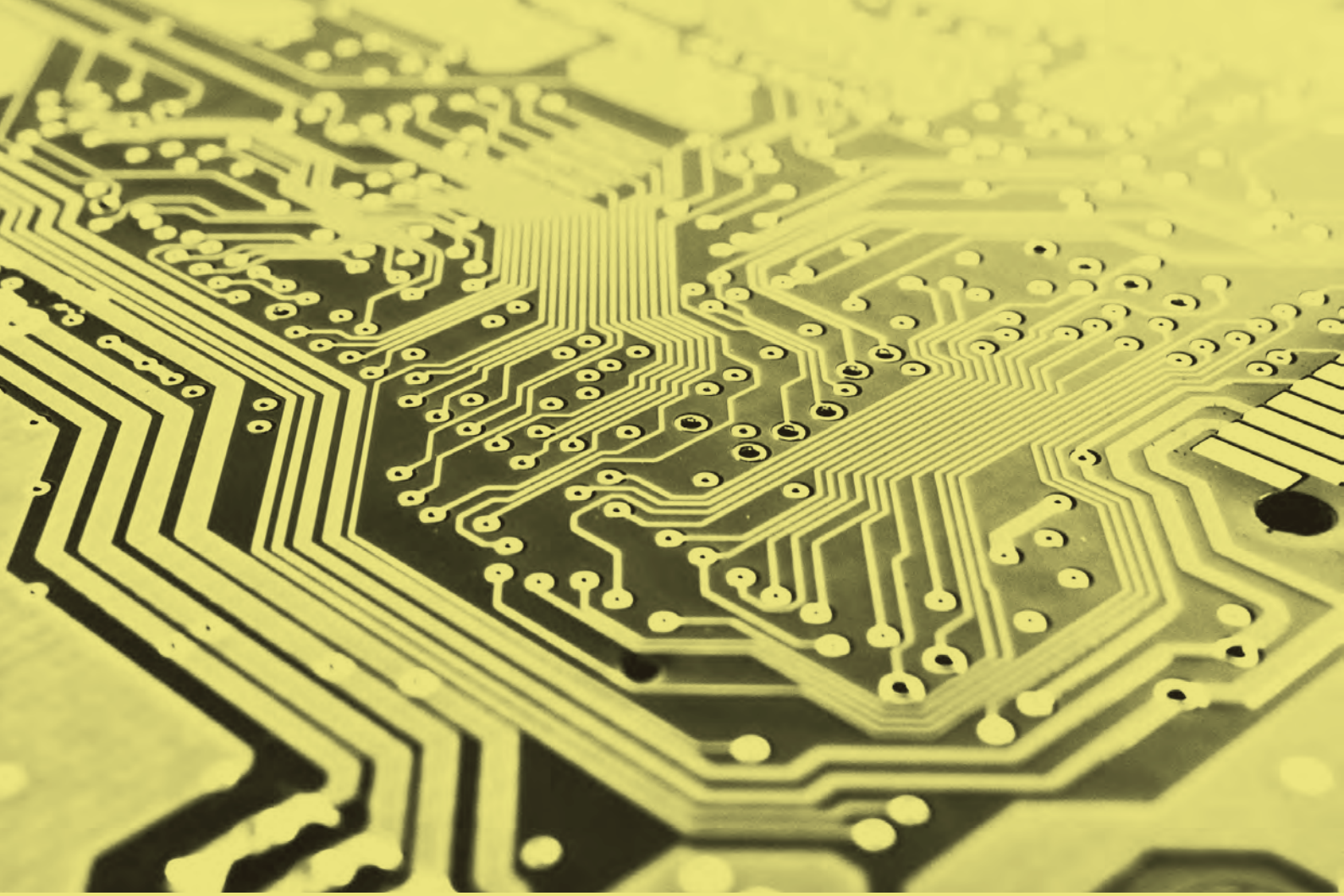
But I'd grown bored of my job, so when Rob had the idea to create an ophthalmology medical records system, it was just perfect timing and I quit my job. The idea was interesting, but neither of us were techies at all (I'm still not) so we knew we'd need some help. Rob wrote a spec and I got a friend of mine in Leeds to write a very rudimentary demo program. I showed it to some of the ophthalmologists I'd met selling Dysport, and asked them if they'd buy the fully working system. The response: "Yes, definitely!"

In early 1997, we formed the company. But the original objective was just to have a patient record system that permitted easy data collection and analysis of that data, including a good audit of outcomes. It's not possible to do a comprehensive audit of all patients seen in an eye department by trawling through the paper notes. Rob's vision was that if all the data is stored in the right way on a computer system, detailed comprehensive audits of the data will be possible at the click of a button.

AT: But back then, audits were rudimentary even in the UK. Nevertheless, I think Rob and David could see the importance of looking at quality outcomes and how it would be vital in the future for all sorts of reasons. They recognized this very early on, before anyone else. It took a lot of courage to start that kind of project in the mid-1990s environment.

DJ: That may be true! But I could see that the chances of me crawling to the top of the greasy pole in an established pharma company were even more remote, so I was dying to do something else! I deeply respected Rob and had complete faith that his idea would work. I knew he wouldn't have considered starting the enterprise unless he was confident that it would work out in the long term.

Of course, audits were paper-based at the time: crude and



GOING ABOUT THINGS IN THE RIGHT WAY

with Adnan Tufail

I got involved with Medisoft through the retina side – just talking to Rob and seeing the fantastic EMR analysis work they were doing on cataract surgery and what they'd been able to show in terms of the impact of the introduction of anti-VEGF agents. We could see that it would be a really important area to look at – these are expensive, intensive therapies, and we really need to know that our patients in the real world are doing as well as those in the clinical trials. I managed to convince a pharma company to cough up a trivial amount of money to pay for the data collection, and we did the rest ourselves. And within two months of thinking of the idea, we wrote to 16 Trusts, got replies from 14 within a month, and a month after that we had data from Moorfields. Imagine that – just two months after having the idea we had outcome data on over 100,000 injections, representing 300,000 patient visits and about 2.8 million data points!

Our first attempt was in 2011; at that time, our statisticians were not used to handling big datasets, so I actually did it myself on my laptop. I am probably very fortunate in that, although I am not a proper "techie," I was lucky to have been given a computer – a BBC Micro – as a kid, and I learned to do basic coding. But then I went to medical school. I have always been okay with numbers, but medical school knocks it all out of you! When I started doing my research, I got back into analysis. The Medisoft EMR data is very structured, but it is very difficult to deal with big datasets and link them together in something like Excel, so I wrote some basic scripts in an SPSS software package, which took me a few months to do, during my holidays in Australia. Anyway, we got some really good data out – and the first two papers were published in Ophthalmology (4,5).

Everyone now realizes that you need to treat early and it is all about visual acuity state, not gained visual acuity. If you have poor vision, let's say in AMD, and then treat it, the average patient will gain a lot of letters; but if you have good vision, the average patient loses vision. And the way that most people audit outcomes or the way that the data is presented in all the trials on ANCHOR and MARINA is visual acuity gain from baseline – but that isn't what's important to the patient. What is important to the patient is visual acuity state: not whether they have gained two letters, but whether they can

still drive. It is all about getting the patient early. And it has huge implications, because it really influences clinical trial design – non-inferiority trials, superiority trials, because you can almost game the population you want to enter. So there were huge implications even in that first paper – it's not just about asking, 'how are we doing?'

And we realized that, at least in the UK, we weren't giving as many injections as we thought we were (4). The vogue was not to over-treat because we were worried about the injections and the side effects, so there was a natural reluctance. The outcomes were not disastrous, but nothing like ANCHOR and MARINA – and with very few injections. So we realized we probably needed to alter the way we do things. In the second paper on second eye involvement (5) – I think Javier was the first author of that – we realized that the risk of the second eye succumbing was actually much greater than we thought. Once you start treatment in one eye, if you have reasonably good vision in the fellow eye, you have a 50 percent risk of developing wet AMD within three years. Again, this has huge implications in terms of the extent of treatment required, and what happens when both eyes are involved.

"WE JUST STARTED FREE-THINKING ABOUT WHAT WE COULD DO, AND NOT JUST LIMITING OURSELVES TO CONVENTIONAL OUTCOMES."

I did the analysis of the first two myself – but it was pretty tiring to do the day job as well. I realized that it would be nice to get much better coders involved and I was very fortunate to meet some extremely good data guys, who also understood the eye. There was Dave Crabb's group at City University in London, and a fellow, Aaron Lee – a rare individual who not only codes brilliantly but is also a retina specialist. So we then developed a group with me, my wife [Cathy Egan], Dave Crabb, and Aaron – and then it really took off; my ability to code was no longer the limiting factor. Once we had brilliant people on board, we just started free-thinking about what we could do, and not just limiting ourselves to conventional outcomes. For example, we started looking at novel health economic analysis, such as how in the UK at the moment you still can't treat eyes with vision better than 6/12 (20/40).

