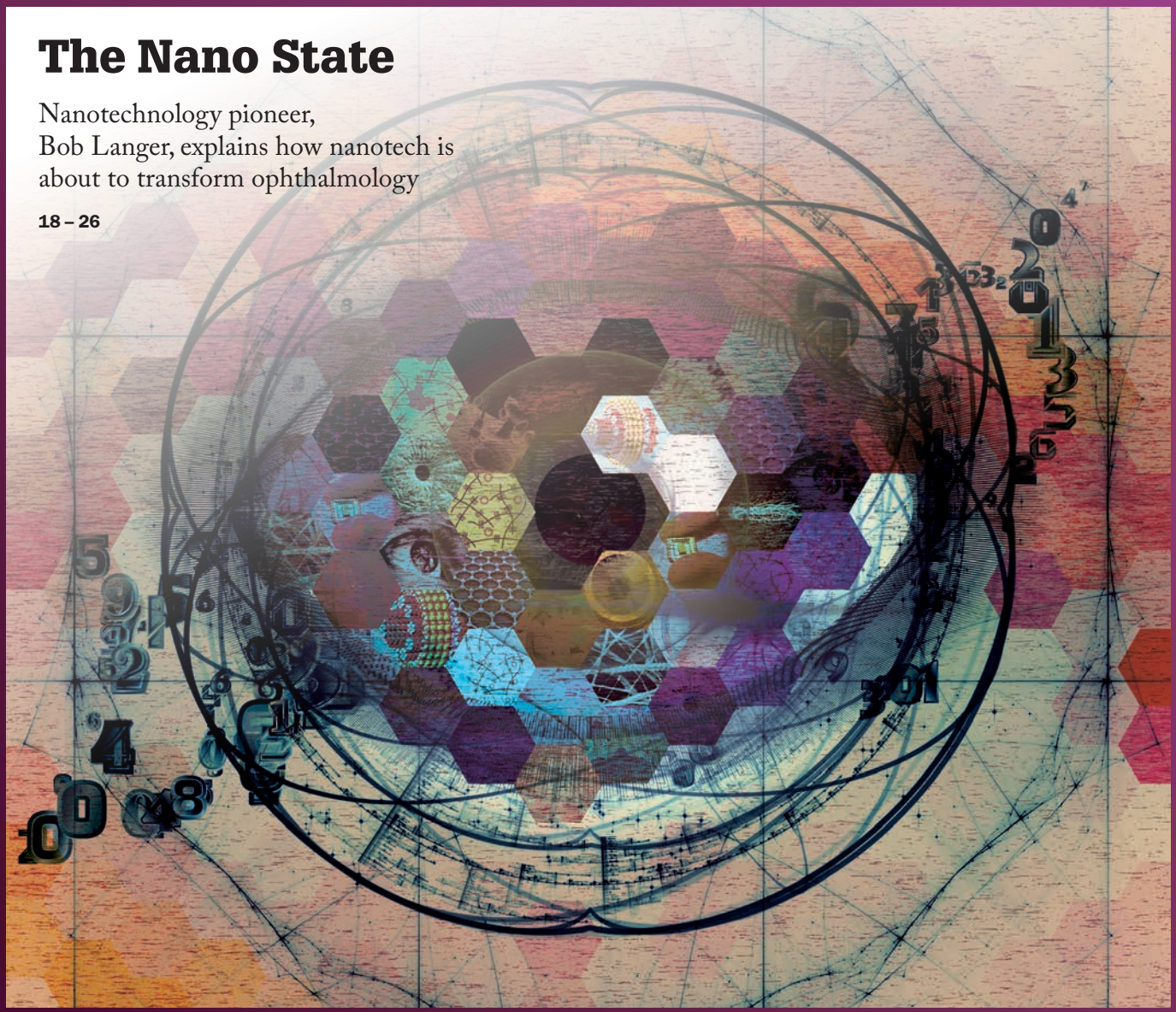
SEPTEMBER 2014 # 11

the Ophthalmologist

The Nano State

Nanotechnology pioneer, Bob Langer, explains how nanotech is about to transform ophthalmology



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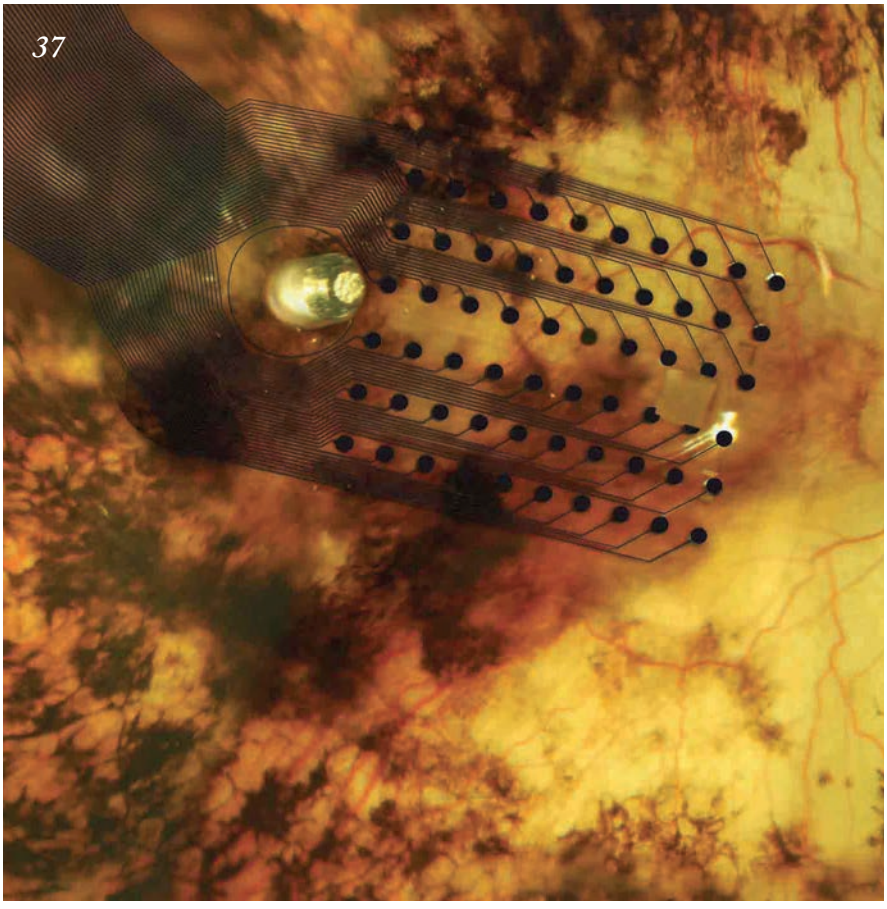

On The Cover

A representation of the eye formed from hexagonal units, much like those present in carbon nanotubes.

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the Ophthalmologist

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DON'T LET DRY EYE RUIN THEIR AUTUMN

ALLERGAN Ophthalmology

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Time to unpack your scarves and woolly jumpers; autumn has arrived, bringing golden leaves and bracing winds. Millions of Dry Eye sufferers also have to brace themselves. With symptoms including burning, stinging, excessive tearing and dryness, it can be tough on eyes.[1-3] Fortunately, the OPTIVE® Family works effectively in either aqueous or lipid deficient Dry Eye sufferers.[4-6] Recommend it to your patients and help make their autumn epic.

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EU/0159/2014b; Date of preparation: July 2014

Being Engaged

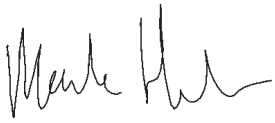
The Ophthalmologist is one year old. We promised to tell you ophthalmology's most engaging stories, and we've traveled the world to do so.

It's late April in Boston. People in business attire are pouring out of cabs, over the cobblestone pavement, and rushing through the revolving doors of the Renaissance Waterfront hotel to get out of the rain. They ignore the reception desk and its display of colored glass orbs to their left, and continue onwards at a pace, following the signs that lead to the Brewster Room. The smartly-dressed but slightly damp people are ophthalmologists and they've come to the annual ASCRS meeting in part to see the main attraction: Robert Langer.

Langer is no ophthalmologist – he is a chemical engineer – but his work may transform the discipline – and many other areas of medicine. In 2001, Time Magazine and CNN named Langer as one of the 100 most important people in America and Forbes Magazine selected him as one of the 15 innovators worldwide who will "reinvent our future". Why? He's a pioneer of nanotechnology and its application in healthcare. Some of the technologies commercialized by companies he founded are beginning to transform medical diagnostics, vaccine design, cancer therapy and (appropriately for us), ophthalmology – something that Bob and his colleagues outline in this month's feature article on page 18.

It's been a year since we published the first issue of The Ophthalmologist. For me, Langer's cover story epitomizes the type of content that we want to deliver to you: informative and important. In September 2013, we promised to tell the stories of ophthalmology – stories that inform, educate and bring a fresh perspective. We wanted to offer insight: useful information that is pertinent to your practice; industry and trend analyses that highlight where ophthalmology has been, and where it is going. In addition to nanotechnology, this current issue covers everything from the ophthalmic consequences of interplanetary space travel to ensuring that you give the best consultation you can. I hope that we are living up to our pledge to bring you engaging, informative stories – and I trust that you will let us know if we aren't. After all, it's your publication.

Mark Hillen
Editor



Robert Langer

Chemical engineer, nanotechnology guru, and pioneer of tissue engineering, Robert Langer is the David H. Koch Institute Professor at MIT, and oversees the biggest biomedical engineering laboratory in the world. Langer is the most cited engineer of all time, and in 2002, Forbes magazine named him "one of the 15 innovators worldwide who will reinvent our future."

Justin Hanes

Justin Hanes is the Lewis J. Ort Professor of Ophthalmology at the Wilmer Eye Institute at Johns Hopkins University, and the director of the Center for Nanomedicine at the Johns Hopkins University School of Medicine… and a former student of Bob Langer. His principal research focus is on using nanotechnology to improve drug and gene delivery strategies to the eye.

Hongming Chen

Another former student of Langer's, Hongming Chen is now the Chief Scientific Officer at Kala Pharmaceuticals, and is responsible for the pre-clinical and clinical development of the mucus-penetrating nanoparticle drug formulations first developed in Justin Hanes' laboratory.

Read Robert, Hongming and Justin's article on how nano-scale drug formulations are about to transform ophthalmology on page 18.

Theo Seiler

Number one in our 2014 Power List, Theo Seiler is a pioneer of refractive surgery. Among his achievements are the development of the first clinical dye laser and the invention of corneal crosslinking (CXL); he also performed the first ever PTK, PRK and wavefront-laser guided surgical techniques on the human eye, and was the first to combine LASIK and rapid CXL.

Read Theo's thoughts on the current state of ophthalmology and where he thinks it's heading on page 50.

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Upfront

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

We welcome suggestions on anything that's impactful on ophthalmology; please email

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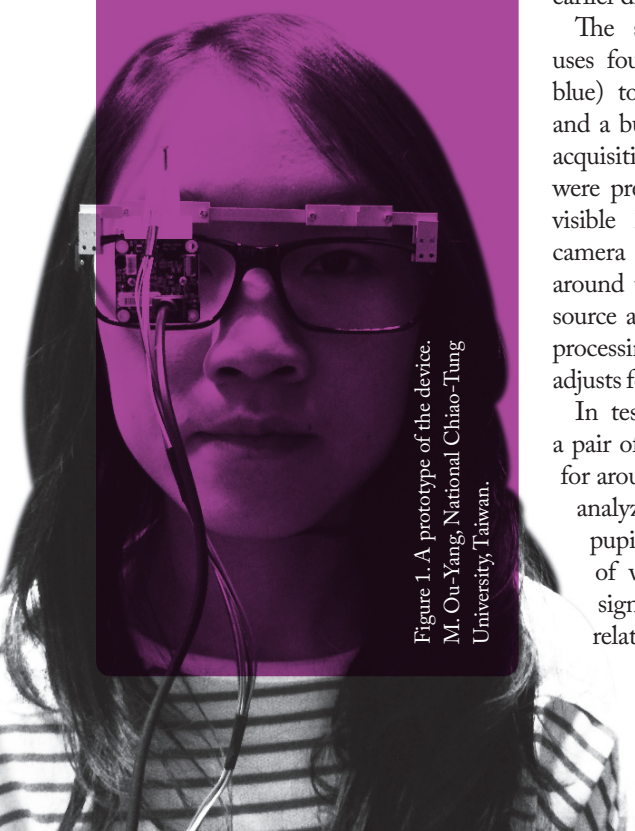

Figure 1. A prototype of the device. M. Ou-Yang, National Chiao-Tung University, Taiwan.

Analytical Eyeglasses

A new wearable device detects the early signs of diabetic autonomic neuropathy before damaging symptoms appear

Typically, people are only diagnosed with diabetic autonomic neuropathy (DAN) once symptoms appear, but unfortunately by this point, moderate nerve damage and organ dysfunction has already occurred. Clearly, anything that can help provide an earlier diagnosis leads to improved outcomes. To that end, Taiwanese researchers have developed a wearable pupillometer (Figure 1) that can detect some of the earliest signs of DAN (1). Pupillary autonomic neuropathy (PAN) manifests itself as smaller horizontal pupillary diameters and impaired pupillary light reflexes (2, 3); detecting these defects predicts DAN, and should help give an earlier diagnosis.

The spectacle-mounted pupillometer uses four LEDs (white, red, green and blue) to stimulate a pupillary response and a built-in infrared camera for image acquisition. A number of helpful features were present: a beam splitter that filters visible light from infrared to reduce camera noise, an LED arrangement around the IR camera to eliminate light source artifacts (Figure 2), and an image processing system that compensates and adjusts for the effect of blinking.

In tests, the device was mounted on a pair of glasses and worn by the patient for around 30 minutes. The pupillometer analyzed ten parameters relating to pupil diameter and response time, of which five were found to differ significantly in those with DAN relative to healthy controls:

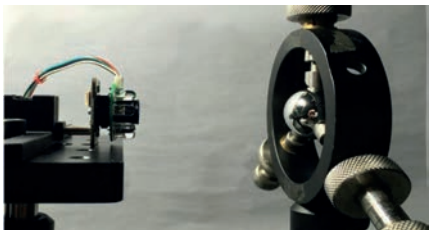

Figure 2. The original experimental set-up. On the right is an eye model, and on the left is the pupillometer (note the LED arrangement around the central infrared camera).

- resting pupil-to-iris ratio in the dark room
- minimum pupil diameter after simulation with lighting
- restoration to 75% resting pupil diameter
- latency to constriction
- maximum pupil restoration velocity.

If you're reminded of Google Glass as you read this, you're not the only one. The study authors note that the 78-gram pupillometer is only "slightly heavier" than Google Glass (50 grams). However, the new pupillometer only runs a single app and is not yet ready for commercialization – the authors are aiming for this in 2020.

In the meantime, Yuan Ou-Yang and his fellow researchers are hoping to improve the device by reducing its size and experimenting with ways to view both eyes simultaneously; they also want to collect more data from patients with diabetes. *RM*

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Choroid Cartography

Why are certain regions of the choroid more prone to disease than others? To answer that, you need proteomics

Part of the pathology of age-related macular degeneration (AMD) – and many other posterior segment diseases – is inflammation of the choroid and the accompanying retinal pigment epithelium (RPE). But it's a patchy pathology; some regions are more susceptible to inflammation than others. North American researchers Jessica Skeie and Vinit Mahajan wanted to know why.

Skeie and Mahajan are based in the Department of Ophthalmology and Visual Sciences' "Omics" laboratory at the University of Iowa Carver College of Medicine. They had the means to identify the proteins across multiple regions of the choroid-RPE regions, the bioinformatical know-how to process the information, and three non-diseased eyes from the Iowa Lions Eye Bank. The plan was simple: take tissue samples from multiple regions of the choroid-RPE complex – the fovea, macula and the periphery Figure 1) – and create a map. So what map did they draw?

A molecular map that catalogued more than 4,000 unique proteins in each of the three areas examined, with differential regional expression patterns for almost 700 proteins that had previously been identified as risk factors for retinal diseases related to oxidative stress (1). Of note, the peripheral region contained unique antioxidant activity proteins, whereas many inflammation-related proteins and complement cascade activators were predominantly expressed in the fovea and macula regions sampled. One highlight was complement factor H (CFH). Certain CFH gene mutations can accelerate the development of AMD, and the study protein expression map revealed that CFH is most abundant in the fovea – the authors suggest that monitoring CFH expression in that region might act a marker of AMD disease status in certain experimental models.

"This molecular map now gives us clues why certain areas of the choroid are more sensitive to certain diseases, as well as where to target therapies and why," explained Mahajan. "Before this, we just didn't know what was where. Now you can see all those differences that you couldn't see before."

Previous studies have compared the abundance of single proteins in the fovea, macula, and periphery. The UI choroid-RPE map corroborates findings from these studies, but has also identified a treasure-trove of thousands more proteins that may be involved in vision loss. Mahajan likens it to a leap from the first topological drawings of a landscape to the detailed satellite images we have now. *MH*

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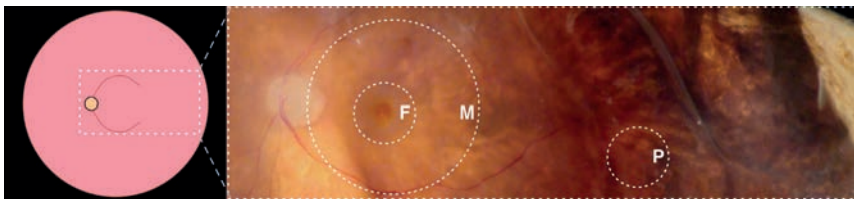

Figure 1. A schematic of the three sampled choroidal regions, in relation to the entire eye (left) and as regions (F, fovea; M, macula and P, periphery).

CXL Excels

Two studies demonstrate the safety and potential of decentered corneal collagen cross linking

Corneal collagen cross linking (CXL) with ultraviolet (UV)-A light and riboflavin is a well-established treatment for corneal ecstasias and keratoconus. But are we using it to its full potential? This was the question pondered by Geneva and Lausanne-based researchers, who believe there are other conditions that might benefit from CXL, such as pellucid marginal degeneration and peripheral ulcers. However, these diseases require decentered, eccentric illumination profiles, meaning that partially irradiating the limbus with (potentially mutagenic) UV-A light is unavoidable. Corneal limbal stem cells are needed to repair the corneal epithelium following epi-off CXL, and damage affecting their regenerative capabilities would be detrimental to recovery. So the big question was, does UV-A light harm corneal stem cells? According to the researchers, no (1).

