MAY 2018 # 53

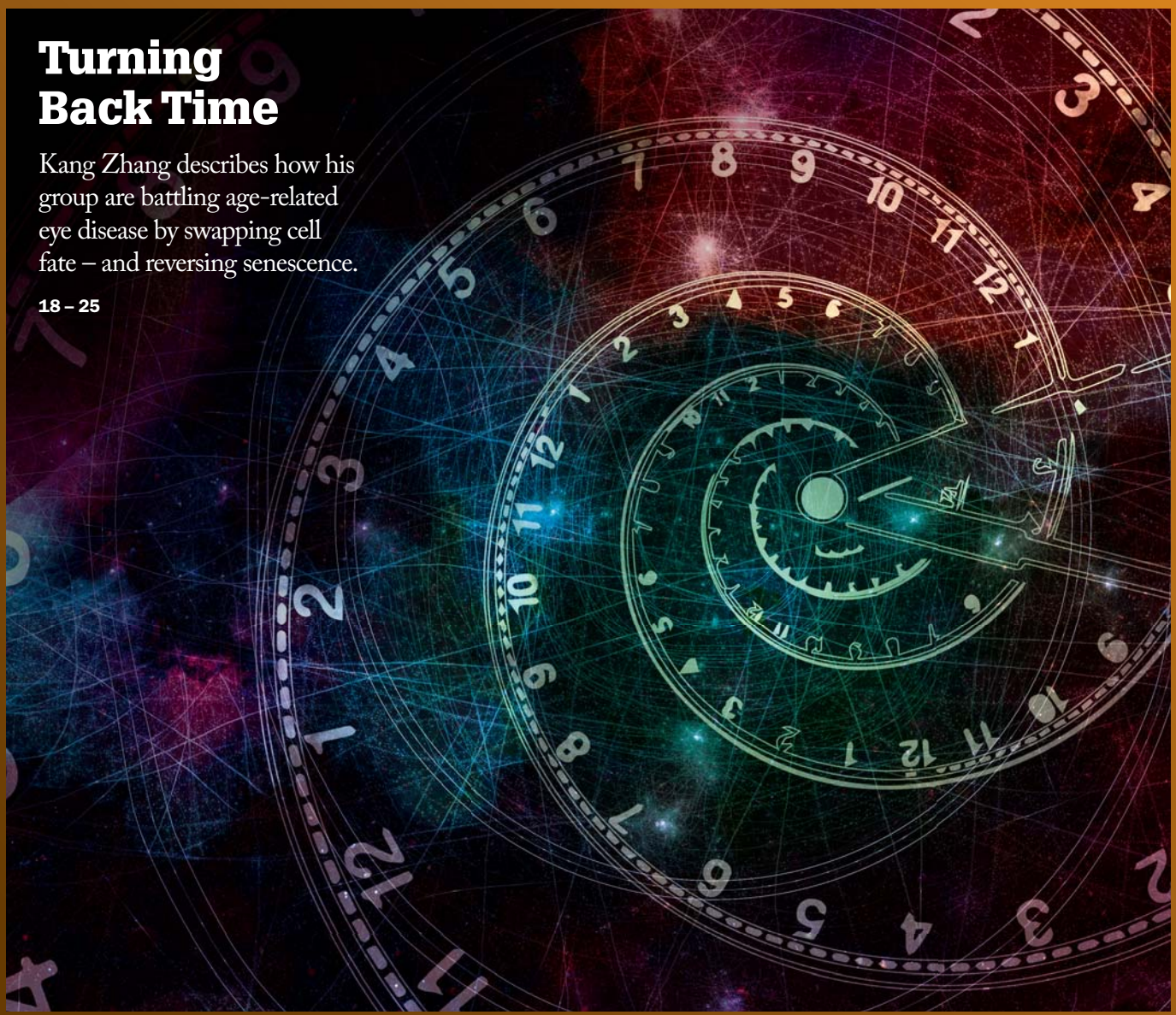
the Ophthalmologist™

Upfront
VA gains in dry AMD with an RPE patch
10

In Practice
Corneal stigmatism: Taming the irregulars
28 – 33

NextGen
Should we embrace the exosome over stem cells?
39 – 41

Profession
How to approach surgery in your early career stages
47 – 49



Turning Back Time

Kang Zhang describes how his group are battling age-related eye disease by swapping cell fate – and reversing senescence.