With health economics analysis, you need to establish that what you are doing is incrementally more cost-effective than the standard of care. But the standard of care is unknown because in the trials there is no control arm better than 6/12. It was Rob who bounced the idea around and realized that the data probably existed in Medisoft. There were a few areas in the UK where they were funding vision better than 6/12, so we mined that fellow-eye data, and their OCT data, and when we had a leap on the OCT for two successive visits, we followed it through until they got an injection. That was the natural history arm; then there were centers that had the injection, and that was the real arm. So we then did a health economics analysis, and showed it was highly effective even with an ICER analysis; there is a whole level of complexity above that. It has been studied in the current NICE AMD review, and we hope it will change things.

We have done a similar study now with AREDS, which was published recently (6). The UK doesn't offer AREDS vitamin supplementation. The AREDS formulation is known to be effective for preventing wet AMD in people who've got the wet form in one eye and the dry form in the other, and we were very lucky to do a hybrid health economic model. Emily Chew of the NEI gave us full access to the original AREDS dataset; we merged that with real-life outcomes and got a NICE-level health economic model. It turned out that AREDS aren't just "cost-effective," if you've got wet in one eye and dry in the other – they are what's called "dominantly cost-effective." In other words, if you pay for it, it still saves the NHS money – to the

tune of £130 million a year per cohort you enter. It wouldn't be possible to show that without our combination of data. I believe the approach is going to be transformative, not only for outcomes – by ensuring that we are modifying our behavior in the UK – but also for health economics.

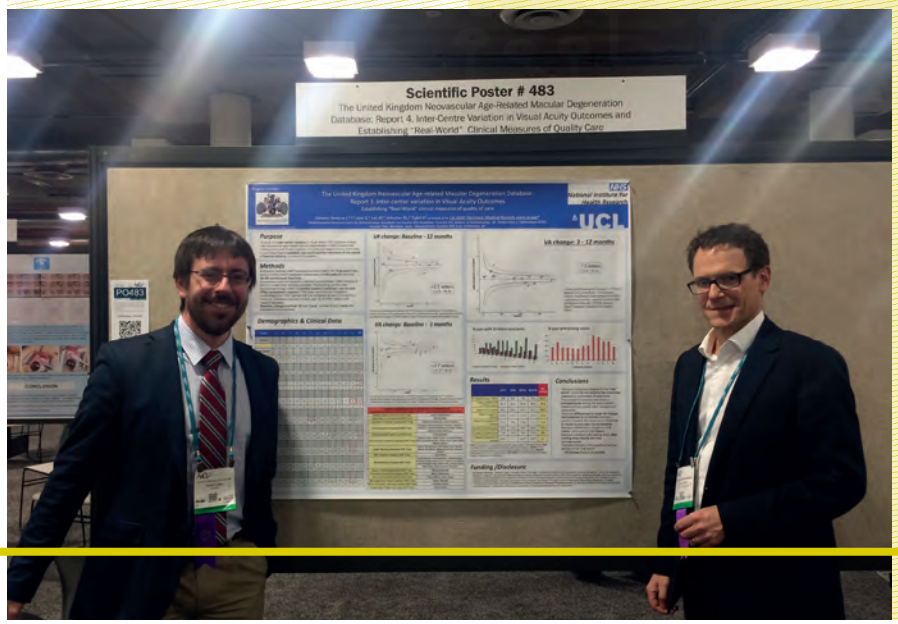
We also have the potential to "free think." I had a fellow operating on my list, a brilliant surgeon, and he had a complication. We looked up the EMR records and found that the patient had received about 22 anti-VEGF injections. A few weeks later, the same thing happened. We looked up the notes and found that the patient had received 30 injections! I thought, we're injecting the eye, we're not seeing obvious trauma, but this may be because you are injecting and somehow weakening the lens. As I said, this is a rare event, and it has been very difficult to prove the association – even when it's the two most common procedures in ophthalmology – cataracts and injections. Within 48 hours of asking the question, Aaron analyzed the whole dataset (because he had access to the cataract data and rupture rates) and realized that actually there is an increased risk per intravitreal injection: when you have more than 10 injections, your risk of complications or posterior capsule ruptures is the same as a junior surgeon or a resident surgeon – it has that much of an impact! Such knowledge is important as it changes how you advise your patients. We realized that we can actually do more than simple outcomes. We are now at the next stage: looking at different procedures within the eye, and how they interact – and trying to understand how that affects the rest of the body.

Now, the challenge is merging other public EMR datasets, which is ethically complex; however, we are now linked to the Farr Institute, one of the four government-funded Health Informatics Institutes, to link eye data to cardiovascular data to GI data. We can start looking at uveitis (we did an editorial on big data in uveitis in Ophthalmology not so long ago [7]), about how it interacts with the body. What drives machine learning and trains a deep-learning algorithm (or any machine learning algorithm) is lots of data. Now, we are using our data to drive the next generation of machine learning, and not just in terms of analysis of images. We're working with a number of groups: we are linked to the University of Washington, where Aaron is now, and we are part of the last ever big European grant. We are also doing more complex things; we have a very large pharma grant of about £2,000,000 to link imaging to the EMR data in search of the Holy Grail: can we predict what is going to happen to a patient, and select them out? In other words, if we've got a predicted poor responder on the basis of various factors, can we switch them onto other clinical studies or other therapies? We have 43 million OCT slices from the service at Moorfields now linked to the EMR data, which is going to drive all of that effort. It's our next big challenge.

"AND ALL OF THIS WAS INSPIRED BY ROB – NONE OF IT WOULD HAVE HAPPENED WITHOUT HIM."

And all of this was inspired by Rob – none of it would have happened without him. He has also inspired other important research in this area. On that basis, I thought it would be a good idea to do a Special Interest Group at ARVO a few years ago; I invited Mark Gillies – because he was doing some FRB, and we also talked about cataracts – and I invited Dave Crabb to talk about glaucoma, and Aaron to talk about data visualization, and the group really took off. Then, the American IRIS registry group came on board, and kind of took responsibility for it last year, and invited me to be on an all-day big data course. Many pharma companies were present, and now they're all interested in big data research.

This whole evolution of data-driven research was triggered by Rob's work. Without him, the tipping point would probably have been many years later.



basic. To do an audit of cataract surgery, for example, you'd have to pick 100 patient notes randomly and then transcribe information from the notes into an Excel file... It was incredibly slow and painstaking manual work, prone to error, and then only sampled a small subset of all the patients seen. We knew that computerization would enable the audit to cover everybody, and that would be really powerful. So when we designed the system, we started by considering what you would need in the audit – that was the first thing we thought about. Then we designed the system around that; whereas most EMRs are just about collecting information, but not in a structured way. We designed a system where you could press a button and get your audit.

"EVEN NOW THAT EMRS HAVE TAKEN OFF IN THE US, MOST OF THEM ARE ESSENTIALLY GLORIFIED BILLING SYSTEMS"

Even now that EMRs have taken off in the US, most of them are essentially glorified billing systems. You'll have paperless records, but you can't extract and analyze the data because they were never designed to do that. To go back and redesign those kind of systems would be a nightmare. Rob did it better because he and the Medisoft team actually took into account what clinicians wanted to measure and designed the software with that in mind.

We designed the first version for cataract surgery – a very sensible and pragmatic decision by Rob (a VR surgeon), as it's the most commonly performed eye operation – the most common surgical procedure of any type in the world, I believe. It was only in the last three or four years that Medisoft developed a VR module, because Rob always looked at it from the point of view of hospital needs and customer needs. Cataracts came first,

then it was glaucoma, and then medical retina.

So, our first system was essentially a cataract surgery EMR system with a very good audit function. Once we'd got that into five NHS Trusts, the Royal College of Ophthalmologists (RCOph) got to hear about it. They approached us to see if we could pool the data to do a study. That's when we first did anything like 'big data'. We approached these centers, and we got patient confidentiality approval from all the Caldicott Guardians at each Trust so we could extract anonymized data.

JZV: It got published in Eye in 2005 (2), but I think it was 16,500 cataract operations. Compared to what we can do now, that's nothing, but at the time it was a big deal. And it got this really amazing editorial, Rule Britannia, from a fine American epidemiologist who sang Rob's praises (3).

BIGGER DATA – AND SEEING MORE

DJ: Given such studies at that time, it really was revolutionary. It was still very early days for us – now we have over 80 Trusts using the system. In about 2006, we performed a similar study, but this time at 12 NHS trusts, covering 55,500 cataract operations. That study produced many more papers looking at anesthesia, posterior capsule rupture rates – all sorts of things.

AT: Just for context, there are other approaches, such as the Australian Fight Retinal Blindness! (FRB) Dataset. There are some really nice data coming from Australia – but it suffers from selection bias – the data tends to come from high-end private practices, and it's not every patient seen in all the hospitals.

MH: So that is the difference between relying on statistics based on small, random samples of paper notes and using all of the data on patients seen in the ophthalmology unit – the latter is reality?

AT: Yes, statistics based on small samples is modeling the population, whereas we are getting close to analyzing the whole of a population, so you just describe what you see.

JZV: If Rob was still around, he would have loved the opportunity to make the most of all of these advances in big data and artificial intelligence applied to data. It's sad that he's not here.