The team performed eccentric CXL using standard and double fluence (5.4 and 10.8 J/cm^2, respectively) on the corneas of New Zealand White rabbits, then analyzed its effect on the corneal limbus by immunohistochemical examination of the expression pattern of the putative stem cell marker, p63. They found that UV-A radiation – at either standard or double fluence – does not affect the ability of limbal epithelial cells to regenerate, and has no effect on the expression patterns of p63, leading the study's authors to suggest that, when eccentric CXL is "medically mandatory, a partial irradiation of the inferior limbus may be performed in the cornea without harm."

CXL has also come to the rescue of a patient with Terrien Marginal Degeneration (TMD). TMD may be rare, but it is a pernicious disease and particularly challenging to manage. By cross linking corneal collagen, CXL renders a cornea with stroma that are resistant to enzymatic degradation, which appears to hinder the corneal melting process according to a new case report (2). The patient suffered from bilateral TMD and eccentric CXL was employed in the right eye. One year later, keratometry values had decreased and both corrected distance visual acuity and corneal thickness had improved. Three years later, the patient's left eye was treated, with similar results. Follow-up at five years showed that mean keratometric values remained stable, a reduction in maximal keratometry values, a thickening of the corneal stroma, and improvements in visual acuity were also seen.

The case report authors propose that CXL shifts the balance between synthesis and catalysis of stromal collagen towards synthesis, which results in an overall increase in collagen production, augmenting the corneal stroma. The findings suggest that CXL could be used to halt – and even partially reverse – TMD-induced corneal thinning, and perhaps to prevent disease progression if used at the point of diagnosis. *RM*

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Outsourced Cataract Complications

An overstretched UK hospital that subcontracted cataract surgery is faced with a 48.3 percent complication rate. Who foots the legal bill?

National Health Service (NHS) ophthalmology clinics in the UK are having a hard time of it lately. Austerity measures and the pressures of an aging demographic fill waiting rooms to bursting point, day in, day out. For one hospital in Taunton, Somerset, the backlog of patients awaiting cataract surgery was so great that they contracted a private health services provider, Vanguard Healthcare, to help clear it. The contract was £320,000 for 400 procedures, to be performed in a mobile unit parked next to hospital's day surgery unit. The deal was terminated after four days.

The complication rate with cataract surgery is usually very low, at 1 in 400. Unfortunately, in this case it was almost 1 in 2 – or rather, of the 62 patients treated during the time the contract was in place, thirty experienced complications. Most complained of blurred vision, pain and swelling. However, the local newspaper reports that "more than ten" experienced significant issues (1), and it appears that some may require corneal transplantation surgery to retain vision in the affected eyes (2).

Vanguard operate one of the world's largest fleets of mobile healthcare facilities, ranging from operating theatres to accident and emergency services. The unit at Musgrove Park Hospital (MPH) was staffed by highly qualified surgeons with many years of experience working in the NHS. So why did nearly half of their cataract patients experience problems? To date, nobody has an answer to that question – Vanguard and MPH are currently investigating to establish what went wrong.

Understandably, many of those affected are now seeking compensation. Colin Close, the medical director of MPH, acknowledged compensation claims could be made and was quoted as saying, "Any financial responsibility would rest with us" (1), but the hospital now claims that Close was misquoted (2). So, will the NHS ultimately foot the bill? The UK's Department of Health states that it will not: "Patients deserve the safest and best care and the NHS will hold this company to account if things have gone wrong, and reclaim costs on behalf of [the] patients." *RM*

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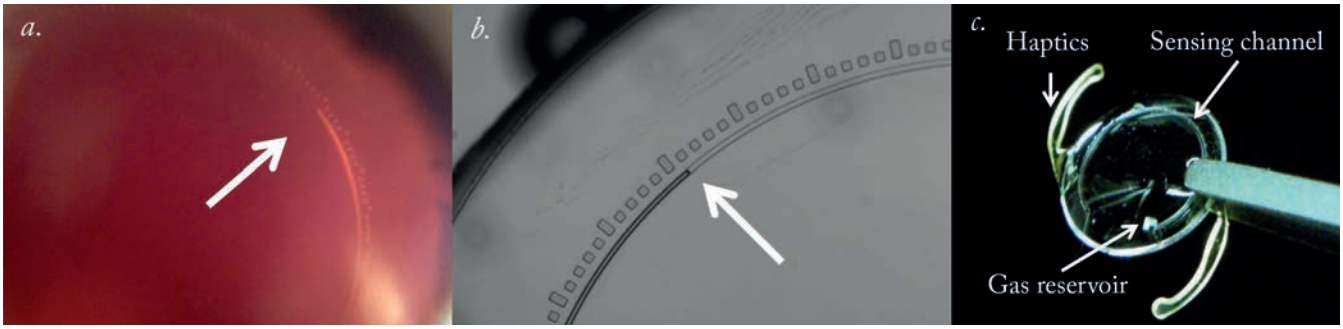

Figure 1. The IOP-reading IOL. a. The air/fluid interface can be easily captured by a smartphone with an optical adaptor; b. Scales can be incorporated onto the outer side of the channel to help measure the location of the air/fluid interface; c. The sensor can be embedded in an IOL and implanted during cataract surgery. Image credit: Ismail Araci, Baolong Su, Stephen Quake and Yossi Mandel.

Feeling the Pressure

Can a new implantable microfluidic sensor put IOP tracking in the hands – or rather eyes – of patients with glaucoma?

American and Israeli researchers have developed an implantable sensor that they say measures intraocular pressure (IOP) with high accuracy and reproducibility – when tested in a porcine model (1). IOP is notorious for fluctuating over the course of the day, which makes getting a truly representative measurement with tonometry tricky; posture makes a difference and peak IOP is often not at the time of measurement – it's when the patient is lying on their back sleeping at night. Furthermore, Goldmann applanation tonometry requires topical anesthesia and can be affected by variations in corneal biomechanical properties, such as thickness or disease state.

The new device uses a passive pressure sensor implant that relies on microfluidic physics principles. In other words, the implant contains a tiny open channel that draws in the aqueous intraocular fluid (due to capillary forces and IOP), that results in the compression of a gas reservoir attached to the channel. The greater the IOP, the more compressed the gas becomes. To calculate IOP, the relative position of the aqueous-gas interface can be measured with a specialized camera, a slit lap during a routine eye examination – or even a smartphone equipped with an adaptor. The device was originally developed as a stand-alone implant (inserted through the sclera and placed directly against the choroid), but has now been incorporated into an intraocular lens (IOL).

IOLs containing the device performed well, first in pressure chamber tests, and also when implanted into the capsular bag of pig eyes as part of a routine cataract surgery procedure. In both cases the relationship between the aqueous-gas interface and IOP was highly linear across the 0 – 16 mmHg pressure range examined. Calibration can be performed in a pressure chamber pre-implantation, and post-implantation via regular Goldmann tonometry.

As glaucoma is associated with an elevated risk of cataract development, many patients undergo cataract surgery and receive IOLs. IOLs that also measure IOP sound like an attractive proposition – especially if they enable patients to easily self-monitor using a smartphone. *RM*

Reference

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Awh versus the NEI

Are people with certain genotypes actively harmed by AREDS supplementation, accelerating AMD?

In an era where you can pay US$1000 to get your entire genome sequenced, it doesn't seem like too much of a stretch to compare your genetic data against the list of drugs your physician's prescribed to you. Most pharmacogenomic testing pertains to drug metabolism (is your liver converting enough pro-drug to drug – or too much?) but it may now apply to the dietary supplements people take to stave off the development of AMD (1) – albeit with a hefty dose of controversy (2).

Carl Awh is a retinal specialist in a private practice in Nashville, TN, who has access to the Age-Related Eye Disease Study (AREDS) dataset,

and the genetic material of many of the patients that participated in the trial. The AREDS trial originally showed that the development of AMD is delayed in people who take certain nutritional supplements – Vitamins C, E, β-carotene, zinc and copper – leading to the National Eye Institute (NEI) to recommend the trial formulation in patients with moderate AMD.

There are a number of genes that, if mutated, increase the risk of a patient developing early AMD; two particularly prominent ones are complement factor H (CFH), and age-related maculopathy susceptibility-2 (ARMS-2). Awh et al's pharmacogenomic analysis of the AREDS data suggested that certain polymorphisms (risk alleles) in either of those genes could lead to a reduction in the benefit patients received from AREDS supplementation (3). At the 32nd Annual Meeting of the American Society of Retina Specialists, he took this further, stating that patients with one or more CFH risk alleles taking Zinc-containing supplements might actually experience an increase in the rate of AMD progression, rather than a reduction. Awh's also a prominent proponent of genetic testing – he believes that genotype-directed dietary supplementation for patients with AMD should be performed regularly (3).

Not everyone agrees with his interpretation. The NEI performed similar analyses on the same dataset and reaches the opposite conclusion – they found no statistically significant differences in AREDS supplementation benefit across all of the CFH and ARMS2 genotypes examined. They conclude that currently, genotyping in AMD is of no benefit for the management of nutritional supplementation in patients with AMD (4). The NEI authors accounted for the differences in their respective results: they had a larger sample size in their study than Awh and colleagues (1237 vs 995).*RM*

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Set Lasers to Fun

Would you recommend vision correction surgery solely to facilitate your patient's enjoyment of virtual reality technology?

Thousands of people undergo laser eye surgery every year, but an individual known only as ceno666 had an unusual motive for opting for laser eye surgery to correct his farsightedness and astigmatism: his glasses annoy him when he uses his Oculus Rift virtual reality (VR) headset (Figure 1) to play videogames (1). In his own words: "For me it is clear, my eyeglasses are like an obstacle for optimal VR experience."

Ceno666 is a Redditor – a user of the popular social media website Reddit – and his recent posts have grabbed considerable media attention and public speculation. Many have questioned whether or not it's a step too far to undergo over US$2000-worth of eye surgery simply to enjoy playing VR videogames more than before. Others have suggested that the Oculus Rift – which is still under development – may eventually contain interchangeable lenses that could correct for vision problems anyway. More pragmatic commenters pointed out that it's a very safe procedure that will improve not only his vision in videogames, but in the rest of his life too – which is quite a bonus.

However, it seems that ceno666 will have to continue wearing his glasses with his Oculus Rift for the time being. A thorough pre-surgery eye examination resulted in a recommendation against surgery. "They want to wait one year and see if my combination of +/- diopters settles," explained the Redditor. His final comments on the subject indicate a level of skepticism about the professionalism of some US ophthalmologists – "I am a little disappointed but also glad that they are really not only after their money and want to do it perfect [sic] […]. To all who consider the surgery, please do your research and be sure that they are really trustworthy and not afraid to reject customers." *RM*

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Figure 1. The virtual reality gaming headset, Oculus Rift.

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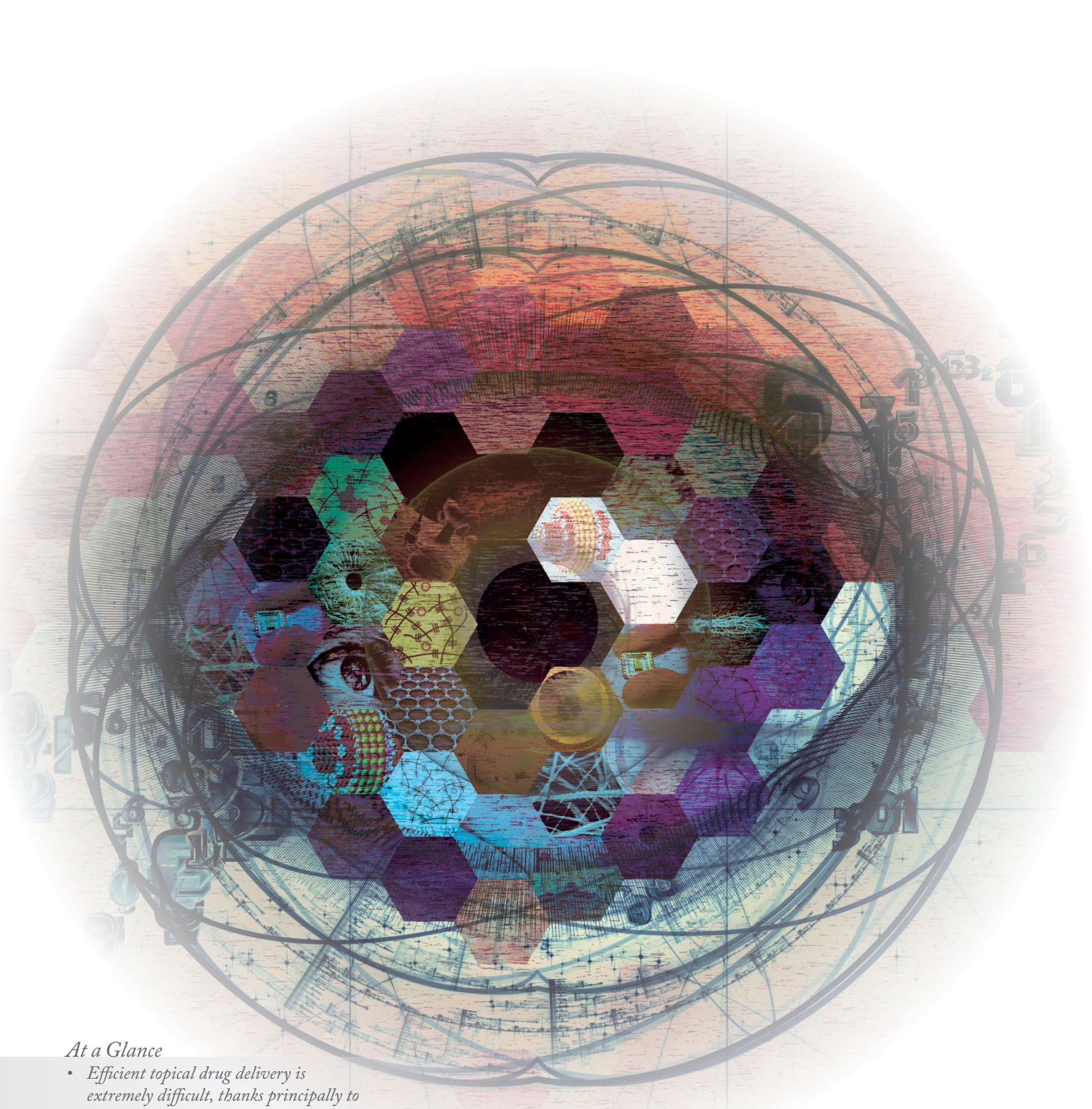


At a Glance

- *Efficient topical drug delivery is extremely difficult, thanks principally to the tear layer and the anatomy of the ocular surface*
- *Topical drug delivery to the posterior segment is, today, totally unachievable, hence the need for intravitreal injections*
- *Nanotechnology – both nano-scale formulations and smart coatings – has the potential to solve both problems*
- *This is likely to be game-changing – the reduction of intravitreal injections for wet AMD represents just a tiny fraction of nanotech's potential*

The Nano State

Imagine prescribing eye drops to treat wet AMD, or delivering genes to the retina of patients with retinitis pigmentosa. Nanotechnology can do both – and it could potentially transform ophthalmology

By Robert Langer, Justin Hanes and Hongming Chen.

Ophthalmology has a problem. The problem is ocular drug delivery, and it's as old as the first drugs used on the eye. In fact, the problem is the eye; its anatomy, and its protective mechanisms. Even if you want to apply a topical therapeutic to the cornea, you have big issues (Figure 1). The aqueous layer of the tear film not only rapidly washes away anything in an aqueous formulation, but the mucus layer gets in the way too: it contains mucins. These highly glycosylated, sticky molecules are wonderful for arresting the progress of foreign objects and pathogens towards the cornea, binding them, and preparing them for removal. But the tear film does the same with topically applied drugs. If you're thinking of approaching the problem with a systemically administered drug, most won't get there: the blood-ocular barrier will prevent most drugs from passing efficiently into the eye. For ocular surface disease, the mainstay option is topical therapy, despite the inefficiencies associated with its use.

If you want to deliver a drug – say ranibizumab or aflibercept – to the back of the eye, your only option is intravitreal injection. These are big drugs – 48 and 97 kDa, respectively – and topical application is totally ineffective in delivering them to the retina. These anti-VEGF agents also have powerful systemic side effects, but this is where the restricted passage of large molecules across the blood-ocular barrier helps; once drugs are injected into the eye, they tend to remain there for extended periods, minimizing systemic effects. But the fact that these big, anti-VEGF agents are the only effective drugs currently available for wet age-related macular degeneration (AMD), and absolutely have to be delivered by intravitreal injection, means that ophthalmology clinics are overflowing with aging baby-boomers, waiting for their monthly Lucentis or bimonthly Eylea injection. This is far from ideal – but it is the status quo. As the population ages, and ever-increasing numbers develop wet AMD, on this aspect alone, things have to change.

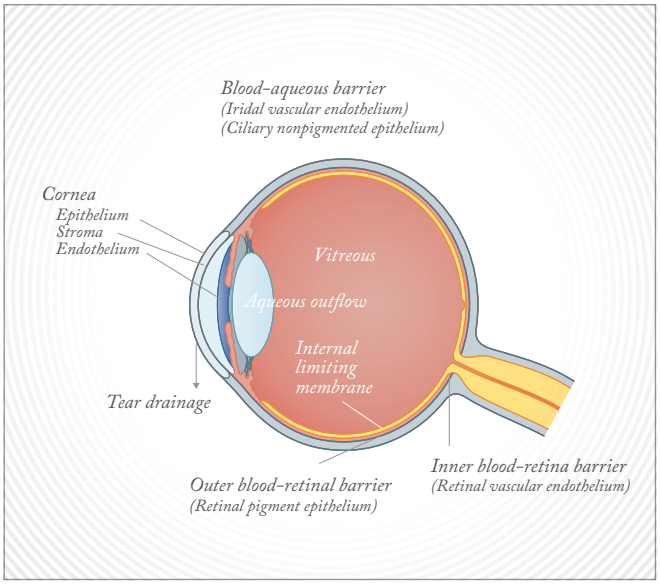


Figure 1. Barriers to ocular drug delivery.