18 – 25

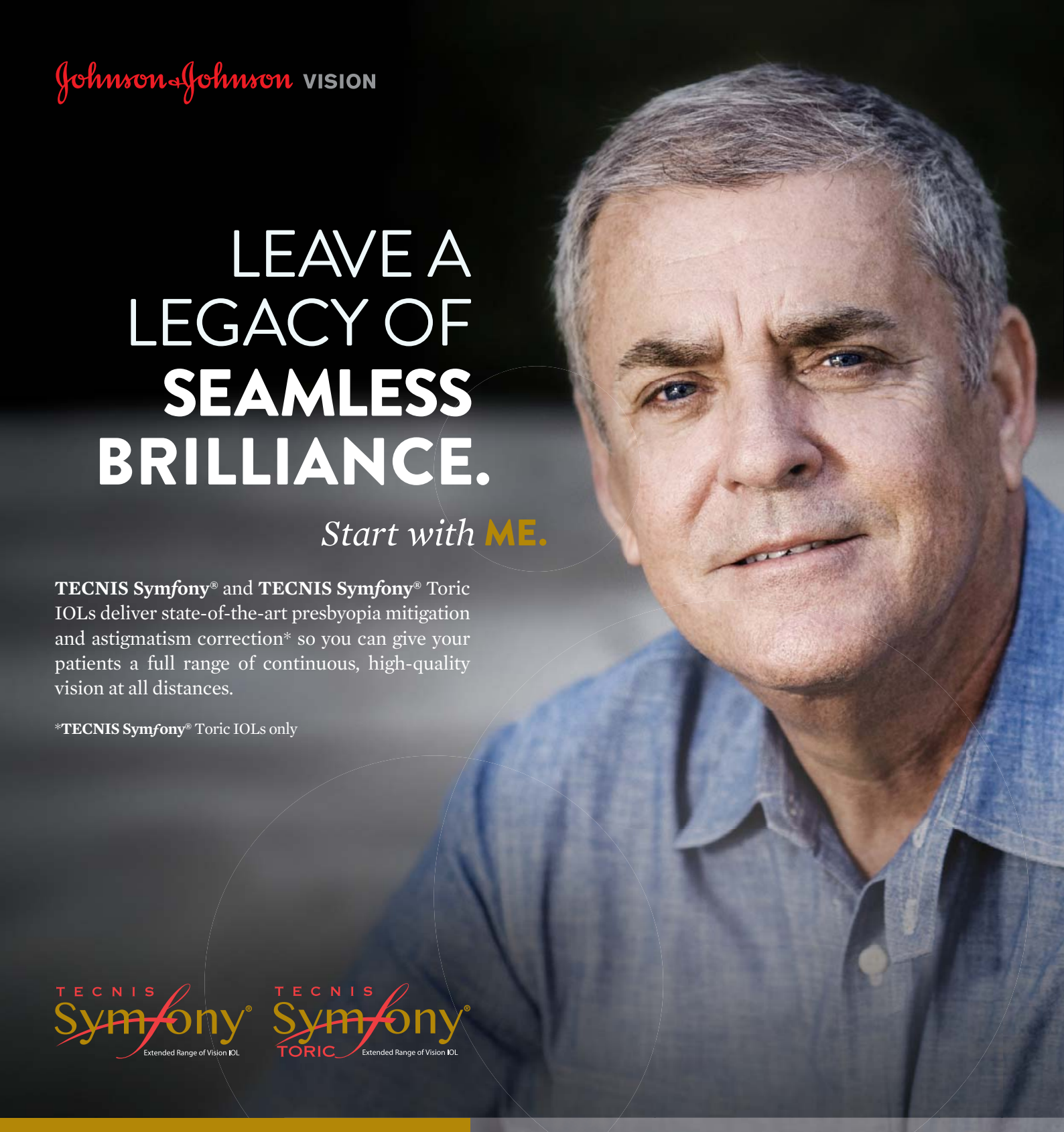


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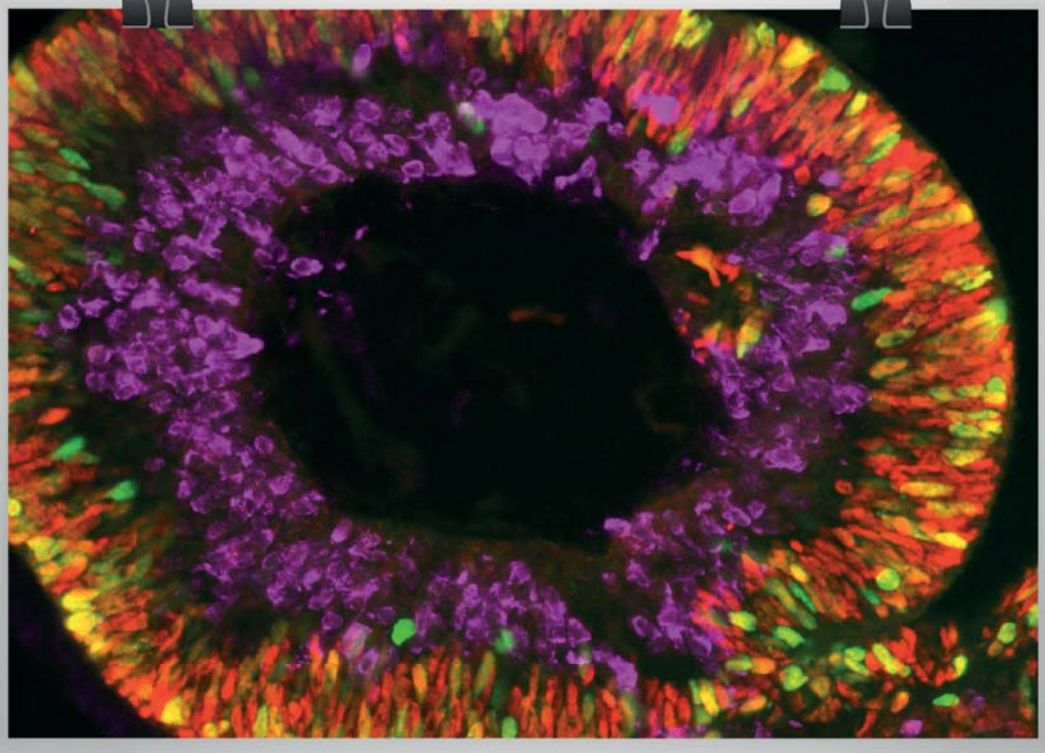
Image of the Month



Retinal Bloom

This image by David Gamm shows a retina organoid, which mimics the structure and function of the human retina, allowing it to serve both as a platform for the study of disease mechanisms and new therapeutics, but also as a source of cells for transplantation. Gamm's group uses a variety of stem and progenitor cells in their research to study retinogenesis and retinal degenerative diseases. In September 2017, Gamm and his group's work was recognized by the National Eye Institute (NEI) as part of their 3-D Retina Organoid Challenge (3-D ROC) with an honorable mention.