AT: To be honest, I would say that, because working in the highly centralized NHS environment, it's much more possible do this than in most other healthcare systems. You have big ophthalmology departments seeing huge numbers of patients, and of course, the NHS wants to know how they are doing.

DJ: In fact, one of the big drivers that made Rob very keen to start a company was a 1996 White Paper on improving healthcare standards in the NHS, which brought in the concept of 'clinical governance'. It said that the chief executives of NHS Trusts shouldn't just be responsible for the financial aspects, they should also be ensuring that systems are put in place to measure the quality of service being provided. This was on the back of certain scandals, such as the Bristol baby heart surgery controversy, which made the NHS realize they needed to start measuring what they were doing. And the only way to properly analyze outcomes is with a computer system, but only if it's designed well.

HUMANITY IN SCIENCE AWARD

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Richard Jähnke

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

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

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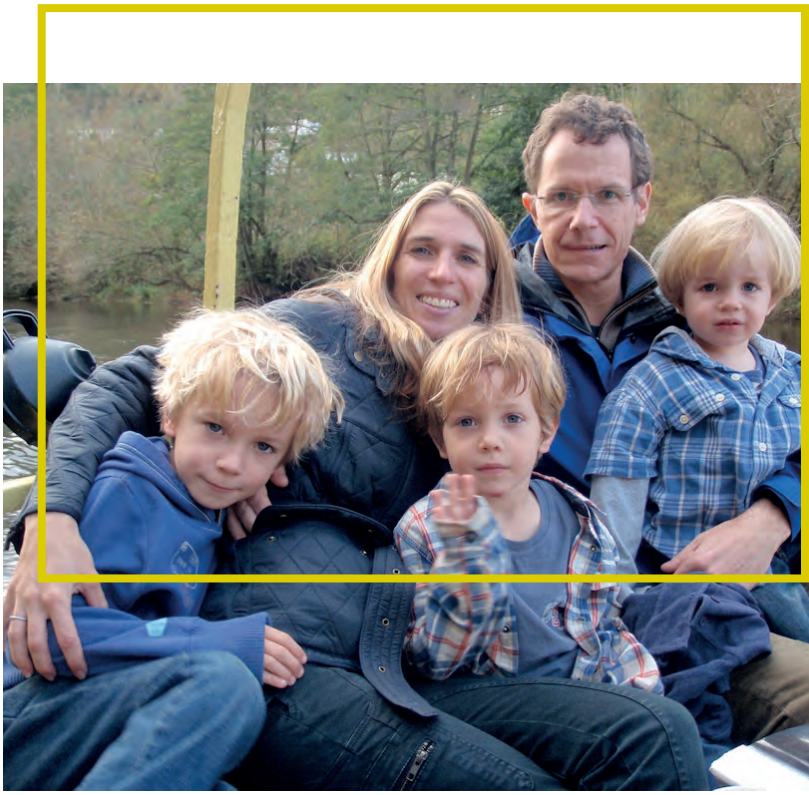
"YOU MUST HAVE STRUCTURED DATA TO ALLOW ALGORITHMS TO LEARN; YOU HAVE TO DO IT RIGHT FIRST TIME."



We used structured data from the start; the whole point was to be able to easily analyze the records. There was very little free text typing. There are some EMR systems where you literally just scribble with an electronic pen or free text type loads of information, but then you losing the richness – the ability to easily analyze all the data. I know a lot of big data analysis involves looking at reams and reams of unstructured data but, in reality, if you want to do things easily and well right now, you've got to have structured data – it's a pre-requisite for decent analysis.

AT: Yes – and you must have structured data to allow algorithms to learn; you have to do it right first time. The free text approach is essentially a document management system; it offers no advantage over just scanning and PDFing your patient records; you could probably convert that to text and then do text mining, but even that would be very complex.

FINDING TIME

JZV: Even when he was the busiest man on earth, Rob always found time for his friends. At every conference we attended, I would get a message from him to meet up for a meal or something no matter how full his agenda was. In the middle of a conference with 5,000 attendees or even 20,000 like ARVO, it felt really special. He once got a cab across Seattle just to have a cocktail with me. I really like attending meetings not just because of all the professional aspects but

also to be with friends – and Rob was more than my mentor, he was one of my best friends in this ophthalmology world. Maintaining any relationship usually requires some effort – but with Rob it was always spontaneous and bilateral. I always did my best, and he was always there, and I am really going to miss him.

MH: Shall we talk about Rob running the New York Marathon?

AT: David, I'll leave this to you, but I understand that it was the first time Rob knew something was wrong, because his time was a bit slow – no?

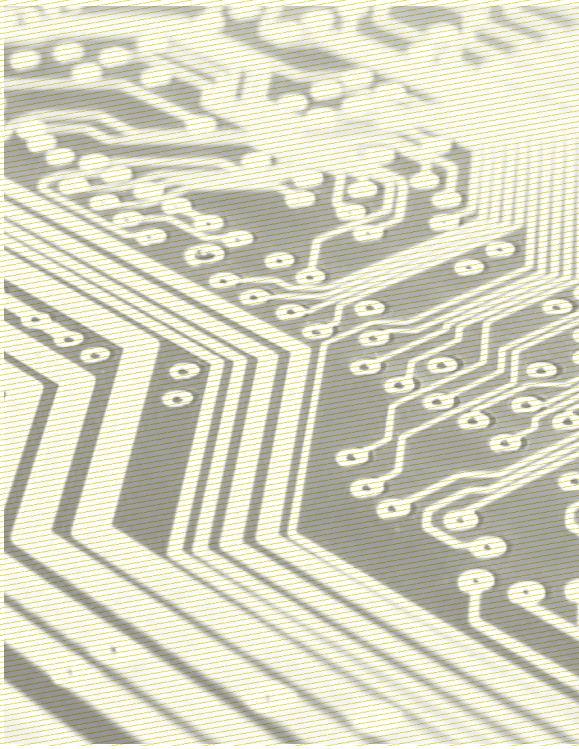
DJ: How I remember it was that he did the New York Marathon on the weekend, and then came back, got straight off the plane to give a talk at Peterborough Hospital about Medisoft; we were implementing it in a glaucoma shared-care scheme at around the end of 2004. While we were waiting to give the talk, Rob doubled up in pain and grabbed hold of his gut – and I knew, because he was a very stoical kind of guy, that it was serious. He still gave the talk. We obviously knew something was wrong, but thought it was Crohn's disease or diverticulitis. I got the news about a week later and we were all devastated: cancer of the colon. He was only 38 at the time.

AT: Rob was just as stoic the whole way through. At the last RCOph meeting, he looked a bit weak, but amazingly he actually had a chemotherapy infusion pump while walking around, meeting and greeting people normally. There were never any excuses with Rob. He was always on the ball and never complained; it was unbelievable.

DJ: Even privately, with his family, he was the same; he never complained, he just got on with it.

JZV: In January of 2016, he came over to Barcelona for a very quick weekend break with his wife, Alice. We went for lunch with my wife and daughter, but this time it was different; he told us that the cancer had come back again – and that it was bad. Later that same day, we ended up visiting Gaudi's Casa Mila (La Pedrera) and we all went to the roof. He was wearing morphine patches and never complained at all during the all-day tour. I was not prepared for his bad news, and I will always be grateful that I had the chance of a proper goodbye six months later (one month before he passing away) we all went to the Boqueria Market for tapas. It is my final great memory of Rob.

DJ: I remember when he had his first chemo cycle back in 2005, he would just have a week off for chemo, and then



go back to work. Here's something that he never even told me – just typical of Rob: after he had quite disfiguring facial surgery for the second primary cancer he got in his parotid gland, he was still seeing patients. One patient thought that it was amazing that he was still working as a doctor and doing his job, so they wrote to Prince Charles. In turn, Rob received a letter from Prince Charles! I didn't even know until Alice showed me the letter...

AT: Typical Rob.

DJ: Just before he died, he got a Queen's Award for Enterprise; he went to Buckingham Palace, but unfortunately missed the Queen – he had to nip off to the toilet suddenly – but Alice managed to meet her.

JZV: I like to think that he is somehow still with me. As I told the crowd at his memorial service (which Adnan and David will remember), I still hear his voice. When I operate, I hear the voices of the three guys that taught me how to perform vitrectomy. First, there's Nigel Kirkpatrick telling

me everything must be under control prior to starting the procedure; then there's Ahmed Sallam, telling me to have a plan beforehand and stick to it; and the third voice is just Rob… When I am operating a case and am in the middle of something and thinking, "What now?"... I can clearly hear Rob telling me (nicely): "You are wasting time!" Therefore, I feel afraid and get on with it. I love the idea that Rob is still with me!

From a personal and a professional point of view – what a star he was!