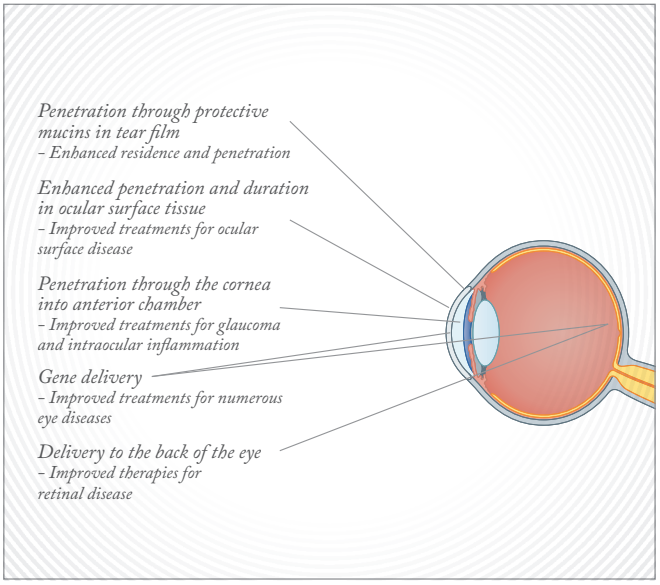


Figure 1/2 by Rachael Tremlett

Figure 2. Nanotechnology may help overcome the barriers to ocular drug delivery.

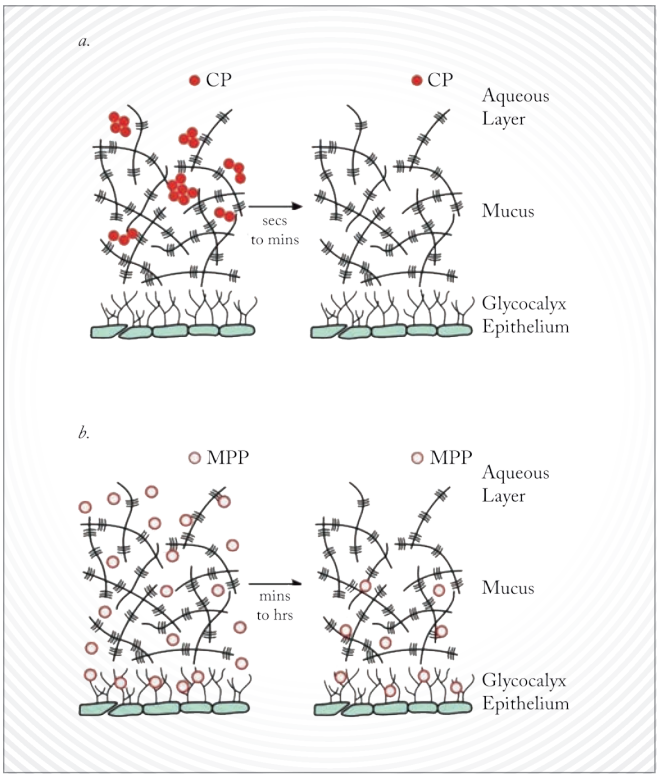


Figure 3. Drug clearance from the ocular surface. (a) Conventional particles: muco-adhesive particles are rapidly cleared from mucus through mucus turnover, and particle aggregation and mucus adherence leads to poor distribution. (b) Mucus Penetrating Particles: muco-inert particles penetrate through tear film mucus layer. Mobility leads to uniform distribution across the mucosal epithelia.

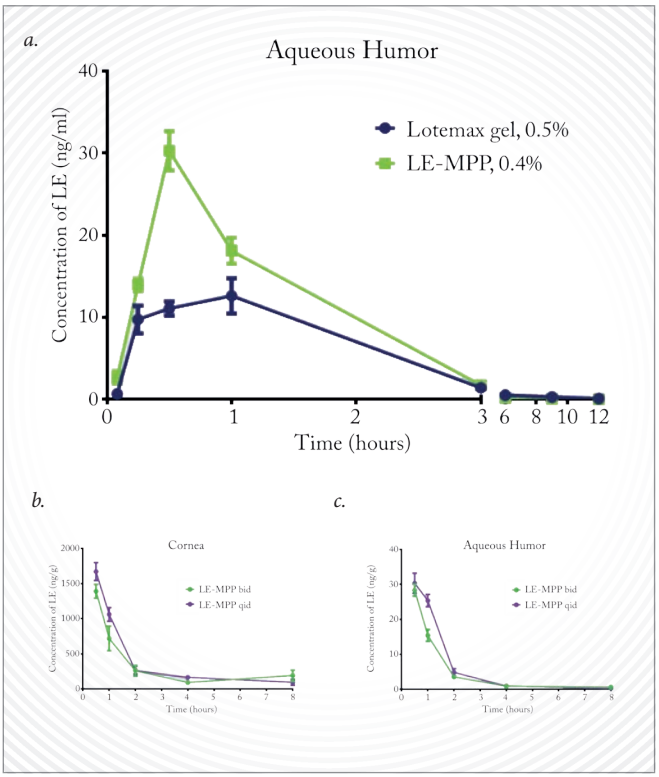


Figure 4. Pharmacokinetic comparisons of (a) 0.5% Lotemax gel with 0.4% loteprednol etabonate mucus penetrating particles (LE-MPP); and (b and c) 0.5% LE-MPP administered twice-daily (bid) or four-times daily (qid) in (b) the cornea and (c) the aqueous humor.

Why small matters

A nanometer is really small: one billionth of a meter. Why, as physicians, should you care? Well, across medicine, nanotechnology is allowing many major potential advances: improved vaccines, speedier and more sensitive diagnostic tests, and most importantly for ophthalmology, dramatically improved – and targeted – drug delivery. So how can nanotechnology specifically help us to overcome the challenges described? Well, nano-scale drug particles are more easily and rapidly absorbed by tissue than their bigger-scale counterparts, and their use tends to be associated with a reduced dosage requirement to achieve the same efficacy – which should result in fewer side effects as a side benefit. We can also modify them, make them hit the desired target by coating them with other molecules – indeed, we can engineer the surface properties of nanoparticles to target them for delivery to specific locations. For example, if you modify the surface to have a ligand that binds a certain cell type, or one that undergoes receptor-mediated endocytosis on a target cell, then you can have a highly specific targeting mechanism for drug – or gene – delivery.

"Nano-scale drug particles are more easily and rapidly absorbed by tissue than their bigger-scale counterparts."

Nanotechnology helps break through the eye's barriers to drug delivery too (Figure 2). Modified nanoparticles can penetrate the mucus barrier (Figure 3), with lower doses and a longer duration of action – resulting in better treatments for ocular surface diseases. If you can penetrate the cornea, you can reach the anterior chamber, which could lead to improved treatments for glaucoma and development of new treatments for anterior chamber diseases. There may even be the possibility of developing nanoparticle eye drops that can take therapies through to the back of the eye. Imagine, an effective treatment that doesn't require injection. How likely then is it that you could one day be treating your patients with nanotechnology therapies? Let's look at the evidence.

Smaller steroids

Many of you probably know the topically administered corticosteroid, loteprednol etabonate (LE), or Lotemax. You may have used it to treat post-surgical ocular surface inflammation, or other steroid-responsive inflammatory diseases of the cornea or conjunctiva. It has other benefits, including that its use is associated with a lower risk of intraocular pressure (IOP) elevation than other steroids. It does, however, have some of the same drawbacks that other eye drops currently have: it gets stuck in the mucus layer of the tear film, the drug particles aggregate, they're distributed poorly and eliminated quickly. So in its current form, as with almost all eye drops, you have to overdose to account for these losses. Nanosuspensions do better, but the mucus barrier is tough to bypass (1).

One of Robert Langer's former students, Justin Hanes, has led the development of polyethylene glycol (PEG)-coated nanoparticles that penetrate the mucus layer of the tear film at a far faster rate than unmodified, 'vanilla' nanoparticles (Online Video 1). The coated nanoparticle can rapidly make its way through the mucus; the plain nanoparticle remains stuck (2). Presumably this, plus LE, should result in better penetration of the mucus and therefore drug delivery (2), right? Another of Robert's former students, Hongming Chen, is involved in precisely that, leading a team that is combining the mucus-penetrating particles (MPPs) with LE to create a better-penetrating – and hopefully safer and more effective – formulation. Can this be done? Results from a rabbit model look good. Hongming and her team compared the ocular pharmacokinetics of nano-scale 0.4% LE mucus penetrating particles (LE-MPP) formulation with the longest-acting currently available ophthalmic formulation of LE, 0.5% Lotemax gel (3). The results looked good, and main findings were clear; despite the LE-MPP dose being a fifth lower, it provided equal or better drug delivery than the gel formulation, reaching greater maximum concentrations at a faster rate, and taking longer to be cleared from the eye, leading to greater drug exposure (Figure 4a).

These pharmacokinetic characteristics led Hongming and her team to investigate whether the LE-MPP formulation needs to employ the four-times-a-day administration that LE eye drops currently require. Naturally, if they could get it lower, all the better for patient compliance (4). But could twice-a-day (bid) dosing be as effective as a four-times-a-day (qid) regimen? Again, in rabbits, the team compared LE concentrations in the cornea and the aqueous humor after twice- and four-times-a-day dosing (Figure 4b,c). Both protocols resulted in similar maximum drug concentrations over a similar timecourse. Of note, the total drug exposure

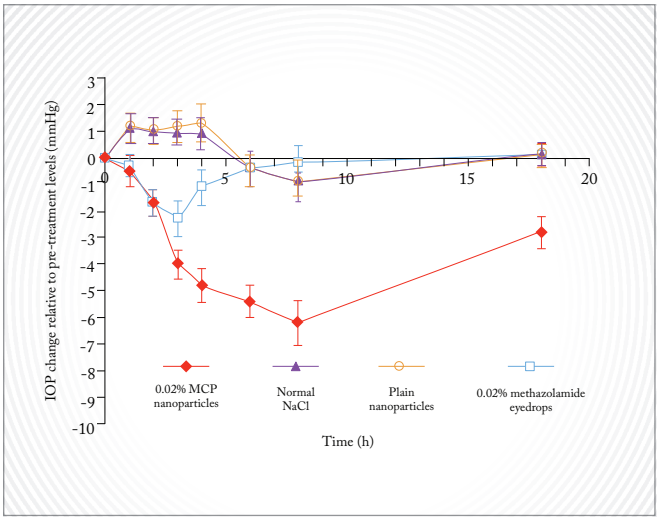


Figure 5. IOP changes following the administration of two eyedrops of study drugs, vehicles or NaCl control, relative to pre-treatment levels. Values are the mean of ten measurements, ± standard error of the mean. IOP, intraocular pressure; MCP, methazolamide calcium phosphate.

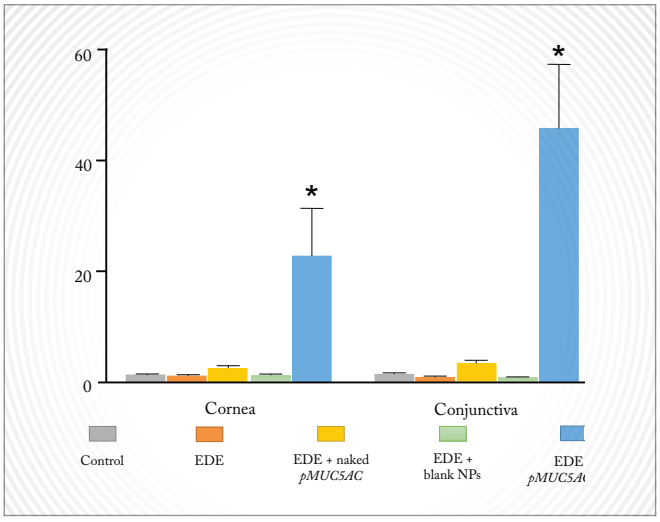


Figure 6. Gene delivery of modified MUC5AC mRNA to the ocular surface via nanoparticles. MUC5AC mRNA levels were significantly greater in experimental dry eye (EDE) mice cornea and conjunctiva than in controls.

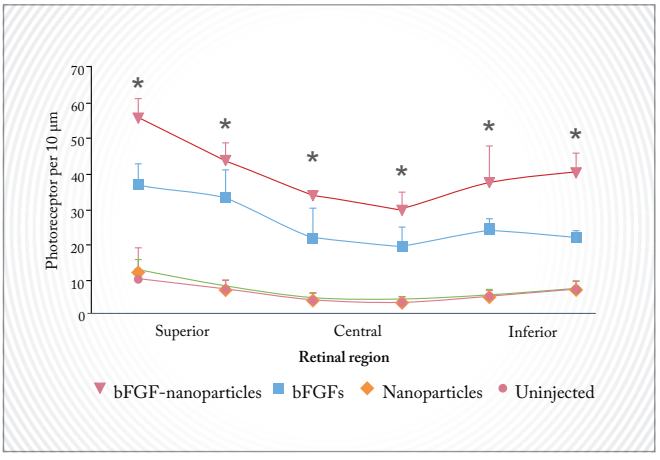


Figure 7. Mean number of photoreceptors per 50 µm for all treatment groups of RCS rats, 8 weeks after injection. The photoreceptor density in bFGF-nanoparticle treated rats was significantly greater than that in bFGF-treated (and control) rats in all regions. * p<0.05 (bFGF-NPs vs. bFGF).

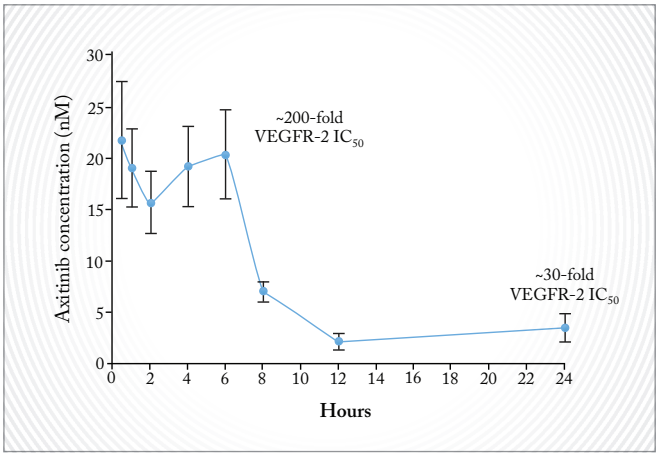


Figure 8. Topical delivery of the tyrosine kinase inhibitor axitinib (2%) formulated as mucus-penetrating particles gives sustained and therapeutically relevant drug concentrations over a 24-hour period.

was slightly reduced (~15–20 percent) when administered bid rather than qid – but remember, this was with a 50 percent lower cumulative dose. So we have increased penetration and a longer duration of action in ocular tissues, by making them at the nano scale and coating them with PEG – a material that the FDA consider to be GRAS – generally regarded as safe. The next step is clinical evaluation, and the first patient was dosed in a phase III trial of LE-MPPs back in June.

Solving the insoluble and making things gel

Here's an example from another research group, who produced a calcium phosphate nanoparticle formulation of the carbonic anhydrase inhibitor, methazolamide (5). As this IOP-lowering drug is water-insoluble, it won't dissolve in the aqueous tear film layer. This means that it's rapidly cleared from the ocular surface, and unsurprisingly, results in poor ocular bioavailability. Calcium phosphates

are both biocompatible and non-toxic (they're important constituents of bone and constantly circulate in the bloodstream) and are readily taken up by cells. Helpfully, they are easily transported through even the smallest of capillaries, and this property enables them to accumulate in target cells. You can also adsorb methazolamide to calcium phosphate nanoparticles, and the combination of the two gives you a much better therapy than methazolamide alone. Rabbit studies (5) have demonstrated a longer duration of action, and a tremendous IOP-reduction response with methazolamide nanoparticles compared with the current formulation of the drug (Figure 5). Even insoluble issues like insolubility can be solved with nanoparticles, it seems.

Interestingly, nanoparticles made from gelatin also hold promise according to a group in Valladolid, Spain, who have been working on a potential gene-based treatment for dry eye disease (6). They are trying to transfect a DNA plasmid that contains a copy of the *MUC5AC* gene – a gene that encodes for an important mucin that plays a central role in tear homeostasis. *MUC5AC* is downregulated in many ocular diseases with a dry-eye phenotype, like keratoconjunctivitis sicca and Sjögren's syndrome. In mice with scopolamine-induced experimental dry eye (EDE), the group showed the application of naked *pMUC5AC* did not significantly increase *MUC5AC* expression relative to control mice (without EDE), EDE mice or EDE mice that had received gelatin nanoparticles alone. The combination of the plasmid and the nanoparticles, however, did result in a big increase in *MUC5AC* in both the cornea and conjunctiva (Figure 6). You can ascertain the extent of dry eye symptoms with fluorescein staining and tear production assays: both were significantly improved with *pMUC5AC*-nanoparticles, indicating that they were alleviating the symptoms of dry eye – no other intervention or control improved either parameter.

Persistence at the posterior segment

So far, I have shown you nanoparticles that are acting at the front of the eye. But is there any evidence that nanoparticle formulations of drugs might make a difference at the back of the eye, at the retina? Based on preclinical studies in rats, the answer to that is yes.