Credit: David Gamm, Associate Professor of Ophthalmology and Visual Sciences, University of Wisconsin-Madison, Madison, Wisconsin, USA.

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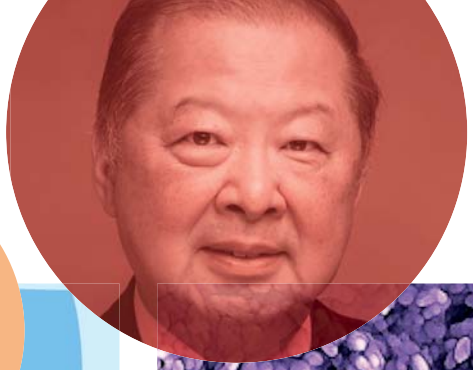
Contents



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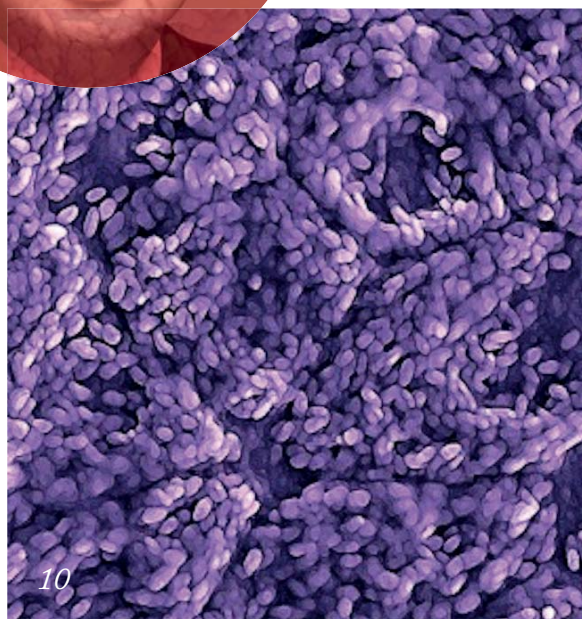


10

Upfront

10 The Regeneration Game

11 When I'm Cleaning Windows

12 Benchmarking the Power List

14 Now You See Them, Now You Don't

In My View

16 **Alan Mendelsohn** makes the case for more ophthalmologists to enforce the stop smoking message with patients.

17 To provide continuous care for the rising numbers of ophthalmology patients, **Keith Austin** says that the profession needs to look beyond the hospital walls.