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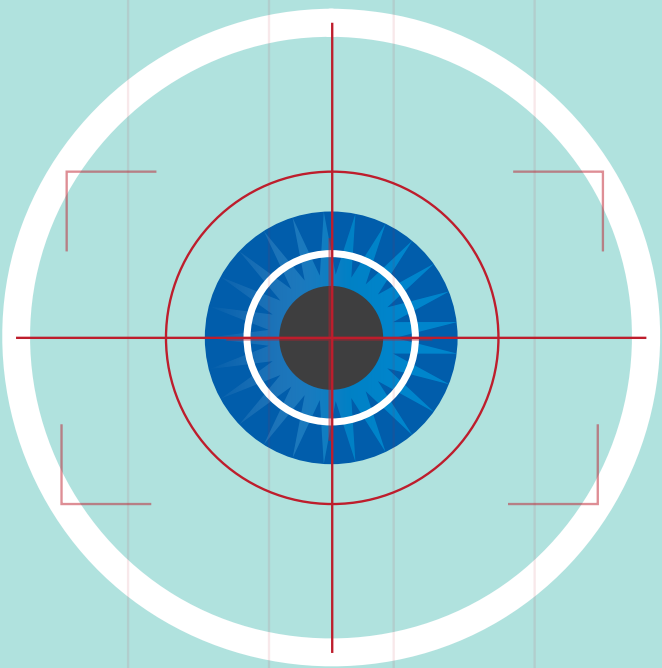

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38–41
Keep on Keeping On
Sustained release drug formulations are the future of neovascular disease treatment. Peter Kaiser looks at what's in the pipeline...

Keep On Keeping On

The future of retinal drug delivery for the treatment of neovascular disease

by Peter K Kaiser

We now accept that neovascular AMD is best treated by fixed intravitreal doses of anti-VEGF drugs; this approach gives the best responses in terms of visual acuity and deviating from it with as-needed treatment regimens results in inferior outcomes. However, patients dislike intravitreal injections, and the frequency of those injections (generally monthly or bimonthly) is burdensome to doctor and patient alike. In short, everyone would prefer fewer injections.

One strategy is to employ sustained drug release formulations, and some of the approaches currently under investigation include biodegradable polymers, lipid-based delivery, reservoir implants, gene therapy, encapsulated cell technology, and choroidal depot delivery. The success of any of these approaches will likely transform the treatment of macular degeneration. So what is the current state of play?

At a Glance

- *The biggest practical drawback of intravitreal anti-VEGF injections is their frequency*
- *Reducing the injection burden is a significant unmet need for patients with retinal vascular disease*
- *A number of approaches might solve the problem – and if any one of them does, it's a game-changer*
- *Here, I review the latest developments in long-acting retinal drug delivery formulations*

Polymer matrix formulations

Loading a drug into a polymer matrix from which it slowly escapes by diffusion as the polymer biodegrades is a well-established drug delivery strategy. The most commonly used polymer backbones are based on repeating polylactides, like poly-lactic-co-glycolic acid (PLGA). These polymers – manufactured as spheres or rods of nanometer to micrometer dimensions – are loaded with drug, injected into the eye, and continue to release the drug until the polymer matrix has biodegraded and is resorbed. In the past, these particles were produced using emulsion technology, a method that generates particles of widely varying sizes (Figure 1). Unfortunately, this size variation means that the surface area:volume ratio is different for every particle – as is the drug release kinetics. It's therefore preferable to generate particles of uniform dimensions. Fortunately, the semiconductor industry has solved this problem – microfabrication technology now enables manufacturers to create a template that gives them tight control of particle size – and with it, control of the drug release characteristics of the final product (Figure 1). The approach looks promising; initial studies with microfabricated PLGA particles loaded with anti-VEGF agents show steady drug release over four months (1,2).

Furthermore, microfabrication technology supports the manufacture of more sophisticated structures, such as multi-layered particles, which opens up the possibility of loading single multi-layered particles with different drugs that are released at different times – as has recently been exploited to good effect with single-dose combination vaccines that deploy at different time points (3).

Further flexibility can be achieved through careful choice of delivery vehicle. For example, drug-loaded particles can be suspended in a solution of the drug itself, providing an initial 'burst' effect at administration, along with the chronic and sustained drug release provided by the particles. Another possibility is to suspend the drug particles in a gel-forming polymer. Here, thermoresponsive hydrogels show great promise – they remain liquid at room temperature, but solidify at body temperature. This means that you could inject a liquid therapeutic agent that becomes a gel soon afterwards – ideal for

depot-type sustained release systems. By way of an example, a hydrogel containing ranibizumab particles was shown to release the drug over a period of at least 210 days from one injection (Figure 2).

Lipid-based delivery

Assembling multi-laminar liposomes in the presence of drug, such that the lipid layers form drug-loaded compartments, offers another approach; as the lipids break down, the drug is released (Figure 3). The kinetics of drug release from the liposomes, including duration of drug release, can be modified by adjusting the phospholipid formulation.

Reservoir implants

Mechanical drug delivery devices have also attracted much interest. One example is the Replenish intraocular pump (Box 1), which comprises an in-office refillable drug reservoir attached to a programmable micropump that enables controlled ocular drug delivery for as long as nine months. The micropump can be both recharged and reprogrammed wirelessly, permitting its functions to be fine-tuned as required without physical external access.

Similarly, a port delivery system allows infusion from an intravitreally-positioned drug reservoir. The device is implanted surgically, using a 3.2 mm scleral incision without sutures, and slowly releases the drug over 3–4 months (Figure 4). At the end of this period, the reservoir can be refilled via the subconjunctival port; this step requires only a minimally invasive in-office procedure. A ranibizumab port delivery system is currently under Phase II clinical evaluation (NCT02510794).

Gene therapy

Gene therapy offers the hope of permanent intraocular drug release by exploiting the protein synthesis machinery of ocular cells (4). Genetic

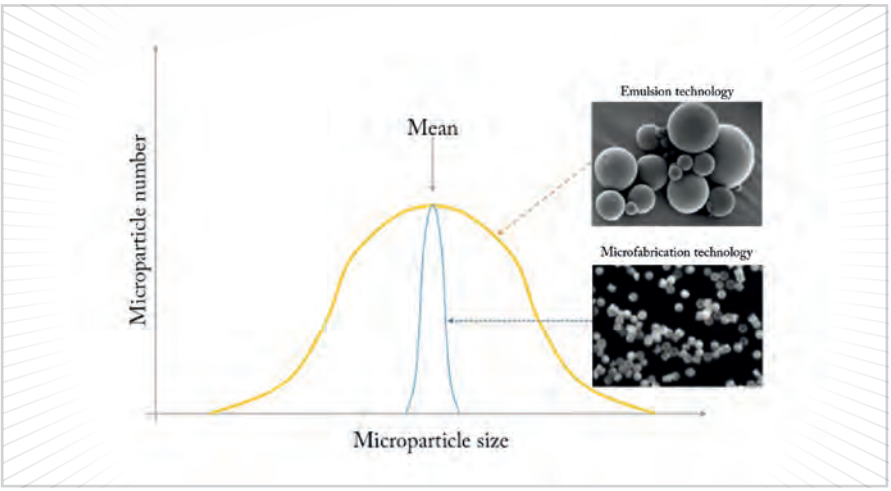

Figure 1. The use of emulsion technology to make biodegradable polymers results in a broad range of particle sizes (and less predictable drug elution), whereas microfabrication approaches provide a narrow range of particle sizes and more predictable drug delivery rates.

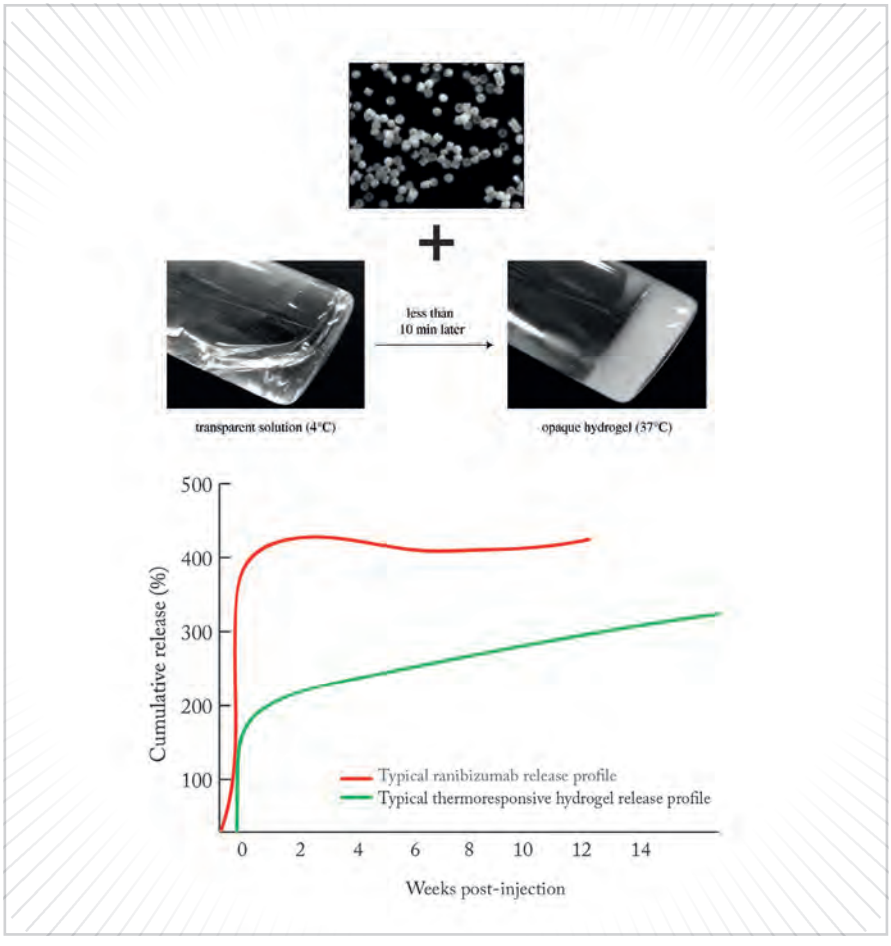

Figure 2. Cumulative drug release from hydrogel formulation of ranibizumab.