Royal College of Surgeons (RCS) rats are a commonly-used animal model of retinal degeneration, and it's long-established that intravitreally-injected basic fibroblast growth factor (bFGF) exerts a protective effect on the retina in these mice, delaying photoreceptor degeneration. But the effect is as short-lived as bFGF's half-life; you

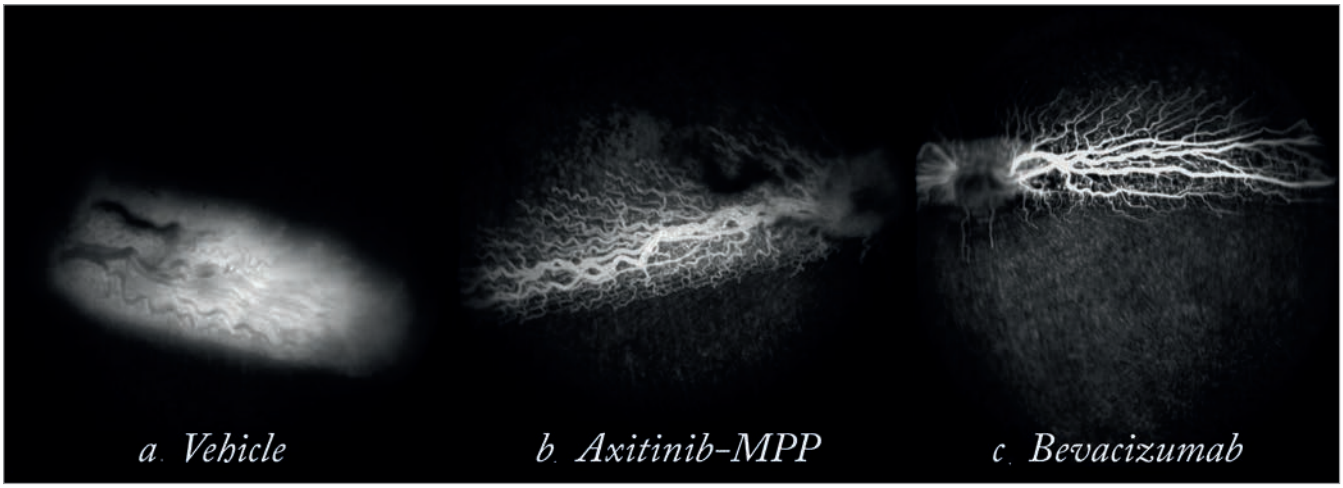


Figure 9. Topical delivery of axitinib-MPP (b) reduces VEGF-induced retinal vascular permeability to a similar extent to bevacizumab (c) relative to control (a) in a pigmented rabbit model.

really need continual drug delivery to protect the retina in any meaningful way.

Gene therapy with viral vectors is one method – although this is not without risks, like unwanted immune system reactions or insertional mutagenesis. The ideal alternative would be a delivery system that gets an effective amount of bFGF to the target site and gives sustained drug – or gene plasmid – release without causing serious complications. Again, gelatin nanoparticles are a proposed solution to this problem. A group of researchers in Japan created ^{125}I-radiolabelled gelatin nanoparticles, injected them intravitreally into the eyes of RCS rats, and measured how long the radioactivity persisted for, as a marker of how long bFGF-containing nanoparticles could persist at the retina (7). The answer: at least 30 days. They then went on to intravitreally-inject bFGF-containing nanoparticles into the RCS mice and determined the photoreceptor density of these mice eight weeks later (Figure 7). RCS rats injected with bFGF nanoparticles retained a significantly greater photoreceptor density than all of the other treatment or control groups (7). This has worked with DNA too – an Oklahoma-based group has used PEG-and-peptide nanoparticles to deliver plasmids into the retina, achieving gene expression and impressive improvements in the phenotype of genetic mutant mice with a retinitis pigmentosa-like phenotype (8). As promising as these studies appear, they are still using intravitreal injections – something that, ideally, we want to avoid.

"Imagine what localized and specific gene delivery could do for patients with inherited vision disorders."

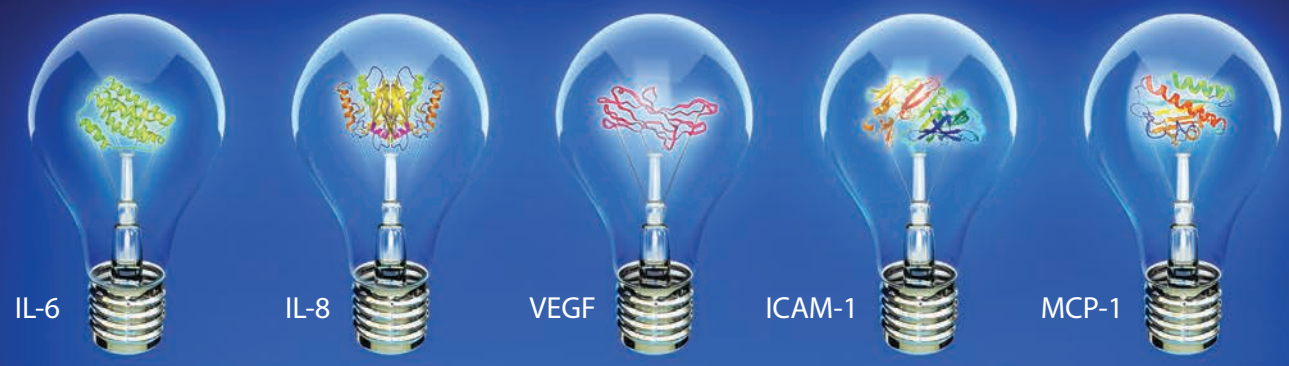
Eye drops for retinal disease

Earlier, I told you that nanoparticles had the potential to deliver topically-administered drugs to the back of the eye. Well, that's been done too.

Axitinib is a small-molecule receptor tyrosine kinase inhibitor. Like ranibizumab, it inhibits VEGF signaling. Like Fovista, it also inhibits platelet-derived growth factor (PDGF) signaling. Unlike both, it also inhibits c-kit, a survival factor for developing blood vessels. Unlike both, it also has a half-life of a few hours, whereas ranibizumab and aflibercept each have half-lives of several days in the human eye. This means that axitinib needs to be dosed regularly – perhaps even daily – to exert its therapeutic effect on the retina. Clearly, daily intravitreal injections are not an option. Could a topically administered nanoparticle formulation be the answer?

Hongming's team formulated axitinib molecules into the aforementioned MPPs in an attempt to do so. They wanted to establish if a topically administered axitinib-MPP formulation

TARGETING THE MEDIATORS OF INFLAMMATION[1]



Delivering efficacy in the clinical setting[2-5]

Ozurdex®
(dexamethasone intravitreal implant) 0.7mg

These images are for illustrative purposes only and do not represent inflammatory mediator levels in the eye.

OZURDEX® (Dexamethasone 700 micrograms intravitreal implant in applicator)

Abbreviated Prescribing Information

Presentation: Intravitreal implant in applicator. One implant contains 700 micrograms of dexamethasone. Disposable injection device, containing a rod-shaped implant which is not visible. The implant is approximately 0.46 mm in diameter and 6 mm in length. **Indications:** Treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO). Treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis. **Dosage and Administration:** Please refer to the Summary of Product Characteristics before prescribing for full information. OZURDEX must be administered by a qualified ophthalmologist experienced in intravitreal injections. The recommended dose is one OZURDEX implant to be administered intravitreally to the affected eye. Administration to both eyes concurrently is not recommended. Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk. Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by OZURDEX, should not be retreated. There is only very limited information on repeat dosing intervals less than 6 months. There is currently no experience of repeat administrations in posterior segment non-infectious uveitis or beyond 2 implants in Retinal Vein Occlusion. Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs. Single-use intravitreal implant in applicator for intravitreal use only. The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). The patient should be instructed to self-administer broad spectrum antimicrobial drops daily for 3 days before and after each injection. Before the injection, the periocular skin, eyelid and ocular surface should be disinfected and adequate local anaesthesia should be administered. Remove the foil pouch from the carton and examine for damage. In a sterile field, open the foil pouch and gently place the applicator on a sterile tray. Carefully remove the cap from the applicator. Once the foil pouch is opened the applicator should be used immediately. Hold the applicator in one hand and pull the safety tab straight off the applicator. Do not twist or flex the tab. With the bevel of the needle up away from the sclera, advance the needle about 1 mm into the sclera then redirect toward the centre of the eye into the vitreous cavity until the silicone sleeve is against the conjunctiva. Slowly press the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully pressed and has locked flush with the applicator surface. Remove the needle in the same direction as used to enter the vitreous. Immediately after injecting OZURDEX, use indirect ophthalmoscopy in the quadrant of injection to confirm successful implantation. Visualisation is possible in the large majority of cases. In cases in which the implant cannot be visualised, take a sterile cotton bud and lightly depress over the injection site to bring the implant into view. Following the intravitreal injection patients should continue to be treated with a broad spectrum antimicrobial. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Active or suspected ocular or periocular infection including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases. Advanced glaucoma which cannot be adequately controlled by medicinal products alone. Aphakic eyes with rupture of the posterior lens capsule. Eyes with Anterior Chamber Intraocular Lens (ACIOL) and rupture of the posterior lens capsule. **Warnings/Precautions:** Intravitreous injections, including OZURDEX can be associated with endophthalmitis, intraocular inflammation, increased intraocular pressure and retinal detachment. Proper aseptic injection techniques must always be used. Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection. Patients must be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay. All patients with posterior capsule tear, e.g. those with a posterior lens, and/or those who have an iris defect (e.g. due to iridectomy) with or without a history of vitrectomy, are at risk of implant migration into the anterior chamber. Other than those patients contraindicated where OZURDEX should not be used, OZURDEX should be used with caution and only following a careful risk benefit assessment. These patients should be closely monitored for any signs of implant migration. Corticosteroids should be used cautiously in patients with a history of *ocular herpes simplex* and not be used in active *ocular herpes simplex*. The safety and efficacy of OZURDEX administered to both eyes concurrently have not been studied and is not recommended. OZURDEX is not recommended in patients with macular oedema secondary to RVO with significant retinal ischemia. OZURDEX should be used with caution in patients taking anti-coagulant or anti-platelet medicinal products. **Interactions:** No interaction studies have been performed. Systemic absorption is minimal and no interactions are anticipated. **Pregnancy:** There are no adequate data from the use of intravitreally administered dexamethasone in pregnant women. OZURDEX is not recommended during pregnancy unless the potential benefit justifies the potential risk to the foetus. **Lactation:** Dexamethasone is excreted in breast milk. No effects on the child are anticipated due to the route of administration and the resulting systemic levels. However OZURDEX is not recommended during breast feeding unless clearly necessary. **Driving/Use of Machines:** Patients may experience temporarily reduced vision after receiving OZURDEX by intravitreal injection. They should not drive or use machines until this has resolved. **Adverse Effects:** *RVO* In clinical trials the most frequently reported adverse events were increased intraocular pressure (IOP) (24.0%) and conjunctival haemorrhage (14.7%). Increased IOP with OZURDEX peaked at day 60 and returned to baseline levels by day 180. Elevations of IOP either did not require treatment or were managed with the temporary use of topical IOP-lowering medicinal products. The following adverse events were reported: Very common (≥1/10): IOP increased, conjunctival haemorrhage* Common (≥1/100 to <1/10): Ocular hypertension, vitreous detachment, cataract, subcapsular cataract, vitreous haemorrhage*, visual disturbance, vitreous opacities* (including vitreous floaters), eye pain*, photopsia*, conjunctival oedema*, anterior chamber cell*, conjunctival hyperaemia*, headache Uncommon (≥1/1,000 to <1/100): Retinal tear*, anterior chamber flare* Headache. *Uveitis* In clinical trials the most frequently reported adverse events in the study eye were conjunctival haemorrhage (30.3%), increased IOP (25.0%) and cataract (11.8%). The following adverse events were reported: Very common: Increased IOP, cataract, conjunctival haemorrhage* Common: Retinal detachment, Myodesopsia, vitreous opacities, blepharitis, sclera hyperaemia*, visual impairment, abnormal sensation in the eye*, eyelid pruritis, migraine. (*Adverse reactions considered to be related to the intravitreous injection procedure rather than the dexamethasone implant). Please refer to Summary of Product Characteristics for full information on side effects. **Basic NHS Price:** £870 (ex VAT) per pack containing 1 implant. **Marketing Authorisation number:** EU/1/10/638/001 **Marketing Authorisation Holder:** Allergan Pharmaceuticals Ireland, Castlebar Road, Westport, Co. Mayo, Ireland. **Legal Category:** POM. **Date of Preparation:** May 2013.

Adverse events should be reported.
Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse events should also be reported to Allergan Ltd. UK_Medinfo@allergan.com or 01628 494026.

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Date of Preparation: June 2014 UK/0430/2014c

ALLERGAN ophthalmology

could get therapeutic doses of the drug to the retina. Their first preclinical pharmacokinetic analyses were performed in the eyes of rabbits, and what they found was clear: compared with the control of regular axitinib applied topically to the eye, topical axitinib-MPP resulted in a fivefold greater retinal drug exposure (9). The fact that they got the drug to the retina is one thing – but were these therapeutic doses?

Ranibizumab exerts most of its action by binding VEGF, thus preventing its binding to VEGF receptors. Axitinib's IC_{50} – the concentration at which a drug antagonizes 50% of its target receptors – for a key VEGF receptor (VEGFR-2) is 0.1 nM. A single topical 2% axitinib-MPP administration resulted in axitinib concentrations that were between 10 and 200 times greater than its VEGFR-2 IC_{50} in rabbits (Figure 8). No irritation was observed with the axitinib-MPP eye drops – a good sign if you're proposing regular topical administration to the eye – and experiments that compared axitinib-MPP eye drops with intravitreally-administered bevacizumab (in a rabbit retinal vascular permeability model) showed that both drugs significantly and similarly improved vascular leakage (Figure 9) – confirming that therapeutic concentrations were achieved with the topical administration of axitinib-MPPs.

Hongming and her team are currently evaluating other small-molecule receptor tyrosine kinase inhibitors – but the principle has been proven. Nanoparticle technology allows one to topically deliver drugs to the posterior-segment, at least in rabbits. Would it be premature, then, to imagine a future where the frequency of intravitreal injections is significantly reduced?

Imagine the potential

Medicine has already begun to see significant progress driven by nanotechnology, but its tremendous promise is only just beginning to be realized: improved drug delivery really is just the tip of the iceberg as to what modern technologies like nanotechnology will achieve over the next ten, twenty or thirty years. Just imagine being able to prescribe eye drops for wet AMD: rather than having clinics bursting-at-the-seams with patients requiring their monthly anti-VEGF injection, you'll just need to see them for their regular checkups instead. Imagine the impact that better eye drop regimen compliance and fewer drug-related adverse events could make to patients with glaucoma or ocular surface disease. Imagine what localized and specific gene delivery could do for patients with inherited vision disorders. The application of materials science and chemical engineering to just one aspect of medicine – drug formulation – is just one of many ways nanotechnology can transform ophthalmology. But if you're looking at the big picture, think small – really small – about how you can improve things.

Robert Langer is a chemical engineer, the David H. Koch Institute Professor at the Massachusetts Institute of Technology, author of over 1,250 publications, owner of over 1,000 patents, and the most cited engineer of all time.

Justin Hanes is the Lewis J. Ort Professor at Johns Hopkins, where he holds appointments in the Schools of Medicine, Engineering, and Public Health, and where he directs the Center for Nanomedicine at the Wilmer Eye Institute. The MPP technology was discovered in his lab.

Hongming Chen is the Chief Scientific Officer at Kala Pharmaceuticals, Inc. Kala is the licensee of the MPP technology and is developing the technology for applications in various mucosal organs including the eye.

See videos of conventional and MPP nanoparticle movement in mucus at: top.txp.to/0814/301

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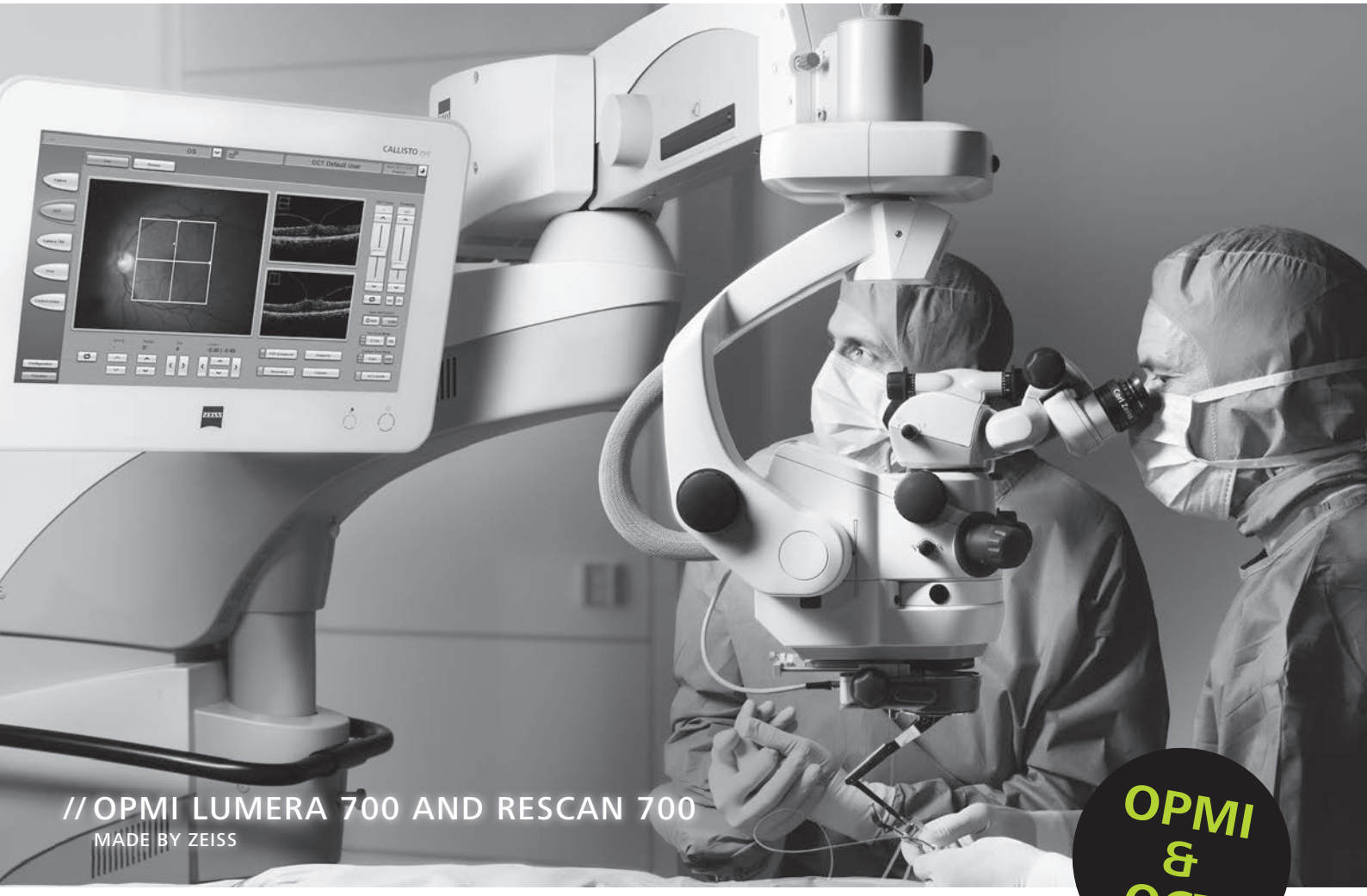

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VIIP: A Space Odyssey

Many astronauts develop eye problems in space. NASA wants to know why, so they've established the Vision Impairment and Intracranial Pressure (VIIP) program. The future of interplanetary space travel is at stake…

By Mark Hillen

It was an incredible feat of engineering that thrust astronauts into space, and an even greater engineering and political achievement establishing the International Space Station (ISS). But why stop there? NASA intends to send a manned mission to Mars, which will hopefully represent humankind's greatest space exploration achievement. However, having never evolved in microgravity, humans aren't built for space travel. Indeed, the medical implications of being in space aren't trivial (see Table 1), and these need to be better understood before humankind can boldly go anywhere in the cosmos for any length of time. Unfortunately, ocular health is something that the microgravity environment in space has the potential to seriously and permanently harm (see Table 2).