Features

18 **Turning Back Time**
The genetic toolbox enables us to do more than correct one gene at a time. Kang Zhang asks: why not sidestep disease, by genetically reprogramming cell fate, or even better, turning back the clock on senescent cells in age-related disease?

03 **Image of the Month**

09 **Editorial**
That's Life, by Mark Hillen.

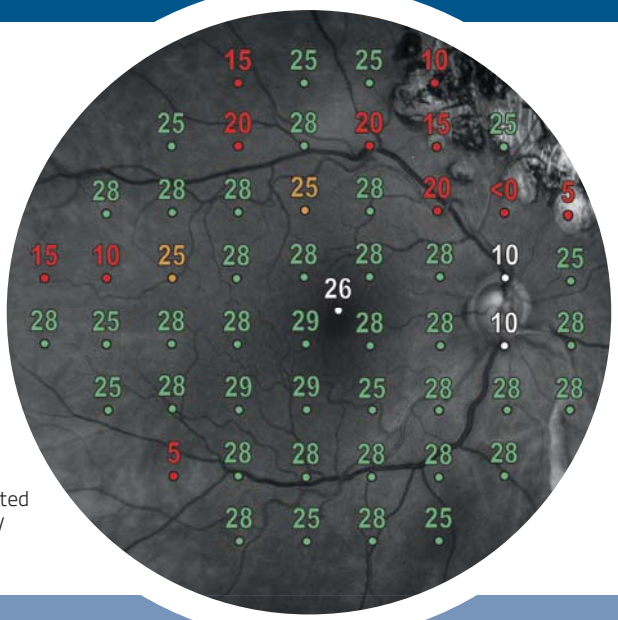
On The Cover

What's the best way of representing turning time back?

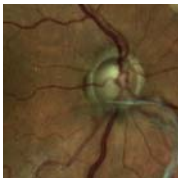
compass

Fundus Automated Perimetry

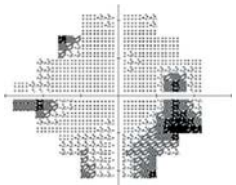
The new paradigm in Glaucoma Management



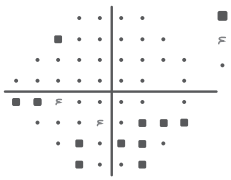
Fundus related perimetry



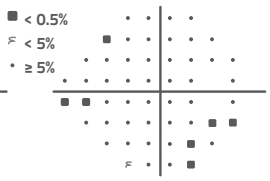
ONH detail



Gray Scale Map



Total Deviation



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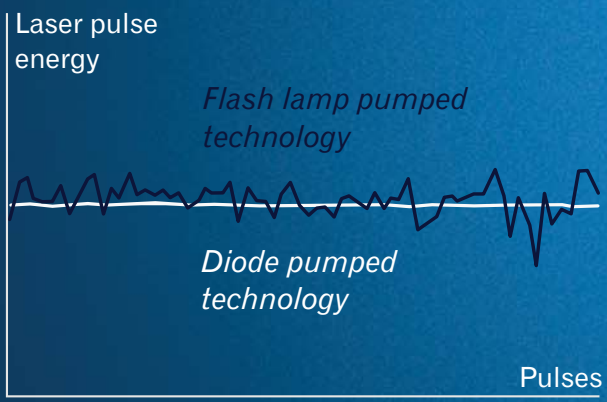

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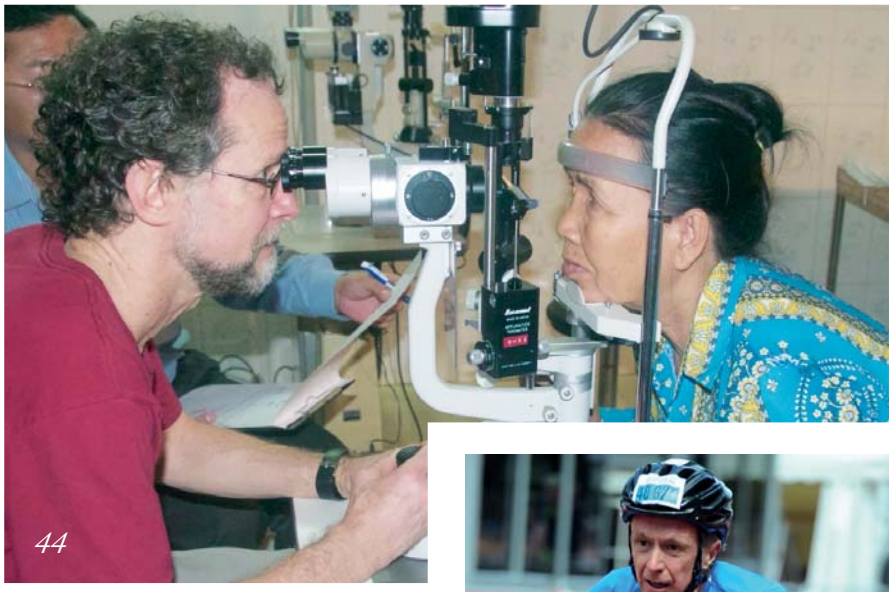