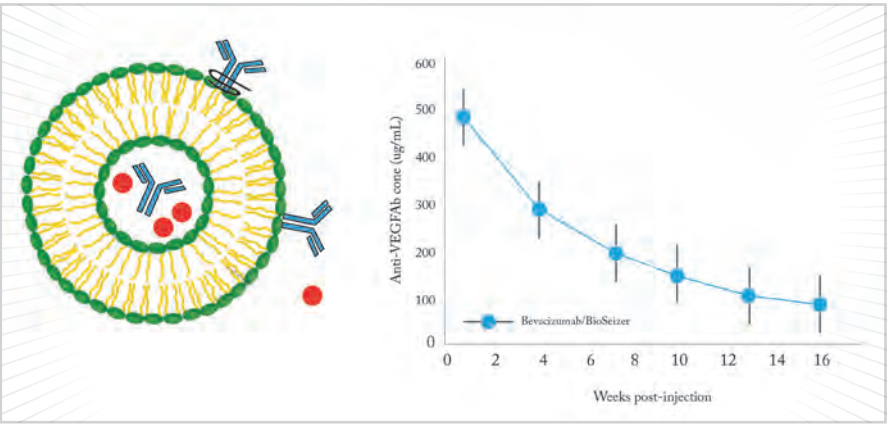

Figure 3. Drug release from multi-laminar liposomes loaded with bevacizumab.

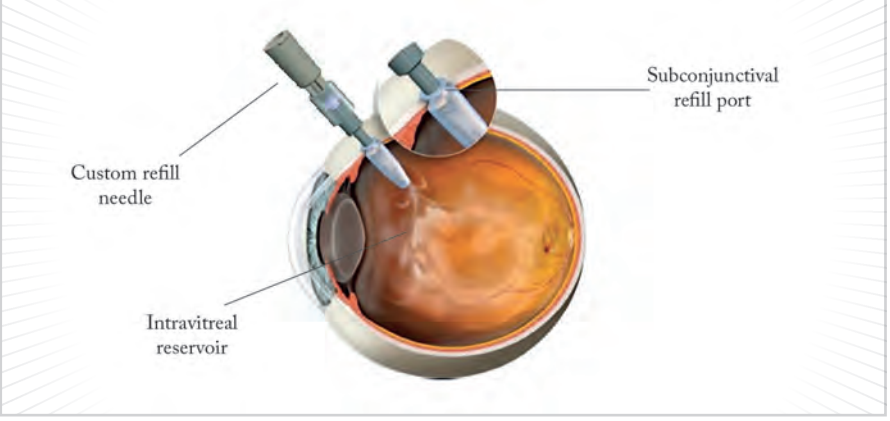

Figure 4. Port delivery system comprising intravitreal reservoir and subconjunctival refill port.

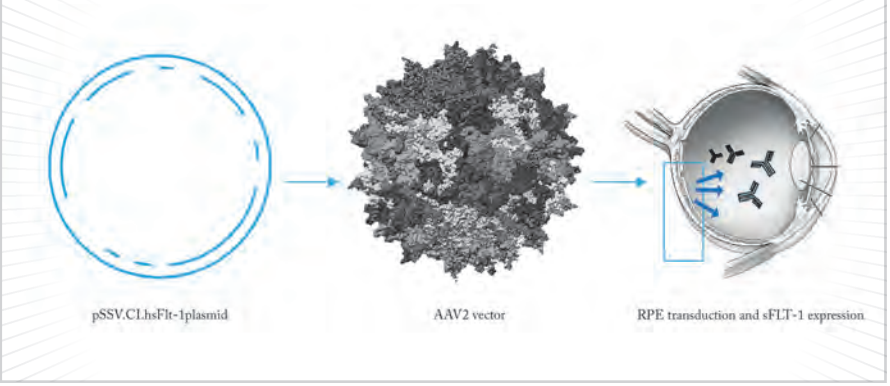

Figure 5. Expression of therapeutic transgene sFLT-1 in RPE after subretinal injection of AAV2 vector.

modification of ocular tissue is effected by means of vectors, such as replication-deficient adenovirus, carrying DNA that encodes a therapeutic protein that is expressed by the target cells. Modes of administration of ocular gene therapy include intravitreal injection and subretinal injection of vectors – the approach varies by the retinal cell type you wish to transfect. For example, an adenoviral vector has been used to transduce cells with material encoding a chimeric protein, sFLT-1, that can bind and block both VEGF and PLGF. Similarly, Avalanche Biotech has used a vector based on adeno-associated virus to transduce RPE cells such that they express sFLT-1 protein. This approach resulted in strong sFLT-1 expression over the entire area of the subretinal injection (Figure 5). However, phase 2 studies were not successful. RegenexBio is looking at even better AAV vectors to deliver anti-VEGF plasmids.

"We can also exploit the natural anatomy of the eye for drug delivery purposes."

Cell therapy

Encapsulated cell technology (ECT) involves implantation of devices containing populations of living cells that secrete a therapeutic protein (5). These cells are separated from host tissues by a semi-permeable implant wall, which protects the encapsulated cells from the patient's immune system while permitting inward diffusion of oxygen and nutrients and outward diffusion of therapeutic protein(s). At present, ocular ECT strategies use a proprietary cell line derived from human RPE cells; the cell line has been selected to be non-tumorigenic, viable under nutrient-poor / oxygen-poor conditions and capable of producing clinically relevant levels of therapeutics in vivo.

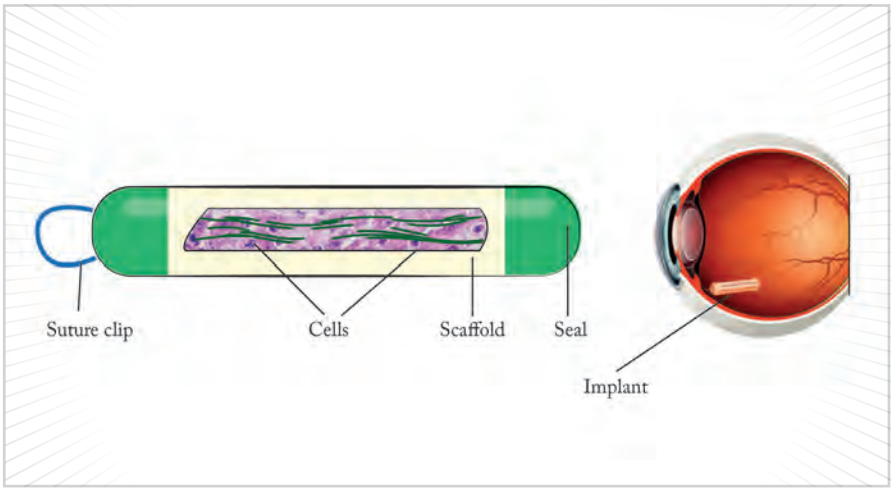

Figure 6. Multiple membrane encapsulated cell implant device.

The normal form of the ECT device is a cylinder, which is surgically implanted into the eye and tethered to the sclera by a titanium clip (Figure 6). Since drug release is correlated to surface area, adequate doses – for example, 10–12 µg/day – may require multiple cylinders to be implanted per eye. One example of this technique comprises human RPE cells that have been genetically engineered, by plasmid transfection, to secrete sFLT1.

Choroidal depots

We can also exploit the natural anatomy of the eye for drug delivery purposes (6). In particular, we can use the choroid as a depot; administration of drug can be achieved by cannulating the suprachoroidal space and injecting drugs either with a microcatheter or by using microneedles with lengths of between 800 and 1000 µm. Top-ups are then a matter of injecting drugs through these devices into the suprachoroidal space, from where the therapy can diffuse into the eye.

Keeping hopes high

The injection frequency associated with the current AMD standard of care is widely recognized to be problematic, which has led to a number of technical innovations aimed at improving ocular delivery of biotherapeutics. Sustained-release solid implants are the most advanced right now, but it is still too early to say which of the various procedures under development will have the most impact in AMD. No matter who the victor, I hope that we will be able to offer our macular degeneration patients an alternative that demands far fewer injections in the near future. Keep watching this space!

Peter Kaiser is Professor of Ophthalmology, Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio, and Senior Vice President of Product Development at Ohr Pharmaceutical. He is a consultant for Alcon, Allegro, Allergan, Aerpio, Bayer, Biogen, Digisight, Genentech, Neurotech, Novartis, Ohr Pharmaceuticals, Regeneron, Santen, Shire and Thrombogenics, and is both a consultant and stockholder in InSitu Therapeutics, Neurotech, and Ohr Pharmaceuticals.