NASA has been aware for over four decades that space flight is associated with visual acuity impairment, but for many years these visual changes were thought to be minor, transient and not accompanied by other symptoms or significant clinical findings. In 2012, they reported that 15 male astronauts, aged between 45 and 55 years of age, had experienced visual and anatomical changes during or after long-duration flights (1, 2). The changes were not trivial, and included optic disc edema, globe flattening leading to hyperopic shifts, choroidal folds, retinal nerve fiber layer thickening, and increased intracranial pressure (see Figure 1). Some astronauts experienced transient changes that resolved post-flight, but others reported persistent visual acuity changes with varying degrees of severity. Such cases aren't just a worry for the astronaut, but also their fellow crew, ISS managers, and all of Earth's space agencies – you can't have astronauts suddenly becoming unable to read the dials. Something had to be done. Missions to Mars are unlikely to succeed with visually-impaired astronauts.

At a Glance

- *Astronauts experience cephalad fluid shifts in space, and this can harm ocular health*
- *Many of the issues have been linked to elevations in intracranial pressure – but not all astronauts have this problem*
- *NASA's ocular health program aims to screen astronauts' ocular health on the ground and in the ISS to try and understand when and why these changes occur*
- *Successfully understanding the underlying pathologies is key not only to developing prophylactic or treatment strategies – but these findings may also directly impact the future of manned interplanetary space flight*

Hunting the cause

Immediately, suspicions fell on fluid shift (3). On Earth, gravity constantly forces fluid in the body downwards. On the ISS orbiting the Earth, the gravitational forces are almost zero. In space, both intravascular and extravascular fluid shifts towards the head, leading to the characteristic "bird-legged and puffy faced" appearance of astronauts after extended periods in space. This has multiple, interrelated consequences – principally in the cardiovascular, nervous and ocular systems.

Cerebral cephalad shift consequences

Microgravity exposure almost immediately raises intraocular pressure (IOP), and this may be explained by the cephalad shift causing vascular engorgement of the choroid. As the

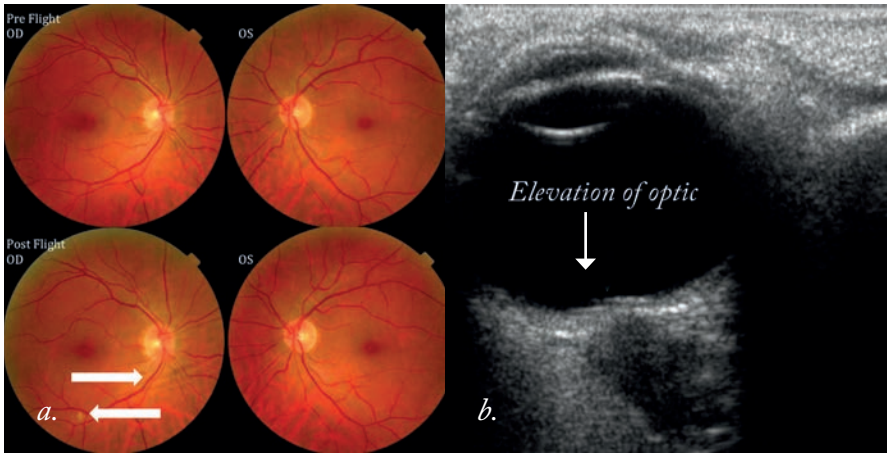

Figure 1. Fundus examination of second case of visual changes from long-duration spaceflight. a. Fundoscopic images showing choroidal folds (white arrows) in the papillomacular bundle area in the right eye and left eye and a cotton-wool spot (bottom arrow) at the inferior arcade in the left eye. Both optic discs show grade 1 disc edema. b. On-orbit ultrasound of posterior orbit of the fourth case of visual changes from long-duration spaceflight. In-flight ultrasound image of the right eye showing posterior globe flattening and a raised optic disc consistent with optic-disc edema and raised ICP (1).

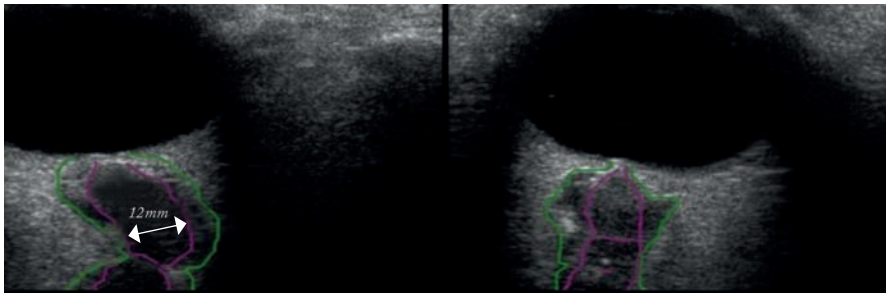

Figure 2. In-spaceflight ultrasound shows proximal kinking and increased optic nerve sheath diameter (ONSD) of approximately 12 mm that is consistent with raised intracranial pressure. Optic nerve shown in purple and the ONSD in green (1).

sclera remains rigid and does not expand as ocular volume rises, the consequence could be a rise in IOP. A rise in IOP has been well documented even with transient exposure to microgravity during parabolic flight (4). A cephalad fluid shift can lead to increased perfusion of the ciliary body and increased aqueous humor production. If you combine this with the fact that the fluid shift also causes venous system congestion (and as a consequence, also raises pressure within the episcleral vessels), you increase the resistance to aqueous humor outflow… raising IOP.

But raised IOP is likely not the cause you're looking for. The initial IOP spike on exposure to microgravity is soon followed by a decrease in IOP over the next few days, and it's been hypothesized to be a result of a compensatory decrease in aqueous volume. Christian Otto, the lead scientist of NASA's VIIP project, explained that, "so unconvincing have the IOP values been on the ISS, that Medical Operations has scrubbed regular IOP measurements from the Medical Requirements Integration Document, and no ISS crewmembers have experienced ocular hypertension". The tonometer will likely be staying in its case then...

If not IOP, then is raised ICP the culprit? ICP is the central feature of idiopathic intracranial hypertension (IIH), which serves as the closest terrestrial clinical equivalent. The elevated ICP that occurs with IIH on earth can cause many problems – the pressure increase can compress the sixth cranial nerve, resulting in problems with ocular abduction, double vision, and optic disc swelling, which can cause transient vision obscuration, which, if left untreated, can result in progressive and permanent vision loss. Cephalad fluid shifts are well known to cause jugular venous distention which suggests that cerebral venous congestion may occur during microgravity exposure. CSF is thought to be largely produced in the choroid plexus and drainage depends on a pressure differential between the CSF and the venous system. Thus a rise in venous pressure in the head and neck, produced by cephalad fluid shifts may cause impairment of CSF outflow, as well as cerebral venous congestion, both of which could lead to a rise in ICP not unlike that which occurs with IIH. However, what the astronauts are experiencing is not IIH. So far the ICP elevations seen in patients with IIH are far greater than that seen in the astronauts on the ISS, and the astronauts are spared the severe, disabling headaches that many of those with IIH suffer. Whatever is happening may have similarities to IIH, but it's certainly a unique pathology with a unique etiology. Another possible explanation is that the disc swelling and optic nerve sheath expansion described during long duration space flight may result from localized elevation of optic nerve sheath pressure occurring at the level of the intraorbital optic nerve (i.e. optic nerve compartment syndrome) with or without a rise in ICP.

Table 1.
Medical problems associated with space travel.

- Loss of bone density and muscle mass
- Cardiac disorders
- Fatigue and sleep loss
- Psychological issues
- Cognitive decline/ accelerated development of Alzheimer's Disease
- Decompression illness
- Barotrauma
- Immune dysfunction
- Spaceflight radiation carcinogenesis
- Orthostatic intolerance
- Ocular disorders

Table 2.
Ocular findings in astronauts.

To date, 21 US ISS long-duration spaceflight astronauts have developed some or all of the following:

- Hyperopic shift (50% of astronauts)
- Scotoma
- Cotton wool spots
- Choroidal folds*
- Optic nerve sheath distension*
- Globe flattening*
- Optic nerve edema*

** All three are associated with elevated ICP on Earth*

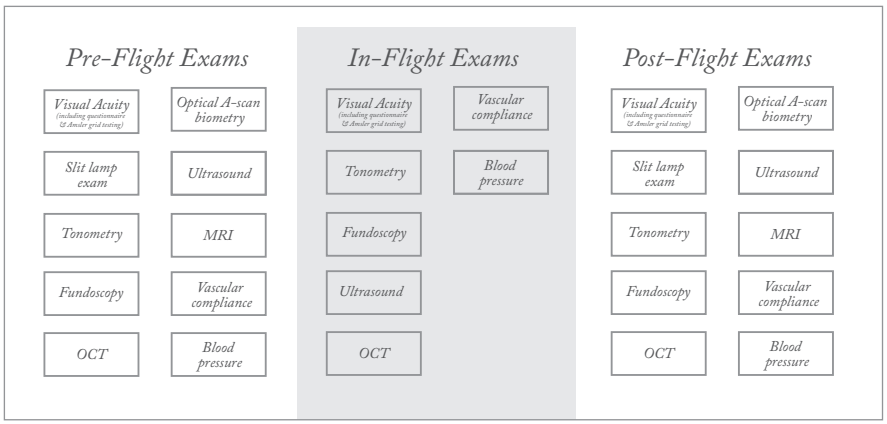

Figure 3. The NASA Ocular Health Study: Pre, peri- and post-spaceflight exams (1).

Floating in a tin can, far, far away

The ISS is a sealed environment, with little in the way of ventilation, and a typical crew of six, respiring, astronauts. Carbon dioxide removal systems are in place, but CO_2 levels are still ten to twenty times greater on the space station (2.3–5.3 mmHg) than they are on Earth (~0.23 mmHg). Poor ventilation and microgravity can result in local pockets of elevated CO_2 levels – like in the region around a sleeping astronaut's mouth. If you remember your physiology classes, elevated atmospheric CO_2 almost immediately raises ventilation and heart rates. It also results in cerebral blood vessels, increasing cerebral blood flow, CSF production and ICP.

Salt and sweat

Astronauts have a pretty sodium-rich diet: more than 5 grams per day in some cases (something that NASA is currently trying to reduce by 40 percent), which can affect fluid balance, and potentially exacerbate the VIIP symptoms. On-board exercise has also been hypothesized to cause transient ICP elevations – either from the short-burst exertions involved in resistive exercise, or from the increased cerebral blood flow that results from a good aerobic workout.

Not all men, not all women

Not all astronauts – even those on extended missions – experience problems, raising a number of questions. NASA believes that there is a "high probability that all astronauts have intracranial hypertension (IHT) to some degree" and that, in some astronauts, "if the IHT is not treated, there is a risk of damage to the optic nerve and possible reduced vision capability [in the] long term" (1,5). This means that once the initial IOP spike recedes, it's likely that most astronauts will have higher ICP than IOP – imposing a subtle anterior force on the lamina cribrosa of the optic disc. Perhaps some astronauts simply adapt better than others. But why?

Feeling the pressure and assessing the damage

NASA needed to know more: they required a non-invasive way of screening for retinal, choroidal and optic nerve abnormalities. Basically, they needed to perform a whole suite of health exams – both on Earth and in space (Figure 3) – to ascertain the astronaut's eye health. A key part of these exams is optical coherence tomography (OCT).

Spectralis ad astra

It's one thing wanting to perform OCT imaging on the ISS. It's quite another thing doing it. For a start, once you get a device, you have to get it up there. For Heidelberg Engineering, manufacturer

of the Spectralis range of OCT instruments, it all started with a phone call, asking if they would like to work with NASA. They agreed – and the work began.

Heidelberg Engineering's Kester Nahen explains: "In February 2013, we took an off-the-shelf product and sent it to NASA. In April, they performed some tests on it, sent it on a parabolic flight for some microgravity tests, where they assessed how the instrument would work in microgravity, and then trained their staff to use it under those conditions." It looked like the instrument could operate in microgravity conditions – but could it survive a rocket trip?

As NASA was testing the Spectralis on the "vomit comet" back in Germany, Heidelberg Engineering's staff were strapping a Spectralis to a shaking table, in order to see if the instrument could withstand the vibrations of a rocket launch. It seemed that it could; the Spectralis was ready for space. Kester's colleague, Gerhard Zinser, explained the short timeline of these events: "On June 5, it was launched into space on an Ariane 5 rocket from the European Spaceport in Kourou, French Guiana. It reached the ISS on June 15, was unpacked on June 18, and on June 21, the first OCT image was taken in space – of a test target." The next step for NASA was to set up the satellites to stream the images down to Houston, Texas, where a team of experts on the ground could remotely guide the astronauts through the procedure. On October 16, the first crew examinations were performed over live video streaming.

Snapshots from space

Nimesh Patel, an Assistant Professor at the University of Houston, College of Optometry and a consultant to NASA reported some early data obtained from four astronauts by in-flight OCT earlier this year (6), explaining in some detail how NASA's VIIP program utilizes in-flight OCT to ascertain retinal changes in a microgravity environment.

Patel described how all astronauts underwent a battery of pre-flight ocular tests to set a baseline, including OCT, and that during the mission, the astronaut operating the instrument could use Spectralis' auto-rescan function to ensure that images captured in space were from same region of the retina that was imaged on Earth. He revealed that confocal scanning laser ophthalmoscopy (cSLO) and OCT images showed that some astronauts had developed retinal and choroidal folds during their time on the ISS – pathologies that were not present at the pre-flight, baseline assessment back on Earth. Microgravity-induced hyperopic shift affects half of all astronauts, and infrared (IR)-SLO imaging managed to document the development of this – Patel noted that a progressive decrease of the apparent size

Figure 4. Russian cosmonaut, Aleksandr Yuriyevich "Sasha" Kaleri, inside the Zvezda space module with a Soviet-era Salyut-Mir CHIBIS lower-body negative-pressure suit.

of retinal structures being scanned by the instrument was observed in those experiencing hyperopic shifts.

Pathological changes in the optic nerve head (ONH) were also observed during the mission. Star pattern OCT scans, centered on the opening of Bruch's membrane, revealed that space flight can increase the Bruch's membrane opening minimum rim width (BMO-MRW) in some astronauts by up to 70 µm, and post-mission assessments showed that the BMO-MRW can remain increased even after the astronauts return to Earth. Furthermore, OCT circle scans of the peripapillary architecture also revealed that the retinal nerve fiber layer and the choroid thicken during the mission, and again, remained thickened after the mission.

NASA is not stopping at OCT imaging – the next ophthalmic imaging device to go to the ISS will be a Scheimpflug camera that will enable astronauts to quickly and easily measure IOP, corneal thickness and biomechanics – with Oculus' Corvis ST camera already having demonstrated its utility in microgravity, during two "vomit comet" flights earlier in June this year.

Mitigating against microgravity

To date, the causative mechanisms underlying the pathological changes are still unknown – no definitive proof yet exists, despite theories relating to microgravity-induced cephalad shifts being compelling. Some of the ocular changes are dealt with easily: shifts in visual acuity are remedied with corrective lenses. But the changes to the retina and ONH are less easily resolved. One possibility is acetazolamide (3). It's used for the treatment of glaucoma and idiopathic intracranial hypertension, and helpfully reduces cerebrospinal fluid production, and with it, ICP. Another possibility is actively trying to minimize the effects of cephalad fluid shifts. In the absence of artificial gravity – which is still within the realm of science fiction – interventions like thigh cuffs and lower-body negative pressure suits (Figure 4) may help prevent or treat these spaceflight ocular disorders (3). But fundamentally, a better understanding of how microgravity affects the eye – and why only some astronauts are affected – is central to developing effective treatment and prophylaxis. It's also central to letting a long-duration space mission proceed.