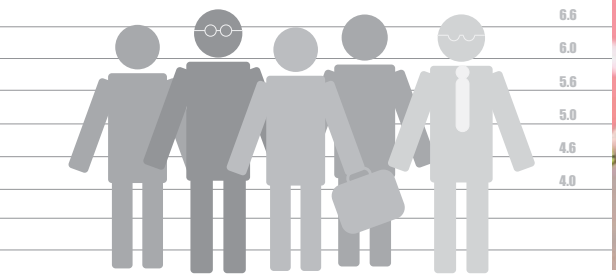

In Practice

28 **Not the Usual Suspects**
Sheraz Daya shares the secret to managing irregular astigmatism: identifying the problem and tackling it at its source...

NextGen

36 **Great Minds Look Ahead**
The 2018 Power Listers offer a glimpse of ophthalmology's future.

39 **Enter the Exosome**
Exosomes are simpler to produce and far easier to administer than stem cells. Since exosomes are all of the "good stuff" stem cells secrete… Ben Mead asks if they could be the answer to our retinal regeneration needs?

Profession

44 **A Question of Capacity**
Marty Spencer writes about how the Seva Foundation is going about adding another million sight-saving surgeries in developing countries – per year – by 2020.

47 **How to Approach Surgery in Your Early Career**
Bobeck S. Modjtahedi and Eduardo Uchiyama give their 10 tips for being a better surgeon after you've completed your fellowship.

Sitting Down With

50 **Keith Barton,** Consultant Ophthalmologist, Moorfields Eye Hospital, London, UK.

the Ophthalmologist

ISSUE 53 - MAY 2018

Editor - Mark Hillen
mark.hillen@texerepublishing.com

Managing Editor - Ruth Steer
ruth.steer@texerepublishing.com

Content Director - Rich Whitworth
rich.whitworth@texerepublishing.com

Publishing Director - Neil Hanley
neil.hanley@texerepublishing.com

VP Sales North America - Molly Phillips
molly.phillips@texerepublishing.com

Sales Manager - Abigail Mackrill
abigail.mackrill@texerepublishing.com

Head of Design - Marc Bird
marc.bird@texerepublishing.com

Designer - Hannah Ennis
hannah.ennis@texerepublishing.com

Digital Team Lead - David Roberts
david.roberts@texerepublishing.com

Digital Producer Web/Email - Peter Bartley
peter.bartley@texerepublishing.com

Digital Producer Web/App - Abygail Bradley
abygail.bradley@texerepublishing.com

Audience Insight Manager - Tracey Nicholls
tracey.nicholls@texerepublishing.com

Traffic & Audience Database Coordinator - Hayley Atiz
hayley.atiz@texerepublishing.com

Traffic & Audience Associate - Lindsey Vickers
lindsey.vickers@texerepublishing.com

Traffic Manager - Jody Fryett
jody.fryett@texerepublishing.com

Traffic Assistant - Dan Marr
dan.marr@texerepublishing.com

Events Manager - Alice Daniels-Wright
alice.danielswright@texerepublishing.com

Marketing Manager - Katy Pearson
katy.pearson@texerepublishing.com

Financial Controller - Phil Dale
phil.dale@texerepublishing.com

Accounts Assistant - Kerri Benson
kerri.benson@texerepublishing.com

Vice President (North America) - Fedra Pavlou
fedra.pavlou@texerepublishing.com

Chief Executive Officer - Andy Davies
andy.davies@texerepublishing.com

Chief Operating Officer - Tracey Peers
tracey.peers@texerepublishing.com

Change of address
info@texerepublishing.com
Hayley Atiz, The Ophthalmologist,
Texere Publishing, Haig House, Haig Road, Knutsford, Cheshire, WA16 8DX, UK

General enquiries
www.texerepublishing.com
info@texerepublishing.com
+44 (0) 1565 745 200
sales@texerepublishing.com

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That's Life

There will always be people who are left behind by MedTech advances.

A 71-year-old white male patient presents with myasthenia gravis (MG), diagnosed from his initial presentation 12 months previously with unilateral ptosis, and confirmed by physical examination and specific antibody testing. Patient commenced neostigmine therapy, but discontinued thanks to an adverse cutaneous reaction to the first dose. He presents today with diplopia, which on examination, is caused by incomitant strabismus in his left, non-dominant eye.