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Your business
Your life

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Straight Talking
What made Robert Osher run his own cataract meeting – on his own dollar, off his own back? We asked Robert this, and more, like how did he make it a compelling option for people to attend, especially when there's no CME on offer?

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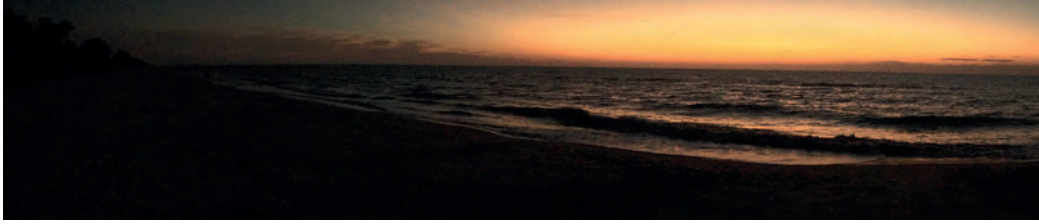
Brain Circulation
Brain Drain is an outdated term. When people leave their home country for another, it's no longer for the long term. The travel is bidirectional, and everybody learns something from the experience, writes C. Andrés Benatti



Straight Talking

Why Robert Osher decided to start his own meeting, Cataract Surgery: Telling It Like It Is, plus what's on offer, and how he runs it

Mark Hillen interviews Robert Osher

A cataract surgery meeting. No CME (continuing medical education). He bears all the financial risks of running it himself. Apparently, when told of his plans, Dick Mackool told him: "You're crazy! There's no possibility that a meeting like this would ever succeed; people come for credit." The man is Robert Osher. The meeting is Cataract Surgery: Telling It Like It Is!

Busy practice. Ophthalmology professor. Globetrotting lecturer. You have enough on your plate. Why do this?

Why? The story is entertaining. At the time, I had chaired the cataract section of the Hawaii winter meeting for over 20 years. Every year, I would put on a symposium and the topic would vary based on what the organizers asked for, and they gave me free rein. But then an educational company was brought in to oversee the winter meeting – and I received a pink slip in the mail, which said: "You are suspended for one year because you violated the CME guidelines." I wrote back and explained that I didn't even know there were CME guidelines! Their response was: "Well, they're new." I asked them what they were and what I'd done wrong. The response: "You're not allowed to mention product names."

To me, this was ridiculous – especially as the organizers had assigned to me the topic of new products in cataract surgery... Did you want me to pantomime the topic? I have to mention the names! "We have a zero-tolerance policy."

In my final reply, I noted a similar symposium I give each year at AAO – "The Cutting Edge" – which covers all things new. "It's one of the largest symposia of the meeting, and the AAO is a careful, extremely professional organization," I wrote. "They've never had a problem with this – and you're telling me I'm suspended for one year? I refuse to accept the suspension, rather, I insist on a lifetime ban; I will start my own meeting to teach the way teaching is meant to be!"

Why did you feel so strongly about this?

I travel over 100,000 miles a year giving lectures and teaching surgeons. I know how to teach. I know how people want to learn – and it's not by restricting information. It's by honest, candid, unrestricted communication.

How did you start?

I went to the surgeons that were the most experienced at cutting-edge off-label procedures; the surgeons with the most confident, rebellious and passionate personalities. I had a simple message: let's start a meeting with no CME. Dick Mackool told me I was crazy and that people want to attend for credits. We didn't need those people. We hoped to attract the people who come to learn and really want to raise their game. The most contemporary beneficial procedures for their patients is what they really care about.

> *"I had a simple message: let's start a meeting with no CME."*

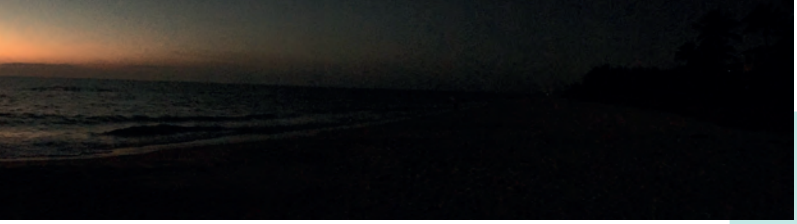
How do you choose what's on the program?

Right from the start, I implemented a detailed evaluation survey from both physicians and exhibitors, so I could learn what people do and don't like. I take the time to read and really understand the feedback – and doing so has been invaluable for the development of the meeting. I change the agenda dramatically from year to year. What people didn't like, I put in red; what people liked, I put in blue. New suggestions were circled in green. I decided that I would try to aim the meeting content at three different levels: one for young surgeons – primarily enthusiastic, yet not very experienced; one for the routine ophthalmologist, who is striving to make his or her practice better; and one for advanced surgeons – I figured I had Ike Ahmed, Mike Snyder and Dick Mackool operating on the most challenging cases in North America, so I had that covered.

We're not afraid to take gambles on new concepts, but we do have the symposia that always work – preoperative challenging cases, for example. I show the routine mature cataract, the white cataract, the posterior polar cataract, the miotic pupil, Flomax, nanophthalmos, extreme myopia... And then we have the Mike and Ike show: they take the symposium to the extremes, managing the most extraordinary,

At a Glance

- *What would make one man want to set up his own annual cataract meeting?*
- *Would surgeons come to a meeting which would provide cutting-edge technique and technology but would not offer CME? That was the question that would make or break the meeting.*
- *A huge financial risk and significant time commitment collided with a need to keep his finger on the pulse of what cataract surgeons wanted to see.*
- *From 'marathoning' the faculty to subsidizing the residents, Osher explains his approach to running the meeting.*

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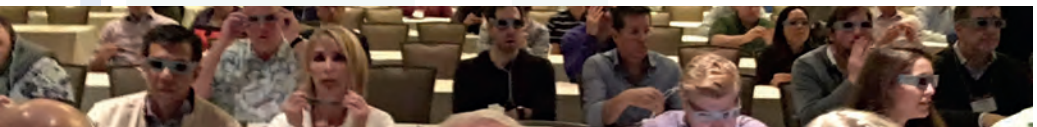
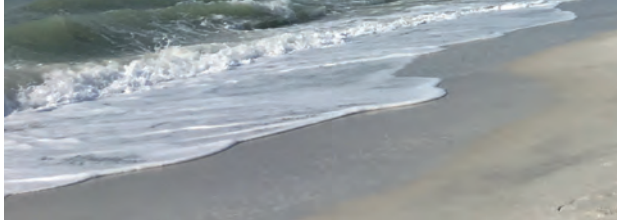
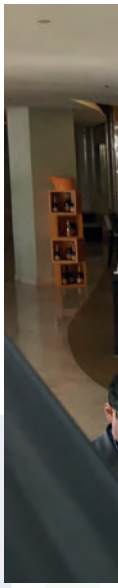




"The faculty interaction is invaluable, especially in the evening when there is plenty of Q&A."



unusually difficult, challenging cases, so people can see what's possible. The presentations progress from the basic, to the intermediate, to the advanced – and everybody stands to benefit.

Is it purely limited to cataract surgery?

No. As the meeting grew over the years, I decided to add subspecialty updates for physicians who wanted to come early (for no extra charge) on the day before the meeting – neuro, uveitis, oncology, refractive, plastics, retina, glaucoma and cornea and more. Then the wet labs were introduced. We started with two – on how to do anterior vitrectomy through the pars plana (which was a scary proposition at the time), and how to use intracameral devices. Later, I brought in Boris Malyugin to teach his ring, and Graham Barrett to discuss IOL calculation. This meeting now offers over 30 wet labs – for example, Ike Ahmed oversees six different glaucoma wet labs, one on each MIGS device. There are many other different courses like intrascleral haptic fixation and iris reconstruction – there's a whole smörgåsbord of opportunity to learn in a didactic environment (in the main hall) or in the private setting of these afternoon wet labs.

It's the same with Warren Hill: we run through 40 or 50 different situations where IOL selection is challenging – from the most basic like monovision (how safe can you be?) all the way to those extreme situations, where you're exchanging lenses and considering power ratios, depending on the strength of the lens; there's so much to cover. Fortunately, despite being the world's expert – bar none – Warren Hill is so generous and kind with his time. And that's another reason why this meeting is unique. The faculty interaction is invaluable, especially in the evening when there is plenty of Q&A.

If you're doing it yourself, what risks are you exposed to?

Boy, is there an astronomical financial risk! The cost of the last meeting was well over a million dollars. I have to give the venue my credit card, guarantee that several hotels will be booked, and commit to a certain amount of food and beverage. Then there is the cost of AV, security, promotion, programs, signs, staff – I get dizzy just thinking about the expenses.

Another reason for the high cost is my belief that the faculty deserves honoraria; I want to compensate them for their time away from their practices, of course, but I also expect so much more from them. I work them to death! I want to maintain the intimate environment of a small meeting, so the faculty must be there for the delegates to meet and question. I also believe in giving the attendee more than expected by 'marathoning;' we're not afraid to go from 7 in the morning until 10 or 11 at night – and the faculty buy in to these informal yet highly informative late night sessions.