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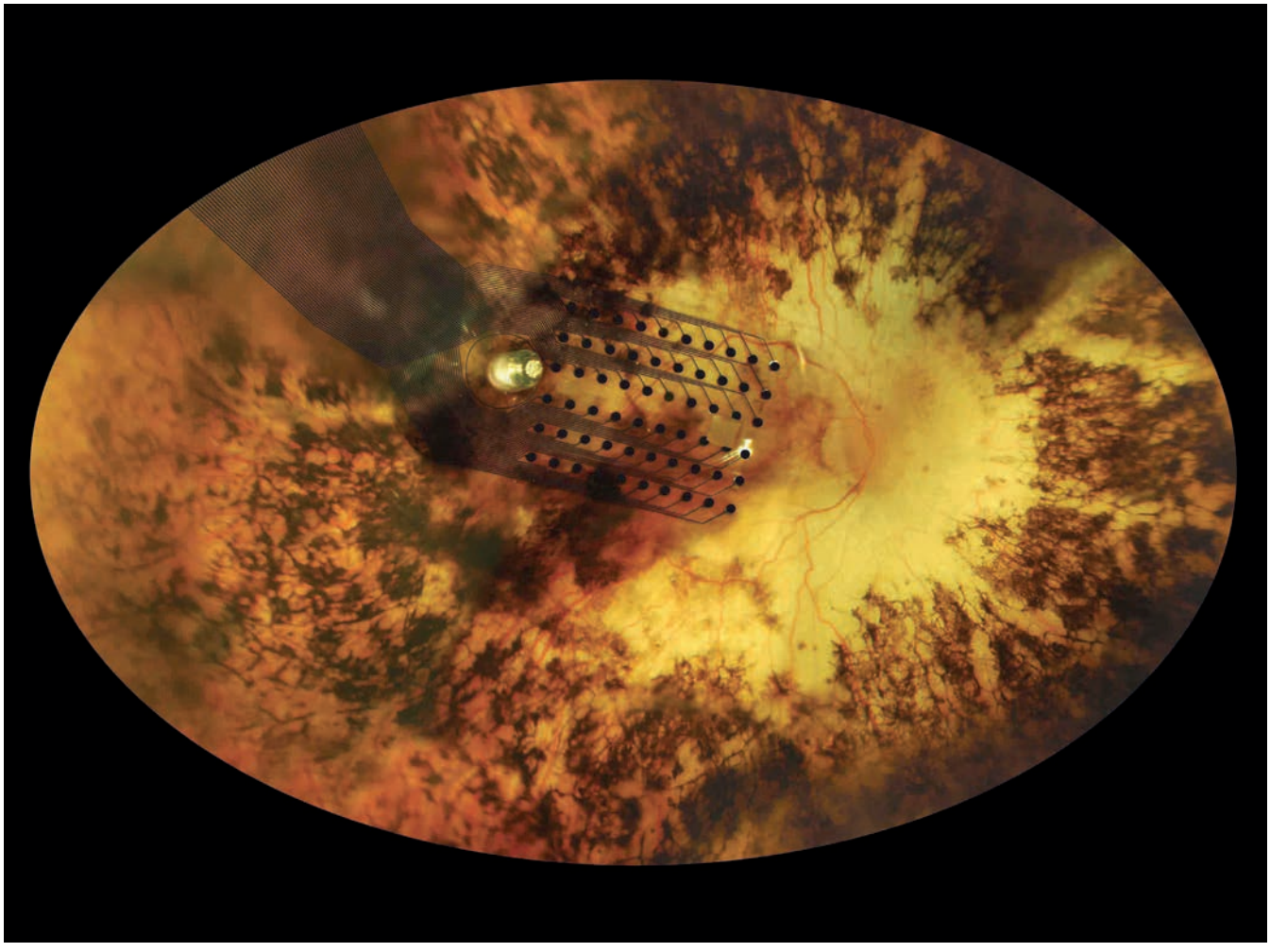


At a Glance

- *Biomedical implants can partially restore vision to patients with retinitis pigmentosa*
- *The Argus II Retinal Prosthesis System is commercially available and nearly 100 patients have received the implant to date*
- *Real-life experience has shown that the implant not only improves visual acuity, but quality of life*
- *The economic arguments stack up: healthcare providers in the EU are beginning to fund the Argus II through various national reimbursement programs*

The Bionic Eye: Fact, Not Science Fiction

As Second Sight's Argus II Retinal Prosthesis System nears its 100 patient milestone, we look at how the device has impacted the lives of those implanted

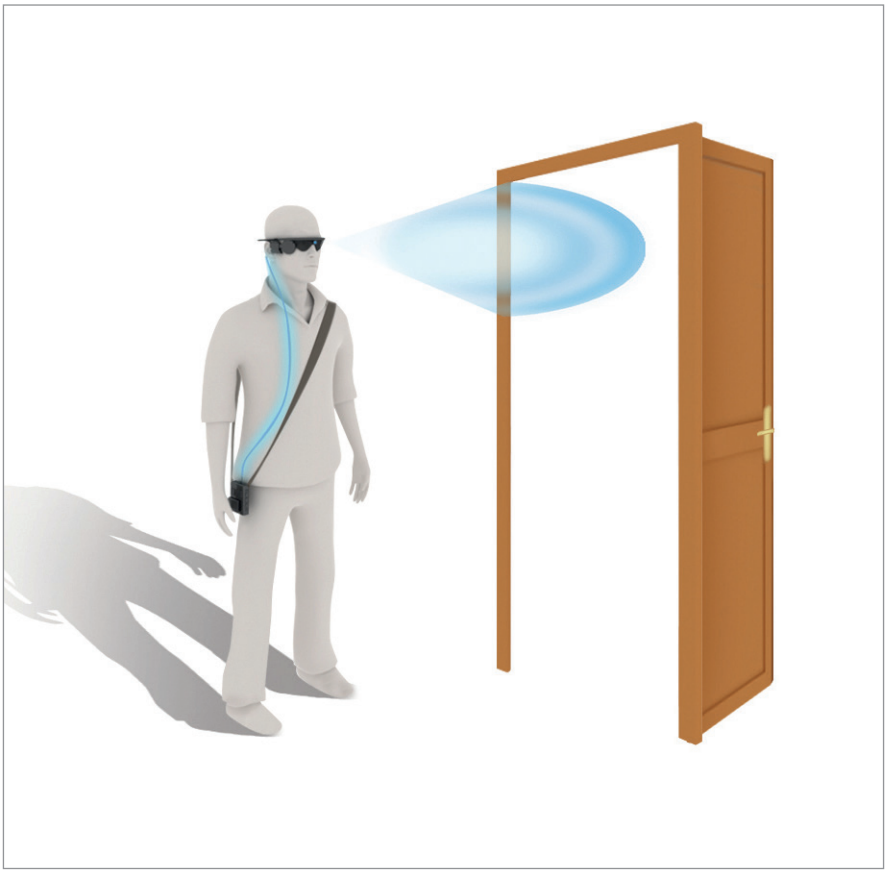
By Amanda Hayhurst

Retinal degenerative diseases, like retinitis pigmentosa (RP) and macular degeneration, primarily affect photoreceptors, leaving the retina unable to sense light, and RP affects over 167,000 people in Europe today. In RP, however, some of the remaining retinal neurons – the bipolar and ganglion cells – retain their ability to signal and can be activated by well-established nerve stimulation techniques. This was the basic tenet of early electrophysiological studies that examined how electrical and magnetic fields could excite neurons in the visual system – phosphenes – to create the sensation of light. In

Burden of disease

There are estimated to be 167,000 people in Europe with RP causing an adverse impact on their quality of life and cost to society. How did we calculate this?

Worldwide, an estimated 1.5 million people suffer from RP (1), which includes about 100,000 in the US (2). Pan-European data is not readily available, but we believe it is reasonable to estimate that the average prevalence throughout Europe is similar to the average prevalence within the US, and so the ratio of populations could be used to estimate the number of Europeans affected to be 167,000 in the 28 EU countries (3,4). Approximately one in four people with RP in the US has vision that is 20/200 or worse (legally blind) (5).



the 1990s, clinical investigations that involved temporary implants of a stimulating electrode array in the eye of blind patients established that potentially useful spots of light could be created, even in a retina that had not been working properly following decades of disease and degeneration. Further, the use of multi-electrode array implants allowed people to perceive lines – and it was this discovery that ultimately led to the creation of implantable retinal prostheses.

Currently available prostheses

Today, a typical retinal prosthesis contains: an imager (such as a camera or photodiode array) that converts light to electrical signals; electronics that process the image and generate electrical stimulation; and an array of microelectrodes that stimulate the retina. Prostheses are typically categorized by the position of the array:

- Epiretinal – on the top surface of the retina
- Subretinal – under the retina
- Suprachoroidal – between the sclera and the choroid.

Two retinal prostheses are currently available to patients: the epiretinal Argus II Retinal Prosthesis System (Second Sight Medical Products, Inc.) which is FDA-approved and CE-marked for the treatment of RP in the US and Europe, respectively; and the Alpha-IMS (Retina Implant AG, GmbH) which is a subretinal implant that's CE-marked. To my knowledge, Alpha-IMS has not yet been commercially implanted. The Argus II is being routinely implanted in Germany, Italy and The Netherlands, and will soon be offered to patients in France. In June, the first Spanish patient was treated at the Barraquer Ophthalmology Centre of Barcelona. Argus II is also now commercially implanted in the US.

So far, so good

The scale of the improvements in Argus II patients' vision is outlined in the latest data from a long-term, international study (NCT00407602) that followed 30 blind individuals (and when completed, reported on 26) with severe-to-profound RP over 60 months. The vision of most of the implanted people improved from a starting point barely detecting bright light, to locating objects and determining direction of movement. The best vision

achieved so far is 20/1260 (0.02–1.8 logMAR).

Users experienced improvements in performing their daily activities, including, for example: locating everyday items, identifying objects at various distances, crossing the road independently by following pedestrian crossings, and avoiding obstructions at head height while walking.

Main findings of a 30-patient review

An international multicenter clinical trial was carried out to evaluate the safety and potential benefit of the Argus II in providing visual function to blind patients with severe-to-profound RP. As well as helping establish the safety and long-term reliability of the implant, the results also demonstrated quality of life improvements.

- As judged by independent low vision rehabilitation experts, the Argus II System had, at some point during the study, a positive effect on the lives of 77 percent of patients by improving their functional vision and/or their well-being.
- Sixteen patients (62 percent) received the positive effects at the time of the study; the other four reported that the System had a positive effect earlier in the study. The System did not negatively affect any of the patients assessed.
- Eight patients (27 percent) demonstrated visual acuity improvement to >2.9 logMAR (best result at any follow-up visit).
- Trial patients consistently performed better with the Argus II System ON vs. OFF on orientation and mobility tests (e.g., finding a door and following a line).

European reimbursement

A recent, pan European study (6) concluded that Argus II is a cost-effective intervention for treating RP, with a low cost per QALY (Quality Adjusted Life Year) ratio, at approximately £11,700 per QALY. A number of EU countries' state healthcare systems are, therefore, starting to offer reimbursement of the costs of implanting Argus II in patients with RP.

In March 2014, the device was selected for fast-track funding under the French government's 'Forfait Innovation' scheme, representing the first-ever medical device approved for support through this reimbursement program. The first

treatment is scheduled for October 2014 and the French Ministry of Health believe that up to 36 blind patients with RP will have received the implant (7).

In Germany, Argus II treatment is reimbursed under the annual NUB (Neue Untersuchungs- und Behandlungsmethoden) funding approval – a mechanism that facilitates prompt introduction of innovative healthcare products and devices.

The reimbursement of the prosthesis is currently under review in England, where that country's NHS Specialised Commissioning is considering funding treatment for a limited number of patients with RP with profound vision loss. If the proposal is approved, the NHS would pay for a defined number of patients with RP and profound sight loss to receive the groundbreaking implant in a similar manner as in Germany and France.

Making a difference today

The fact that the FDA has approved the device, nearly 100 patients have had the device successfully implanted to date, and the fact that national healthcare systems are beginning to reimburse the procedure represents good news for patients with RP – more will have a chance to have the implant, and see something of the world around them once again.

Amanda Hayhurst's background lies in healthcare journalism, having written for the UK's Daily Mirror and the Evening Standard, and held senior editorial roles with both prominent consumer magazines and public relations companies – and currently runs one.

Go to top.txp.to/0813–402 to read what some of the ophthalmologists that have implanted the device have to say about it.

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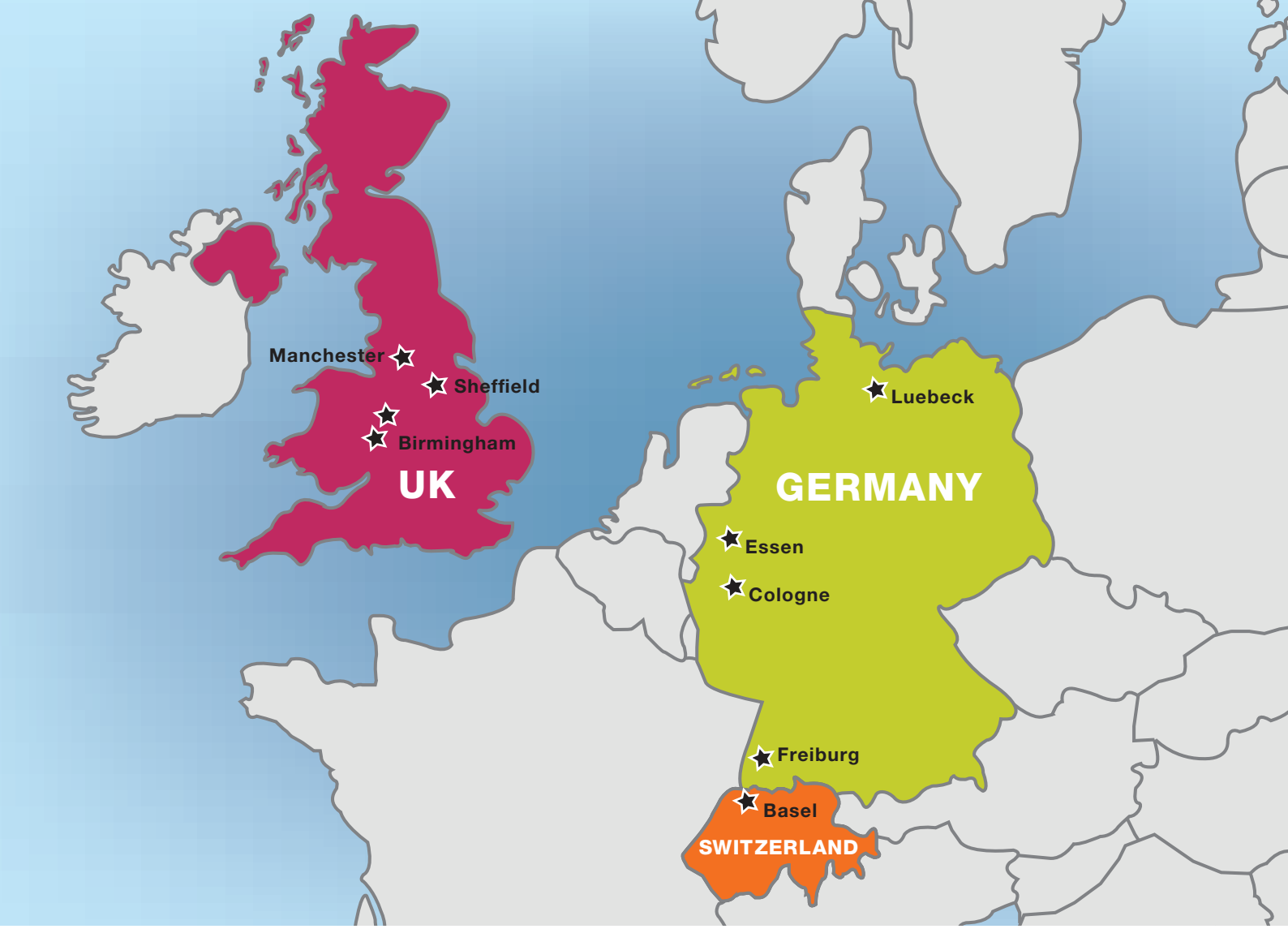

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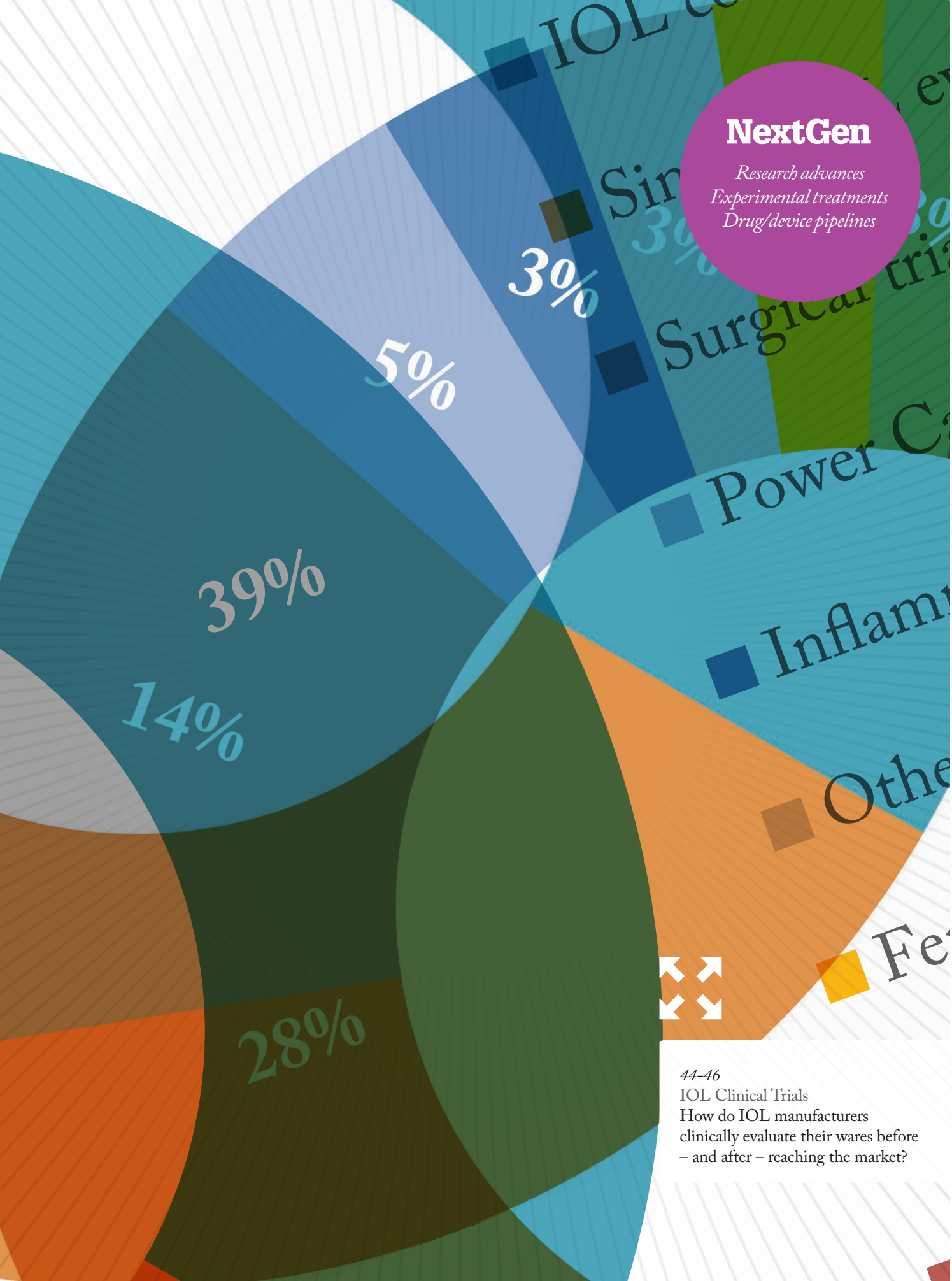


44-46
IOL Clinical Trials
How do IOL manufacturers clinically evaluate their wares before – and after – reaching the market?