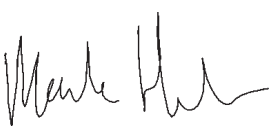
For the moment, let's put to the side the systemic consequences of the MG worsening and the potential treatment options going forward for now. What does it mean for him?

If you're wondering why I'm presenting this case, it's because the patient is my father. His care from NHS Scotland has been great, but the fact is that he is experiencing first-hand the hard realities of the onset of vision loss. He's fortunate (enough) for now to be able to drive. As it progresses, he'll probably be able to drive with a patch over one eye. But this is unlikely to be a permanent solution. He's very lucky that my mother (who was always a better driver than him!) is able to transport him to cafés, choir, church and the clinic, and he can visit most of his grandchildren with relative ease. And so, his social life remains the same – for now. His life is still pretty normal – but it's getting harder for him.

Let's assume two things. His MG and vision deteriorate further to the point that his driving license is surrendered, and my mother is needed elsewhere. We're not at the stage of having Waymo or Uber Level 5 self-driving taxis, so that "co-dependent independence" is gone. Yes, there are taxis, but the cost of those – especially to retirees, quickly adds up. If medical (and potentially surgical – thymectomy) management fails to arrest the rate of his decline, then he'll be totally reliant on family, mostly my mother, to help him through each day. His healthcare resource use will rise greatly (and it'll burn my mother out quite quickly too). If, eventually, the systemic symptoms catch up with him, then I know his local hospital staff will do the very best they can for him, until nothing more can be done.

Perhaps I have a tendency to put my head in the clouds a little too much – evangelizing about the greatness of technology that's just coming over the horizon. Sometimes technology can make a huge difference to people's lives; self-driving cars might help my Dad for a while when they eventually arrive – and I believe they'll make a huge difference to the visually impaired (and society in general) once they're established. But sometimes, there's nothing that can be done, and nothing on the horizon that might bring hope to cling to either. It's just personal tragedy and societal burden. The saddest thing is, as you healthcare professionals know, it's also nothing special.

Mark Hillen
Editor



Upfront

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

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

The Regeneration Game

Could a successful treatment for dry AMD be on the horizon?

March 2018: the news broke that two patients with severe wet AMD gained vision following implantation of a retinal pigment epithelium (RPE) patch derived from human embryonic stem cells (hESCs) (1).

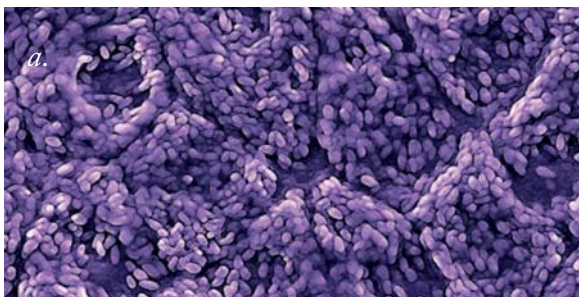
April 2018: a collaborative team from USC Roski Eye Institute and other institutions in California, USA, publish Phase I clinical study results showing safety and functionality of their bioengineered RPE implant in patients with advanced dry AMD (2).

"So many people suffer severe vision loss due to advanced dry AMD; it is estimated that almost 3 million people in the US will suffer from the condition by 2020," says Amir Kashani, lead author on the associated paper (2). As no treatment currently exists, the group were inspired to develop an approach to treat geographic atrophy (GA) – one of the main causes of vision loss in dry AMD. Their implant, named the California Project to Cure Blindness-Retinal Pigment Epithelium 1 (CPCB-RPE1), comprises a polarized monolayer of hESC-derived RPE on a Parylene substrate (Figure 1). After subretinal implantation into the area of GA in four patients, CPCB-RPE1 showed a stable integration with overlying retinal tissue, and there were no reported safety concerns (mean follow-up, 260 days). Three of the four patients maintained vision throughout follow-up, with one patient sustaining a gain of 17 letters from day 60, and two patients showing improved fixation.

Kashani says their work has the potential to address a major unmet medical need – the treatment of advanced dry AMD. "To be able to prevent or reverse vision loss in this population would have a major public health benefit and improve the lives of millions," he says. What's next? "These results are very encouraging and we plan to finish enrollment of about 20 patients to fully demonstrate the safety of the implant, as well as better understand its potential efficacy," says Kashani. "This will help us plan for the next trial in a larger cohort of patients." Could a new generation of AMD treatments be on the horizon?