Despite the high costs, this is a

champagne meeting on a shoestring budget – early bird registration is only $675, and if you want to attend a US winter meeting, this is great value. The hotels next year in Amelia Island will be between $200–$300 a night, depending on whether you stay in the Omni or the Ritz-Carlton. And I actually subsidize residents' registration fees so that they can attend, even on meager salaries (last year, subsidies ran to $42,000). Practicing Ophthalmologists and trainees can register on the meeting website cstellingitlikeitis.com.

How do you make the numbers work?

Exhibitors. Last year we had over 100. They provide breakfast, lunch, and dinner for all of the surgeons (and the exhibitors), and they also make the attendance price very low. We're not about making profit – we're all about educating as many people as possible.

What does it take to plan and run the meeting?

Running a meeting takes an egregious amount of time. I spent a whole weekend on my hands and knees at the venue for the next meeting (often until 4:30 am), mapping more than hundred exhibitor booths and assigning all the wet labs to different rooms. I met with the security team, the chefs, and the housing director. I went on a tour of the beaches, the golf courses, the hotel's gym – everything. My approach to it all is quite simple: I expect nothing less than perfection. It's the same with the A/V team; I tell them that I will pay well but there are to be no glitches – and that means preparing three or four months ahead of time. We can't risk an A/V crash because every moment of the meeting is scheduled down to the minute.

It's surprising just how much time and effort are required. And it must be crammed into a busy surgical practice, a demanding lecture schedule, the regular commitments of a professor of ophthalmology, my video journal, research, and 8 grandchildren.

It can't be just you organizing it, right?

I'm pleased to say it isn't just me organizing the conference; I have an amazing partner in this: Debbie Osborn – a real dynamo. She runs five medical societies in Connecticut and is involved with the best ophthalmology meetings in the country. She also lobbies to protect medicine in the General Assembly. I turn to Debbie when I run into a situation that I simply can't deal with. It's nice to be able to call up a person with the same commitment to the cause, in terms of energy and dedication, who can help resolve some of the issues we encounter. After all, I never learned this stuff in medical school! Debbie always reminds me that it's all about quality; we have a purpose and a mission, and we must stick to it.

Keynote Speakers. Who is next year's?

Over the years, I've brought in top international surgeons who have developed their own innovations – and we give them recognition for what they have achieved. I have picked some of the best surgeons on the planet and recognized them with a named lecture in their honor, so that others could see and meet Doug Koch, Boris Malyugin, Graham Barrett, Abhay Vasavada, Fernando Trindade, and Richard Packard. Next year, we're recognizing Ehud Assia. We are also honoring Sam Masket and Alan Crandall for their wonderful careers.

What is the most important aspect of the meeting for you?

I still insist on retaining that intimate feeling where a surgeon can come up and ask a question – and where the teacher feels like it is a privilege to share his experience. It's not an imposition, rather it's a pleasure to help that surgeon. Our meeting is educational, and everything that is presented and discussed is ultimately about helping the ophthalmologist do her or his job better – and that ultimately benefits their patients too. Our mission is to send each attendee home as a more knowledgeable and confident surgeon.

Robert Osher is Professor of Ophthalmology at the University of Cincinnati College of Medicine; Medical Director Emeritus of Cincinnati Eye Institute; Editor of the Video Journal of Cataract & Refractive Surgery; and the organizer of Cataract Surgery: Telling it Like it is! For more information about the meeting, please visit cstellingitlikeitis.com

Brain Circulation

It's not a brain drain when young, gifted surgeons and researchers work abroad. They come back – and the circulation of ideas and experiences benefits us all.

By C. Andrés Benatti

The great climate, the cultural diversity, the overwhelmingly beautiful landscapes, and an endless list of other wonderful attributes makes me feel immense pride about where I come from – Latin America – but it has, for many years, suffered from "brain drain." Why? The magic of Latin America has coexisted with inequality and unstable economies that has had an undeniable effect on our societies – and a direct impact on our professional and scientific communities. And ophthalmology has not been exempt from this phenomenon.

Andrés Oppenheimer is a brilliant Argentine journalist and lawyer who lives in Miami, who described a new concept: 'brain circulation.' It refers to how (mainly Asian) countries want to give their young professionals the chance to study and work abroad, predominantly in the US and Europe, to attain the highest quality standards. It means that their knowledge and training can be potentiated and exploited later on when they return to their countries of origin. For Oppenheimer, 'brain drain' is a dated concept, and needs to make way for the term 'brain circulation,' which has been spurred by both globalization and a greater access to knowledge.

At a Glance

- *What drives "brain drain"? Why do bright young surgeons and researchers move from their home country to another?*
- *However, the brain drain phenomenon is changing to one of "brain circulation"*
- *Spending a period abroad is opening up new horizons for today's generation of rising stars – and many are returning to improve things back home*
- *Everyone can learn something from the experience, and the traffic can go in both directions!*

Ophthalmology and Latin America

If you've ever attended an ophthalmology congress or course in a Latin American country, you'll encounter a unique collaborative spirit and truly high levels of professionalism. Argentina, Brazil, and Colombia, to name but a few, have offered the world outstanding ophthalmologists who changed the course of specializations, and their legacy is continued by new generations of Latin American ophthalmologists.

Few would deny that Latin America is a great source of 'raw material'; we produce bright brains that produce ideas of a highly innovative character. And we understand the need to have our professionals working at the highest standards in world ophthalmology and want to inspire in them a permanent thirst for innovation, and a commitment to do things in the best way possible. Achieving that comes down to education and knowledge sharing – and being aware of the opportunities that exist to facilitate the process. In the modern world, knowledge belongs to us all – and therefore it must be available to those who search for it, and those who are willing to enhance it and continue transmitting it.

The new era: sharing knowledge

Thankfully, the time when knowledge was guarded by the few from the many is over. We live in an era that sees a constant flow of information, skills and tools, which are (and should continue to be) available to everyone. Knowledge is the common currency in the 21st century. And in the field of ophthalmology, we must understand how crucial it is to equip our ophthalmologists with more clinical as well as surgical experience.

Noelia Kunzevitzky at Stanford University has vast experience in the subject. She was raised and educated in Argentina but emigrated to the US to perform ophthalmic research. Noelia had the chance to work with and train dozens of researchers and prospective ophthalmologists from all over the world. Today, many of them have returned to their own countries, and are developing brilliant professional careers as well as international collaborative projects. What does Noelia have to say?

"Science does not need to be limited by geography. When I left Argentina 13 years ago to pursue a doctorate in Cell Biology at Bascom Palmer Eye Institute at the University of Miami, there were only a few research groups in Argentina asking questions in Ophthalmology. Studying abroad increased my professional network significantly and allowed me to promote several international collaborations, many of which have lasted over a decade. I am proud to be part of a now larger community closing the gap between researchers and clinicians, and ultimately improving the quality of care for patients anywhere in the world."

Brain circulation in reverse

A question worth considering is whether 'brain circulation' may work favorably for many when you look at it from the right perspective. There is an increasing number of ophthalmologists, mainly European, who choose to travel to Latin America to attain post-graduate qualifications. Access to a combination of the latest technology and a large number of cases at regional ophthalmology hospitals makes this a

"I am proud to be part of a now larger community closing the gap between researchers and clinicians."

tempting option. Karim Tourkmani, a Spanish ophthalmologist, didn't hesitate when taking the opportunity to spend a year working for the Asociación Para Evitar la Ceguera (APEC) – the most important Ophthalmological Hospital in Mexico City – for his Fellowship training in Cornea and Refractive Surgery. He now resides in England and shares his feelings about his experience with us:

"It was a fantastic year, where I set up a strong base for my career as a corneal and anterior segment surgeon. Also, I learned many other things about Mexican lifestyle and culture, as well as other Latin American countries, as I made very good friendships with many Mexicans, Argentinians, Peruvians and Colombians. From a purely ophthalmological point of view, I gained vast knowledge about pathologies commonly found in tropical countries, but very rare in Europe, where I come from. Besides, I learned to perform penetrating keratoplasty and LASIK, among other techniques."

Landon Grage, a resident at UCSD Shiley Eye Institute, is another good example of how barriers are being broken. He speaks Spanish, and dreams of pursuing fellowship training at APEC, having learned about the main features of the hospital. "I will finish my residency program in San Diego, then I would like to complete my Fellowship in Mexico, then I will return to my home state in the USA," he says, also proving that brain circulation can flow both ways.

My viewpoint

I strongly believe that the brain circulation approach will pay off because these professionals will be able to offer up-to-date, responsible and highly advanced ophthalmological care – and also help advance it.

For us in Latin America, it means that we can count on a whole generation of excellent specialists who will return to our countries, paving the way for the development of ophthalmology in our region over the coming decades, and continuing the legacy of knowledge exchange. I am convinced that there will be a powerful chain effect and, in a relatively short time, we will not be talking about brain drain anymore, but instead talking about the far more beneficial effect of brain circulation!

C. Andrés Benatti is a Cornea and Refractive Surgeon and Associate Professor at Clinica de Ojos Córdoba, Córdoba, Argentina, International Professor at APEC, Mexico City, Mexico and a former International Fellow at UC San Diego Shiley Eye Institute. Benatti is also co-founder OftalmoUniversity.com.