IOL Clinical Trials

By Mark Hillen
Illustration by Rachael Tremlett

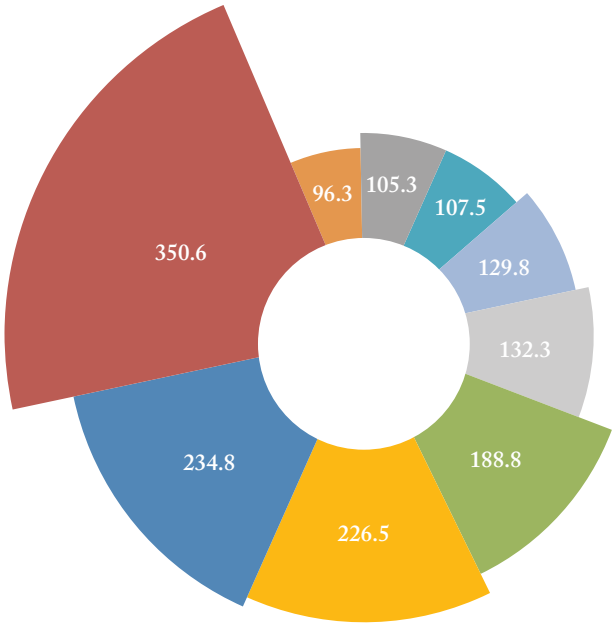
One of the most commonly performed surgical procedures in the world is cataract surgery: the removal of patient's clouded natural crystalline lens, and its replacement with a synthetic intraocular lens (IOL). The procedure has been successfully performed for more than 65 years. Over that time, many new IOLs have been developed, varying by design, material, implantation location and fixing method. Some IOLs were successful, others not; clinical evaluation, for the most part, made that distinction.

We searched clinicaltrials.gov for: ("intraocular lens" OR "implantable collamer lens" OR toric OR multifocal) NOT ("contact lens" OR "contact lenses"), and exported the entire dataset as tab-separated values, for import into and analysis within Microsoft Excel 2013. Inappropriate records (mostly related to multifocal tumors in breast cancer) were removed, and the full text of each record examined for additional details to be recorded into the spreadsheet (such as the type of evaluation performed, or the manufacturer of every IOL mentioned, where possible).

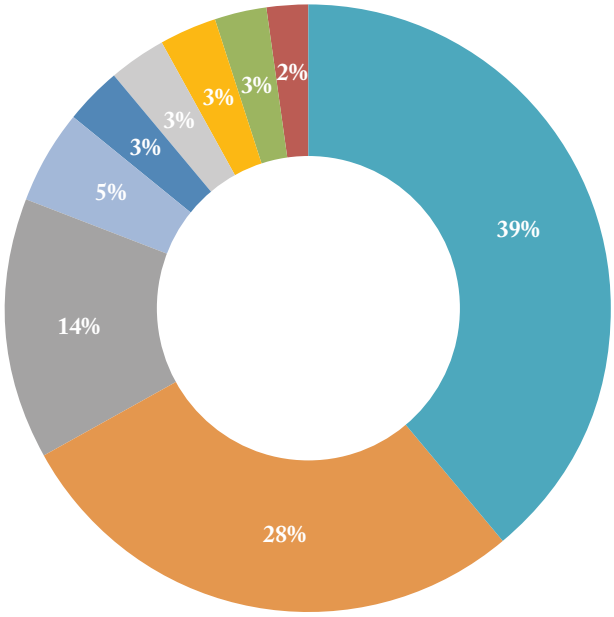
The results presented speak for themselves, but I'd like to point out a few caveats and highlights.

Caveats. It's likely that many trials are missing from the earlier records within clinicaltrials.gov (see sidebar, "Clinicaltrials.gov: its history and why we used it"), but more recent data should be more robust. Basic data like trial Phase is missing from many records; we can only plot what's there; some records were clearly sponsored by an IOL manufacturer, but then no information was then presented in the record regarding whose IOLs were used. Trial enrolment numbers were generally small, and outliers have on occasion skewed the data. For example, "Basic Research" trials (n=5) had the highest average number of patients enroled (at 350.6), but this was skewed by

Average Trial Enrolment



Evaluation Type



IOL comparison
Single IOL evaluation
Surgical trial
Power Calculation/metrics
Femto vs Manual
Viscoelastic
Inflammation
Basic Research
Other

one observational study that enroled 1500 patients; without it, the average enrolment dropped to 63.25. Nevertheless, the overall average enrolment across the entire dataset analyzed was 120.6. Additionally, clinicaltrials.gov's dataset has been expanded to include trials from before its inception: the record with the earliest start date (February 1992) was NCT00453011, which was completed in February 1998, but added to the registry in March 2007. It's worthy to note that all such examples were funded by the US government – either by the NIH or the Department of Veterans Affairs.

Highlights. It's hard not to notice that almost two in every five trials were in Phase IV; such trials are usually post-marketing surveillance studies; here only 35 percent of them followed a single IOL on the market; 43 percent were comparisons of different IOLs. Are some of these cases of "get a product to market, and then see if it's better than the competition in a head-to-head battle"? Perhaps, but many (42 percent) were performed by academics, hospitals and research institutes themselves. On the other hand, only nine trials were earlier than Phase III. If this were a drug, these numbers would be shocking, but as IOLs are made from biologically inert materials, most are now evolutions of well-established designs, and their placement and function are well understood, it should not be too surprising if many go straight into Phase III. Finally, Alcon's IOLs have undergone by far the most clinical trial evaluation, reflecting their market share and range of IOLs, although in many trials, their IOLs were used as the comparator IOL in trials sponsored by other manufacturers.

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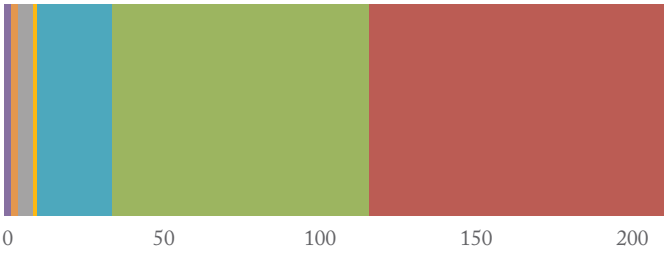
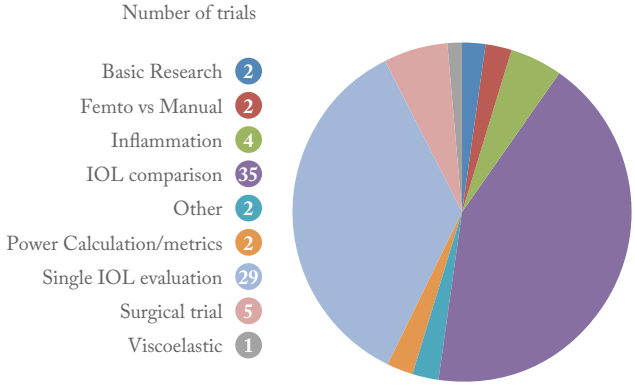
2. *International Committee of Medical Journal Editors: Uniform Requirements for Manuscripts Submitted to Biomedical Journals. http://www.icmje.org/urm_main.html, accessed July 4th, 2014.*

Funding (number of trials)

Clinical trial phase



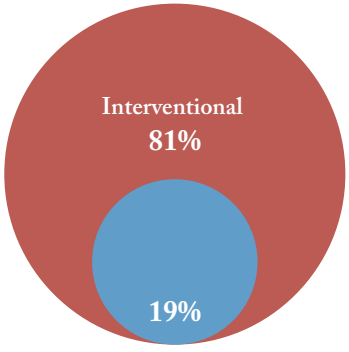
What did these Phase IV trials assess?



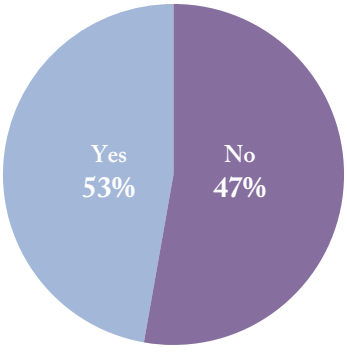
Clinicaltrials.gov: its history and why we used it

This article employs data from clinicaltrials.gov, the US National Institutes of Health's central clinical trials registry (CTR). Launched in February 2000, it was created in order to foster greater transparency from pharmaceutical companies and clinical research organizations (CROs) against a background of allegations that some companies had been hiding any record of trials that produced poor results. It is the biggest and most well-used of all CTRs; most clinical trials, if registered, are registered there. There have been historic concerns of the quality of some of the earlier records (1), and the fact that not all trials were being registered on a CTR (2), although almost all journals should now refuse to publish results from trials not registered on one (2). Despite these notable caveats, clinicaltrials.gov is the biggest and best, and so The Ophthalmologist mined that registry to try to understand the historic, and potential trends.

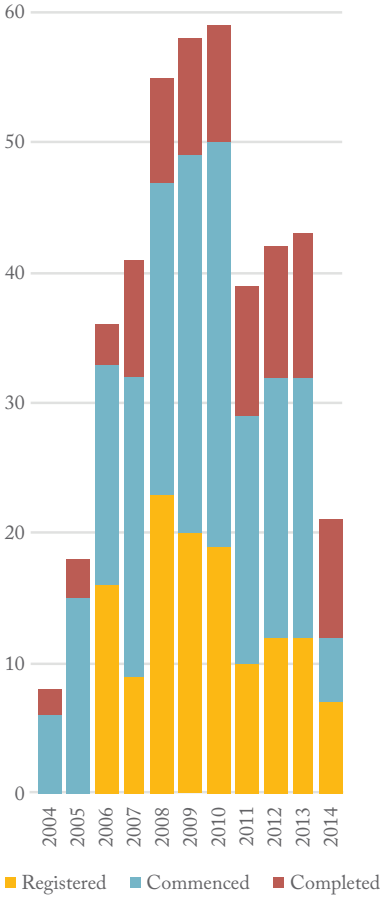
Interventional or observational?



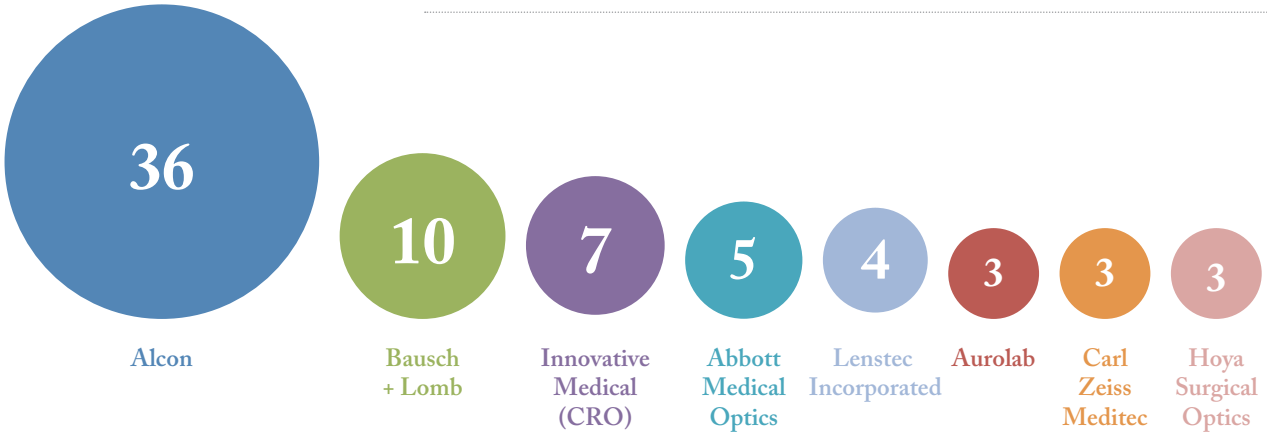
Randomized trial



Trials registered/ commenced/ completed



Industry players: trial sponsorship



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Being Theo Seiler

One of the legends of refractive surgery talks about his career, his successes and failures, and about the state of ophthalmology today.

Theo Seiler topped The Ophthalmologist's 2014 Power List, for good reason – he's a refractive surgery pioneer, having developed the first clinical dye laser and invented corneal cross-linking. He performed the first ever PTK (phototherapeutic keratectomy), PRK (photorefractive keratectomy) and wavefront-laser guided surgical techniques on the human eye, and was also the first to combine LASIK and rapid corneal cross-linking.

Theo Seiler on…

Being Number One on The Power List

That was great! Everybody surrounded me and they found it very funny that I was wearing a pink dress on the cover! It was also a kind of surprise, as I've been working in this area for many, many years. I believe I've been lucky. Our work on the anterior segment has yielded a few important developments – like refractive surgery, cross-linking and new diagnostics in keratoconus – that have had some clinical value and happen to be used in some ophthalmologists' daily work. These are things that have gained recognition for my group, but they are only a minor part of what we do.

Career highlights

The highlight was cross-linking. Back in the mid-to-late 1990s, everybody was performing LASIK, and we started to realize that we were producing keratoconus in some patients. Sometimes it happened, sometimes it didn't, and at the time, we couldn't see a reason for it. In 1998, we published the first cases of kerectasia after LASIK, not only did we detail the complications, but we also found a cure for them. The combination of discovering both is most probably the highlight of my career – the fact that it had value in treating non LASIK-induced keratoconus was a great side effect!

The current state of refractive surgery

If I have to be honest, refractive surgery, with current lasers and techniques, has plateaued. In terms of refractive success, we have a confidence of ±0.5 D, which is comparable to spectacles, and which you cannot improve on. You might be able to improve on safety a little, but it's already very safe. Today, we have a complication risk of 0.1 percent, which is twice as good as contact lenses, which carry a 0.2 percent risk of infectious complications.

…and how it might be improved

What can we make better? Not the results, but the long-term stability and safety. And I believe that, in the long run, rather than removing corneal tissue with LASIK, we need to remove it with small incision lenticule extraction (SMILE). I believe that in 5 years, SMILE will have taken over the market. Unlike other laser refractive surgeries, it doesn't really interfere with the biomechanical integrity of the cornea, meaning that you should no longer see cases of laser surgery-induced keratectasia. Having said that, I don't believe the infrared femtosecond lasers we have today are precise enough do the job… but once we change the wavelength or the aperture of those lasers, we will be able to reach the same precision as we can with the excimer laser. This will take a while, but many companies are well on the way to improving their current systems.

The future of phakic IOLs

We implant these all the time – this is nothing special. The problem with phakic IOLs is when complications arise. If there is an infection after LASIK, in the worst case I would have to perform a corneal transplant; usually, I can handle it with antibiotics or a strong cross-linking. But if I have an infection inside the eye, those options are typically not possible – the eye's defenses are on the outside, not the inside. Doing something inside the eye risks undermining its defenses and, if infection happens, the eye is lost.

In cataract surgery, the infection risk is 3 in 1000. It's one thing taking that risk when it's surgery for a good reason: the patients can't see well because of a cataract. But it's another thing taking that risk when patients can see perfectly well with contact lenses and glasses, which is why many of us refractive surgeons hesitate to use phakic IOLs.

Things going wrong more often than right

My old teacher told me, "If you start ten things at the same time and only one is successful, you are lucky." I've been lucky four or five times in my life, with wavefront-guided LASIK, PRK, wavefront-optimized profiles, cross-linking, and combinations of cross-linking and other refractive surgery techniques. If I've done five, there will be nearly fifty more that weren't successful – I certainly can't remember them all!

One that I do remember clearly was holmium thermal laser keratoplasty. In 1989, we thought it was the best thing, but after a while, we realized that despite getting a huge effect in patients upfront, one year later the whole effect was gone. We had to go to the congresses, stand on the podium, and say, "I don't do it anymore. It didn't work. Period."

Moving from academia to IROC

Being honest, the true reason for founding the IROC was because the University of Zürich and I could not find a common platform to perform industry-based investigations. They always asked to participate moneywise and they

"My old teacher told me, 'If you start ten things at the same time and only one is successful, you are lucky.' I've been lucky four or five times in my life."

wanted to influence the investigation. After a while, it just wasn't working out anymore. We quit and Michael Mrochen and others just moved out. So we started the new clinic here in Zürich, which was very successful.

Forming IROC helped us push things, like cross-linking, forward. When I came to Zürich in 2000, I wanted to investigate cross-linking – you won't believe how many objections I had from the university, reasons why I shouldn't be doing cross-linking – even in an investigative setting. I found that straightforward investigative life wasn't really possible at that time. I should say it has since changed.

Successfully straddling academia and industry

To succeed, I've learned two key things. First, never lie. Always tell the truth, whether it's convenient to your industrial partner or not. It's important that your colleagues believe you. Second, don't take too much money from industry. I saw my industry partnerships as helping me to accomplish something, but I never used these partnerships to enhance my personal income. Whenever it comes to the patent, I usually leave that patent to the industry. I tell them I earn my money with my hands, and they are helping me to do my research.

"To succeed, I've learned two key things. First, never lie. It's important your colleagues believe you. Second, don't take too much money from industry."

Current research interests

We're looking at improving cross-linking. We want to move away from epi-off CXL, and try to bring the riboflavin into the stroma in a way that we can better titrate the cross-linking to enhance its effects by a factor of two or three – and make it less harmful to the eye.

We want to perform cross-linking where the cornea is weakest – and that can mean different layers in different people. This means customizing the cross-linking to the right depth. We can create tiny channels in the cornea with a UV femtosecond laser, where we inject the riboflavin to the appropriate depth for the patient. Thanks to our collaboration with Harvard Medical School, we can measure the biomechanical effect non-invasively and, therefore, titrate the cross-linking effectively. It's very promising.

The great femtosecond laser versus manual rhexis in cataract surgery debate

The femtosecond laser makes the capsulorhexis safer – especially for less-experienced surgeons – and it is an easy way to avoid mistakes. If you don't perform many cataract surgeries in a year, then it's of great value in letting you sleep well! For a high volume, experienced surgeon, it doesn't make much of a difference. I have the new laser from Ziemer and I use it to perform cataract surgery, but being honest, I don't need it that much. My younger colleagues like it.

The current state of ophthalmology

Ever since ophthalmology's inception, it has been in a constant stream of evolution. The generation before me introduced IOLs, the generation before that did the extracapsular cataract extraction… Every generation has brought in new insights and techniques, and so I don't see that this is a particularly special time in ophthalmology. It's not better, it's not worse.