References

1. *L da Cruz et al., "Phase 1 clinical study of an embryonic stem cell–derived retinal pigment epithelium patch in age-related macular degeneration", Nature Biotechnology, 36, 328–337 (2018). PMID: 29553577.*
2. *AH Kashani et al., "A bioengineered retinal pigment epithelial monolayer for advanced, dry age-related macular degeneration", Sci Transl Med, 10 (2018). PMID: 29618560.*



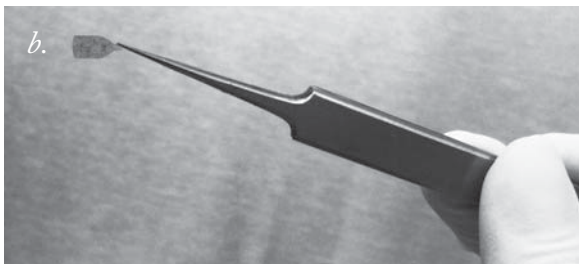


Figure 1. Scanning electron microscope image of hESC-derived RPE (a) and image of the CPCB-RPE1 implant (b). The implant is comprised of a polarized monolayer of RPE on an ultrathin Parylene substrate that is designed to mimic Bruch's membrane. Credit: USC Roski Eye Institute (a) and Britney O Pennington (b).

When I'm Cleaning Windows

Kinoshita's CEC+ROCK approach to treating corneal endothelial cell dystrophies enters the clinic

If you view the cornea as a window, then you might consider corneal endothelial cells (CECs) as the window cleaner. A single layer that resides at the bottom of the cornea, they keep the cornea clear by transporting fluid and regulating corneal hydration. In a healthy cornea, there are about 2,000 CECs per square millimeter; in corneal dystrophies, that number starts to drop. The CECs respond by spreading out to compensate, but by the time the CEC count drops to 400 CECs/mm^2, they're overwhelmed. The cornea swells and becomes opaque.

Shigeru Kinoshita and his research group in Kyoto, Japan, are well known for developing, pre-clinically, a novel approach to increasing CEC count. They harvest CECs from a healthy donor cornea, then culture and subculture them ex vivo (1–3). The cultured cells are recovered and supplemented with a ROCK inhibitor, and then injected into the anterior chamber of the eye, and the recipient lies face down for hours to let gravity (and cell adhesion) do the work of integrating the CECs to the posterior cornea. In rabbits and monkeys, it worked well, increasing CEC levels, and restoring clarity to the cornea. Given that donor cornea tissue is in short supply, what's nice about this approach is that one donor cornea could be used to prepare CECs for multiple recipients – it's usually one donor, one recipient with traditional keratoplasty procedures. But the real question was: could it work in humans?

The answer is yes. Eleven patients with pseudophakic bullous keratopathy, aged between 20 and 90 years, with no detectable CECs, a corneal thickness > 630 µm and a BCVA of 20/40 or worse received the treatment (4). The primary outcome was, at 24-weeks, a restoration of CEC density to > 500 cells/mm^2. At 24 weeks, 11 out of 11 patients achieved this – with cell densities ranging from 947 to 2,833 cells/mm^2. The lack of CECs causes swelling and opacification; replenishing them, after 24 weeks, reduced not only corneal thickness, but also significant improvements in BCVA – nine out of the 11 experienced a two line or more improvement. But the study authors didn't just present 24-week outcome data, they presented 2-year outcome data too. At this point, the cornea was thicker than at baseline in all 11 eyes and each of the 11 eyes maintained transparency.

But there's a safety question. You're injecting cells into the anterior chamber of the eye, and hoping that leaving the patient in a prone position for 3 hours will bind the new CECs to the cornea. What if some unattached cells go on to block part of the trabecular meshwork? Here, there's some good news. Only one patient experienced elevated IOP, and this was ascribed to prolonged glucocorticoid use. No uveitis or systemic adverse events were observed.

It's a small study; more clinical validation will be required before this approach can be used routinely (if at all). But as Reza Dana noted in his accompanying editorial in the New England Journal of Medicine (5), "This study provides clinical proof of concept regarding the use of cultivated endothelial cells in the treatment of corneal endothelial cell dysfunction."