Fortune Favors the True

Sitting Down With… Cynthia Matossian,
Founder and Medical Director of Matossian Eye Associates,
Mercer County, New Jersey, and Bucks County, Pennsylvania, USA

What drew you into ophthalmology?
I entered medical school fully intending to go into ophthalmology, partly because it seemed like a happy field to work in, and partly because of the patients. Not every specialty allows such a breadth of patients: for example, in OB/GYN you see only women and in pediatrics you only treat children, but in ophthalmology, you see all age ranges and both sexes. In addition, the unique aspect of ophthalmology, which I love, is the fact that it combines surgery with clinical medicine. In most specialties, you are either a surgeon or focused on clinical medicine; very few disciplines allow you to have an almost equal focus in both. And to me, that was very attractive because I love working with my hands and I love seeing patients in the office – ophthalmology is a perfect blend!

How did you go from training to setting up your own successful practice?
After training and working in a practice for one year, I wanted to set up on my own – but when I tried to buy an ophthalmology practice from two retiring physicians, I was confronted by two brothers who were startled at the prospect of a woman taking over, which created more resistance than there should have been! I knew that if I could get over that initial hurdle, I could get over any hurdle. I was confident, but always approached things diplomatically and cautiously. I worked extremely hard – I was available for my patients and for the local internal medicine and family practice physicians 24/7, and that's how I grew the practice. We now have 16 doctors, three offices, and a staff of 75.

What's driven you forward in your career?
Both my parents always encouraged me to do the best I could and emphasized that education was really important. They also taught me to always treat others with respect and dignity. I've always taken that to heart, so all patients – regardless of age, race, color, or creed – get treated with equal respect and dignity, and receive the best surgery I can perform. That inclusive attitude has helped the practice grow.

What are the highlights of your career to date?
There are so many highlights... It's hard to specify but it feels wonderful to be so passionate about what I do! I come to work happy and energized every single day. In fact, I don't view it as work, I just feel fortunate to be doing what I love.

What's exciting in ophthalmology at the moment?
There's always something new in ophthalmology; always something slightly better or slightly different from even six months ago. Currently, the expanded range of IOLs are terrific, the micro-incisional glaucoma procedures are super exciting, as are the diagnostic tools and treatment modalities for dry eye disease – all of these things make for an extremely exciting time.

Do you think dry eye will be adequately addressed in the coming years?
Very much so; in the last 10 years, we've come a long way in the arena of ocular surface disease. We have better diagnostic equipment, we have clinical studies and peer-reviewed journal articles about the impact of the tear film on surgical outcomes and how dry eye can interfere with daily tasks. We also have wonderful treatment options whether it's through vectored thermal pulsation or intense pulsed light treatments or newly approved prescription medications. I think this is just the tip of the iceberg: we're going to be able to understand ocular surface disease better and be able to treat and diagnose it earlier.

"Have confidence in yourself and do what's right for the patient; being honest and true to yourself will help you succeed."

How do you think the next 10 years of your clinical practice will pan out?
I think there will be continued innovation in IOLs to provide patients with a more natural, expanded range of vision with less disturbing light phenomena, such as halos, glare or star-bursts. In addition, I think drug delivery will change: we'll move away from instilling drops onto the surface of the cornea and conjunctiva – like we've been doing for a hundred years or more – to finding alternative drug delivery systems. Improved delivery will decrease the patients' drop burden, improve compliance, and possibly enhance drug penetration to give a longer-lasting effect. New drug delivery methods may decrease the frequency of injection for neovascular AMD or diabetic macular edema.

What's the best piece of advice you've been given during your career?
Follow your heart. If your heart's not in it, you'll never succeed.

What key advice would you pass on to younger ophthalmologists?
Have confidence in yourself and do what's right for the patient; being honest and true to yourself will help you succeed.

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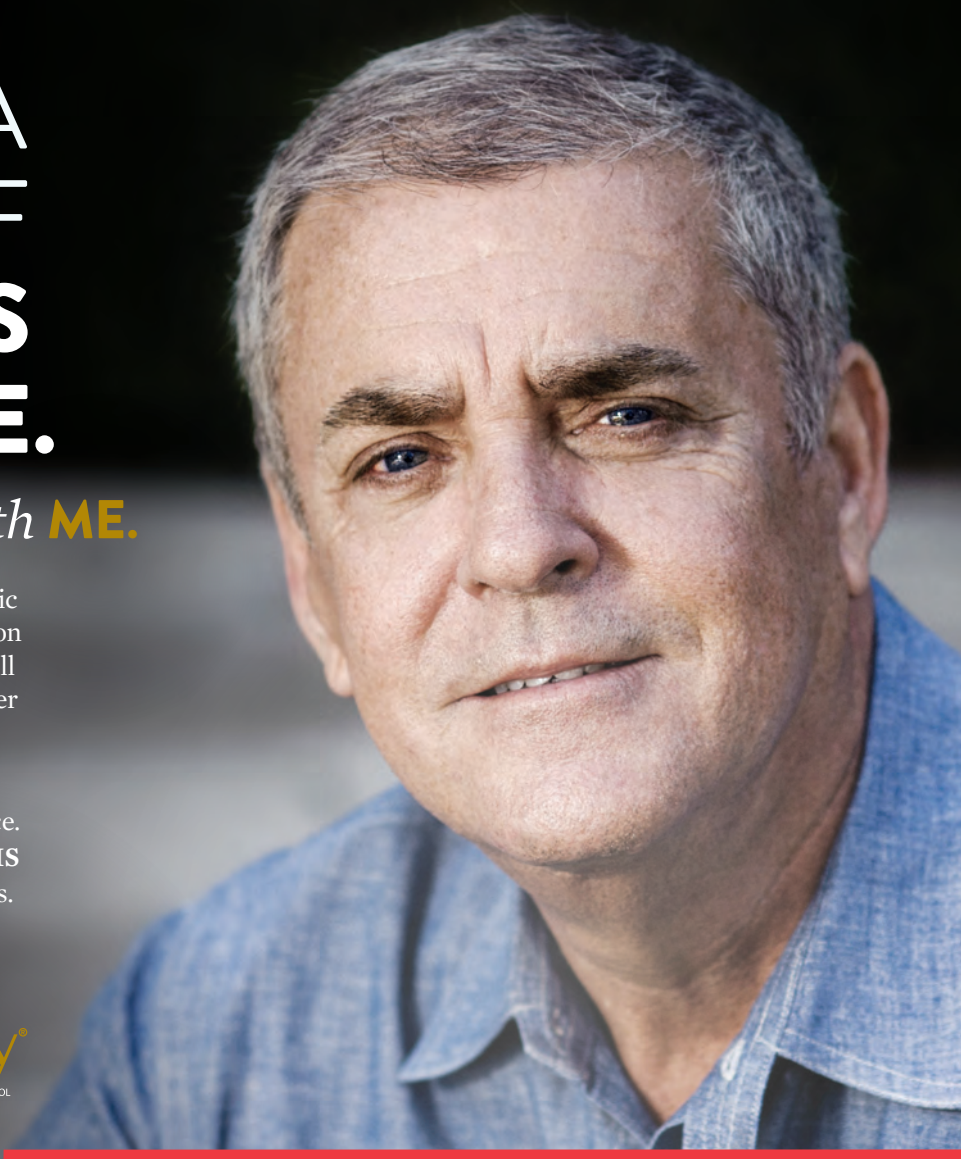

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INDICATIONS AND IMPORTANT SAFETY INFORMATION FOR THE TECNIS SYMFONY® AND TECNIS SYMFONY® TORIC EXTENDED RANGE OF VISION IOLs
Rx Only

INDICATIONS: The TECNIS Symfony® Extended Range of Vision IOL, model ZXR00, is indicated for primary implantation for the visual correction of aphakia, in adult patients with less than 1 diopter of pre-existing corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The model ZXR00 IOL is intended for capsular bag placement only. The TECNIS Symfony® Toric Extended Range of Vision IOLs, models ZXT150, ZXT225, ZXT300, and ZXT375, are indicated for primary implantation for the visual correction of aphakia and for reduction of residual refractive astigmatism in adult patients with greater than or equal to 1 diopter of preoperative corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The model series ZXT IOLs are intended for capsular bag placement only. **WARNINGS:** May cause a reduction in contrast sensitivity under certain conditions, compared to an aspheric monofocal IOL. Inform patients to exercise special caution when driving at night or in poor visibility conditions. Some visual effects may be expected due to the lens design, including: perception of halos, glare, or starbursts around lights under nighttime conditions. These will be bothersome or very bothersome in some people, particularly in low-illumination conditions, and on rare occasions, may be significant enough that the patient may request removal of the IOL. Rotation of the TECNIS Symfony® Toric IOLs away from their intended axis can reduce their astigmatic correction, and misalignment greater than 30° may increase postoperative refractive cylinder. If necessary, lens repositioning should occur as early as possible prior to lens encapsulation. **ATTENTION:** Reference the Directions for Use for a complete listing of Indications and Important Safety Information.