Exciting advances

In the anterior segment, the first big thing for me is new diagnostic modalities with high-res OCT. The next big thing is SMILE, which excites me a lot, because that is the future. In the posterior segment, I think that liquefying the vitreous by injection is fantastic (but expensive); we need to look at ways of making it less expensive. But for all parts of the eye, new things are coming. Gene therapy has been heralded as a wonder cure for years and years, but now we are coming closer to it being used in the clinic, which is exciting.

Issues that need addressing in the next decade

Presbyopia and accommodation – nobody's really solved them. Right now, we can change the biomechanical stiffness of the lens with some femtosecond lasers, making accommodation possible again – in some patients. Alternatively, we may be able to refill the lens capsule after cataract extraction with fluid that, once cross-linked, generates a clear lens that can accommodate again. Those are the things that I am looking forward to seeing in the next 10 years.

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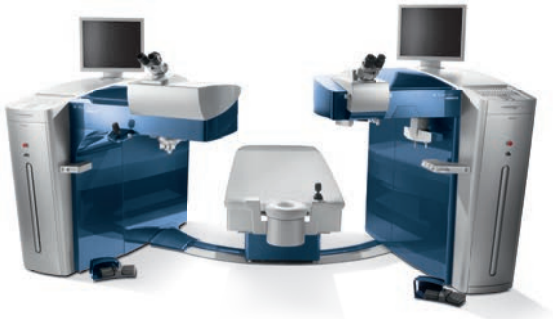

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Great Consultations

Understanding what the Dickens motivates people to consider undergoing an elective ophthalmic procedure will help you guide them to a conclusion that's right for them

By Rod Solar

In the 15+ years that I've spent working with ophthalmologists, I've often not envied some of the challenges that you face. One big one being marketing, because it relies on the patient understanding your explanation of the differences between one medical offering and another, and because the concept of promoting a medical solution doesn't come easily to you.

Nobody trained you in sales

If you're an ophthalmologist offering laser refractive surgery, for example, you may often feel as though you have to "sell" to the person who walks into your consultation room, not simply because you're offering an elective procedure, but also because you work in a commercial business. When you consider that it takes that person an incredible amount of time to even pluck up the courage to make a telephone enquiry, let alone actually undergo the procedure, the task of educating and promoting becomes a challenging one.

It's rare to find a healthcare professional that's trained in selling – healthcare teams even resist the very notion, as they – mistakenly – believe that it's unprofessional. Even worse, when prospective patients finally land in front of you for a consultation, they are often seized with fear related to the very help that they seek. This fear triggers closure, self-protection, and in some cases, defensiveness. This doesn't happen the same way in other industries, and you haven't been trained to deal with it.

Effective consultations aren't about convincing or persuading patients to do things that they don't want to do. They're about removing obstacles that stop people from doing the things they really want to do.

When enough is enough

A remarkable quality of humankind is the ability to adapt. When faced with challenges, we adapt, mitigate and modify our behaviors. We cope. It's a wonderful aspect of our personalities – and it enables us to get on with our lives, despite the constant stream of everyday hassles and

At a Glance

- *To have a great consultation, you need to address the psychological barriers your prospective patient has against the procedure*
- *Getting people to understand their historical motivations for making that change turns inertia and action*
- *Future events (like a wedding or vacation) impose a deadline that also represents a strong motivation for change*
- *Understanding these factors during a consultation can help motivate prospective patients to fulfil their desire, and undergo the procedure*

setbacks. This characteristic can also be limiting. Instead of taking the bull by the horns and dealing with issues, we can just let them slide, ignoring them for far too long. When eventually, the hassles get too much to bear, we experience what I describe as a Past Motivating Incident (PMI, Figure 1). This PMI might be just another daily hassle, but somehow, through repetition or intensity, it marks the time when you've had enough. It's the "straw that breaks the camel's back" and exceeds our power to adapt – and it enables you to cross the threshold that separates inertia and action. So it's usually shortly after experiencing the PMI that patients make an initial inquiry with an ophthalmologist.

That momentum might start to ebb away after the initial call or consultation though, back towards the lethargy of "making do" (Figure 2). You can do something about that to help. Getting prospective patients to relive their PMIs during the initial enquiry is an extremely effective way of helping them take that next step – to make an appointment for a consultation – and it reinforces their decision once they've made it. I advise people to ask open questions that enable patients to remember and share these incidents with them. Retelling painful memories enable prospective patients to re-identify with whatever it was that lead them towards action in the first place.

I also instruct ophthalmologists to use these approaches at consultations. There will be a gap between the first call and the appointment – meaning that the prospective patient is even further away from their PMI. People might have a dip in motivation at this time, which may lead to cancellation requests. Should the commitment to an appointment lead them to attend, they still might need help in reconnecting with their emotional needs to motivate further action: a commitment to have the procedure.

The moment they say "yes" is also an excellent time to prompt prospective patients to remember the reasons why they want to undergo the procedure. I find that doing so reinforces their decision, it could also reduce any regrets and may, ultimately, lead to better testimonials and recommendations. The PMI is an important concept that is easy to understand and relate to, but almost never used in selling situations. It is by far, one of the most useful concepts in my inventory of tools.

Pleasure and pain

The PMI's partner is what I call the Future Motivating Event (or the FME, Figure 1): a deadline – a reason for urgency that often helps prospective patients commit to their choice. The reason is often a pleasurable one, hence a good motivator.

We are all driven by deadlines to a certain degree, but

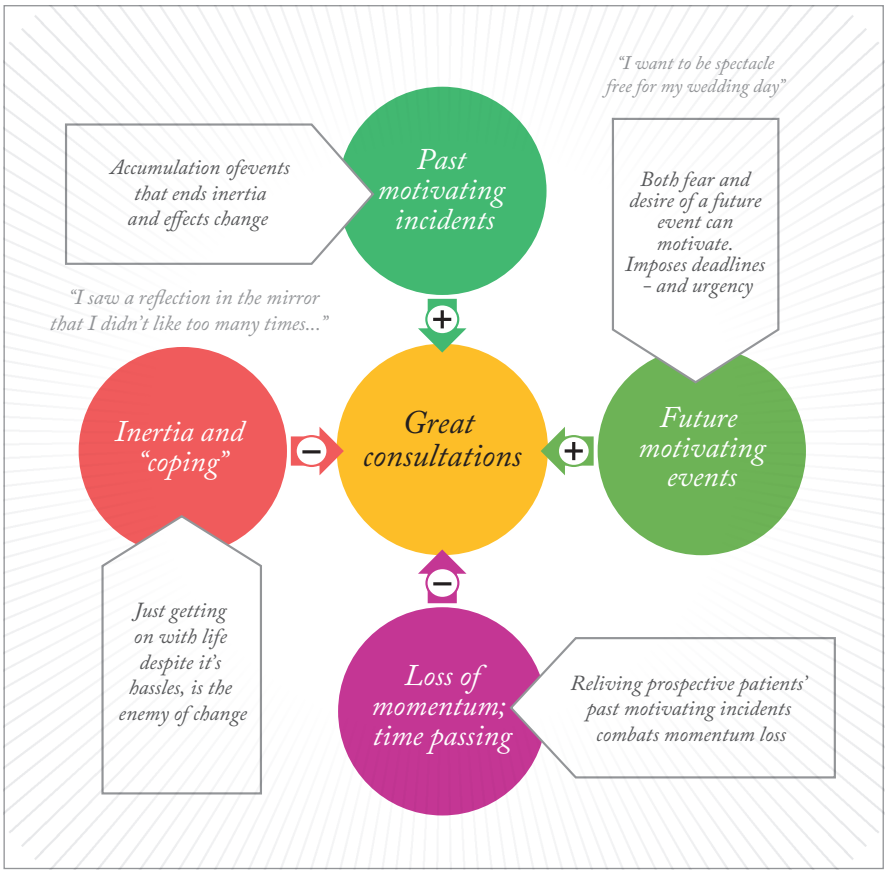

Figure 1. Factors that can motivate – or demotivate – prospective patients to make decisions to do things (like refractive surgery) that they, deep down, want to do.

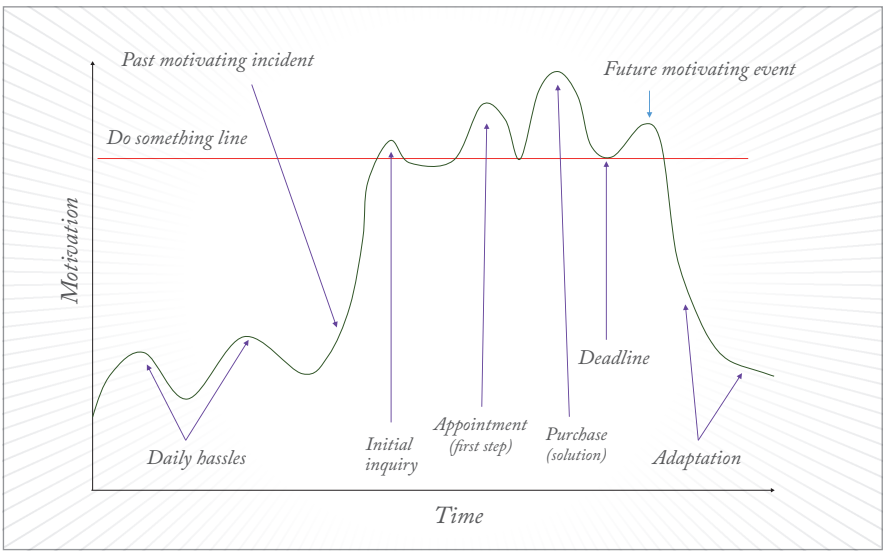

Figure 2. Factors that affect people's motivation to make a change in their life, such as refractive surgery for spectacle independence.

sometimes what a patient wants isn't clearly timely. Despite this, FMEs can be used to reinforce people's motivations for change. I instruct ophthalmologists to ask their prospective patients how they see the future after the solution has been gained. What might be coming up that they might be able to enjoy more, having the solution in place? What painful future will they avoid, if they take action now? Asking these questions makes the person sitting in your office visualize their happier future, and gets them to associate their FME with solving their problems. That solution can now be accompanied by a deadline, and all of a sudden, a problem that has an associated deadline gathers a sense of urgency. Often, this is exactly what's needed – the prospective patient's own urgency – to help them motivate themselves to take action, like booking surgery.

Leveraging human motivation

This strategy is far more compelling to a patient than any incentive or time-limited offer you could provide. It's more compelling, because it's all about them and what they want, and not about what and when you want to sell something to them.

Having a strong FME is a great asset you collect at the consultation, and can often be one of the most effective tools you have when dealing with objections. Having a strong FME will also reduce the need for you to feel like you're applying any pressure to the consultation. In the end, once you help them associate a future event with the solution they are seeking, they'll need no further convincing from you to take that leap.

Rod Solar is the Director of Client Services with LiveseySolar, and is responsible for delivering sales, customer service and communications training to LiveseySolar's clients.

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From Fort Lauderdale to the Future

How We Met: Keith Barton and Kuldev Singh.

Keith Barton

Kuldev and I first met in 1996 during ARVO at a house party hosted by our mutual friend Don Budenz, and his wife Sue. Those parties became an annual institution. I was still a corneal fellow at the Bascom Palmer Eye Institute then. Sixteen years later, in 2012, we were on our way to the very last of these parties in Kuldev's car, and we hatched the concept for what would (four months later to the exact day) become the Ophthalmology Futures European Forum 2012.

Somewhere in between we grew to become friends: we'd frequently meet at TVT study investigator meetings at ARVO and AAO. Kuldev rose to stardom at the forefront of every controversy in glaucoma, challenging mythology and flaky theory. His articles would always gain attention with witty titles such as: "Anti-Metabolite Application: Science or Voodoo?" and "Target Pressure – The Ophthalmologist's Holey Grail".

In 2002, Kuldev invited me to speak at the AAO glaucoma subspecialty day. For a European, this was a great honor. Kuldev quickly became an international opinion leader in glaucoma and was often a speaker at European Glaucoma Society congresses. I especially remember his presence at the Berlin meeting in 2008 when he surprised me after I had finished delivering a long-winded monologue on tube implants to a completely packed and pitch-dark room. The usual request for questions was met with absolute silence, disturbed some moments later by a disembodied voice piping up from the very back in the dark with a penetrating question on my technique: Kuldev.

When I got in to the car with Kuldev at Fort Lauderdale to drive to Don and Sue's house in North Miami yet again in 2012, I didn't think the ride would end with a long term partnership, but working with Kuldev on the Ophthalmology Futures Forums is a delight. His endless supply of fantastic ideas and enthusiasm, and his fast, clear thinking are a real inspiration.

Kuldev now brings those witty titles, as well as his business acumen, high level connections and keen eye for what is likely to become the next "big thing" in innovation to our annual meeting. The fourth Ophthalmology Futures Forum will be taking place this year in London, and we're sure it will be our best meeting yet.

Kuldev Singh

Keith and I are both alumni of the Bascom Palmer Eye Institute Fellowship Program in Miami. For the two decades that ARVO was held in Ft. Lauderdale, Don Budenz – my co-fellow at Bascom Palmer in 1991–92 and long-time friend thereafter – hosted reunion parties for former fellows at his North Miami home. Keith and I regularly saw each other at these dinners, as well as at investigator meetings for numerous surgical glaucoma studies that were held at ARVO and AAO, and the annual meetings of the European Glaucoma Society.

Keith and I shared a common view of glaucoma practice and he became my go-to person for glaucoma care in Europe. Keith always took great care of friends and family members that were visiting London or even Europe.

Our relationship became stronger when Keith invited me to be one of the visiting speakers at the Moorfields Glaucoma meeting in January, 2011; he was a great host during my three days in London. Besides being a terrific ophthalmologist, Keith had established a reputation for putting on creative meetings that were enjoyable for both the speakers and the audience.

In May 2012, while attending ARVO, Keith and I decided that there was a need for an innovation meeting in Europe. Regulatory hurdles in the US meant that novel ophthalmic innovations were increasingly coming from Europe, yet there was no European forum that brought together all stakeholders to move the field forward. We believed that ideally, such a meeting should be driven by ophthalmologists, and include innovators, investors, regulators as well as clinicians. And that's just what we created. The most prominent European ophthalmic congress was ESCRS so we decided that we would hold our first Ophthalmology Futures Forum just before the 2012 ESCRS meeting in Milan, Italy.

Putting together a fully funded new meeting in four months was a daunting task, but Keith and I quickly realized that we complemented each other well in this project. I have to say this meeting would not have been possible without the dedication of Keith's administrative assistant, Abigail Mackrill, who is now Operations Director for Ophthalmology Futures. Keith, Abigail and I spoke regularly, and our strong virtual working relationship allowed us to host a very successful first Ophthalmology Futures Forum in Milan. The subsequent 2013 meeting in Amsterdam was larger and given the strong interest expressed by all stakeholders, we held a third forum in Tokyo, preceding the World Ophthalmology Congress in April, 2014. The Tokyo forum was particularly special – in addition to our usual showcase of new ophthalmic technology, we had panels that discussed improving eyecare in the developing world as well as the global regulatory issues in device approval.

My partnership with Keith continues to be most enjoyable, and our fourth Ophthalmology Futures meeting in London this September promises to be the best to date.

For Glaucoma

Tough on IOP. Easy on Eyes.

taflotan®

15 µg/ml tafluprost

The first preservative-free prostaglandin

- Effective IOP-lowering [1]
- Low risk of hyperaemia [2]

15 µg/ml tafluprost

taflotan®

The preservative-free prostaglandin.

Abbreviated Prescribing Information TAFLOTAN® (tafluprost 0.0015% eye drops, solution, single-dose container). **Presentation:** Low-density polyethylene single-dose containers packed in foil pouch. Each single-dose container has a fill volume of 0.3 ml and there are 10 containers in each foil pouch. The following pack sizes are available: 30 x 0.3 ml and 90 x 0.3 ml. One ml of eye drops contains 15 micrograms of tafluprost. **Indication:** Reduction of elevated intraocular pressure in open angle glaucoma and ocular hypertension in patients who would benefit from preservative-free eye drops or who are insufficiently responsive or intolerant or contra-indicated to first line therapy, as monotherapy or as adjunctive therapy to beta-blockers. **Dosage and Administration:** The recommended dose is one drop of TAFLOTAN® in the conjunctival sac of the affected eye(s) once daily in the evening. Not recommended in children or adolescents (under the age of 18). In renal or hepatic impairment use with caution. **Contraindications:** Hypersensitivity to tafluprost or to any of the excipients. **Precautions:** Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation. Some of these changes may be permanent, and may lead to differences in appearance between the eyes when only one eye is treated. Caution is recommended when using tafluprost in aphakic patients, pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema or iritis/uveitis. There is no experience in patients with severe asthma. Such patients should therefore be treated with caution. **Interactions:** Specific interaction studies with other medicinal products have not been performed with tafluprost. **Pregnancy:** Do not use in women of childbearing age/potential unless adequate contraceptive measures are in place. **Driving:** Tafluprost has no influence on the ability to drive. **Undesirable Effects:** The most frequently reported treatment-related adverse event was ocular hyperaemia. It occurred in approximately 13% of the patients treated with preserved tafluprost and 4.1% of the patients treated with preservative-free tafluprost. Other side effects include: Common (1% to 10%): eye pruritus, eye irritation, eye pain, changes in eyelashes, dry eye, eyelash discolouration, foreign body sensation in eyes, erythema of eye lid, blurred vision, increased lacrimation, blepharal pigmentation, eye discharge, reduced visual acuity, photophobia, eyelid oedema and increased iris pigmentation and headache. Uncommon (0.1% to <1%): superficial punctate keratitis (SPK), asthenopia, conjunctival oedema, blepharitis, ocular discomfort, anterior chamber flare, conjunctival follicles, allergic conjunctivitis, anterior chamber cell, conjunctival pigmentation and abnormal sensation in eye, hypertrichosis of eyelid. **Overdose:** If overdose occurs, treatment should be symptomatic. **Special Precautions for Storage:** Store in a refrigerator (2°C - 8°C). After opening the foil pouch keep the single-dose containers in the original foil pouch, do not store above 25°C, discard an opened single-dose container with any remaining solution immediately after use. **MA Holder:** Santen Oy, Niittyhaankatu 20, 33720 Tampere, Finland. **Date of Preparation:** 11/2012.

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

August 2014

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