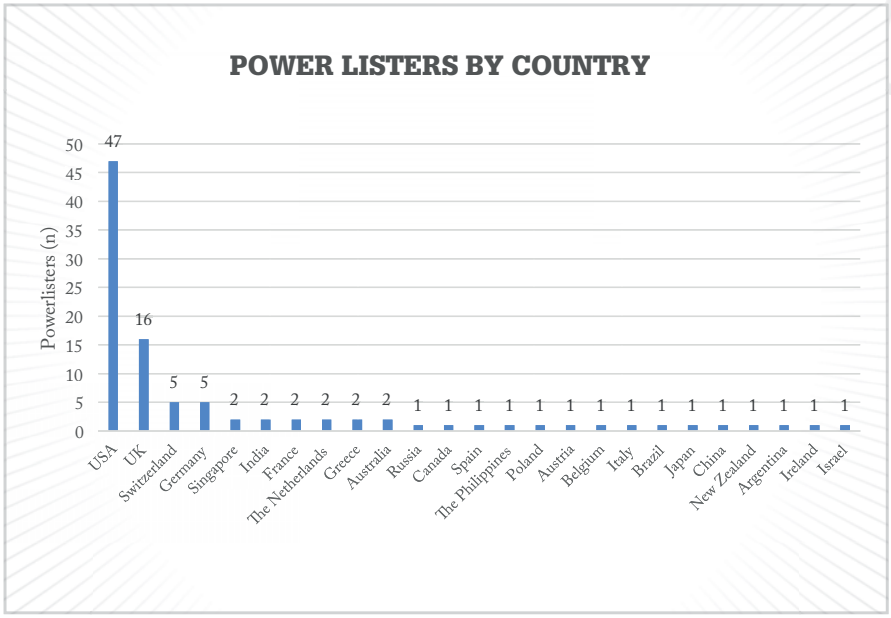
References

1. *N Okumura et al, "Enhancement on primate corneal endothelial cell survival in vitro by a ROCK inhibitor", Invest Ophthalmol Vis Sci, 50, 3680–3687 (2009). PMID: 19387080.*
2. *N Okumura et al, "ROCK inhibitor converts corneal endothelial cells into a phenotype capable of regenerating in vivo endothelial tissue", Am J Pathol, 181, 268–277 (2012). PMID: 22704232.*
3. *N Okumura et al, "Rho kinase inhibitor enables cell-based therapy for corneal endothelial dysfunction", Sci Rep, 6:26113 (2016). PMID: 27189516.*
4. *S Kinoshita et al., "Injection of cultured cells with a ROCK Inhibitor for bullous keratopathy", N Engl J Med, 378, 995–1003 (2018). PMID: 29539291.*
5. *R Dana, "A new frontier in curing corneal blindness", N Engl J Med, 378,1057–1058 (2018). PMID: 29539278.*

Benchmarking the Power List

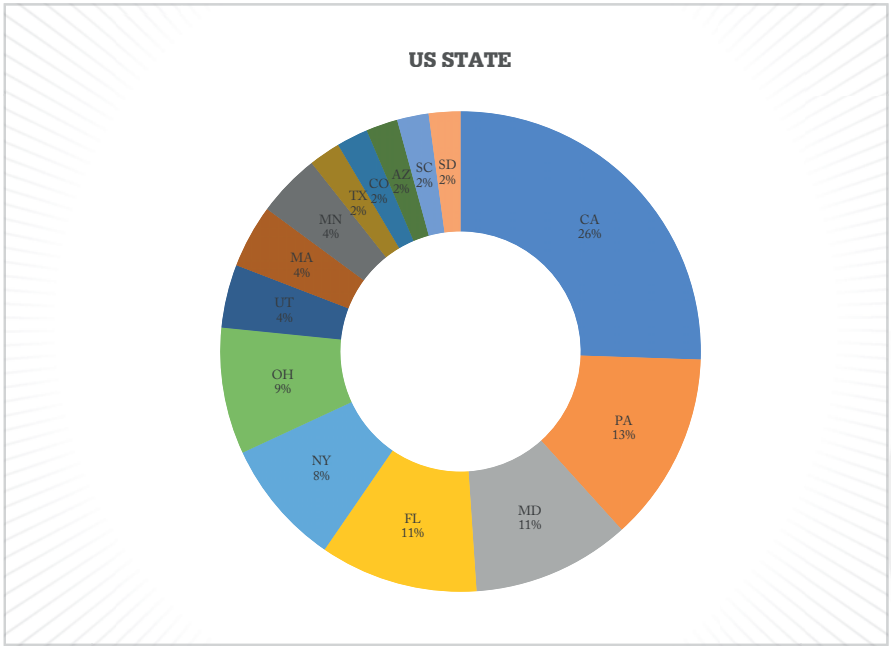
The who, what, where and why of this year's top 100

The 2018 Power List has landed, and while most of the interest lies with the list, there's a considerable amount to be learned from the list. There were a number of questions that we could ask (and answer): Where are the Power Listers? What do they do? Does one specialty dominate? What's the gender balance?

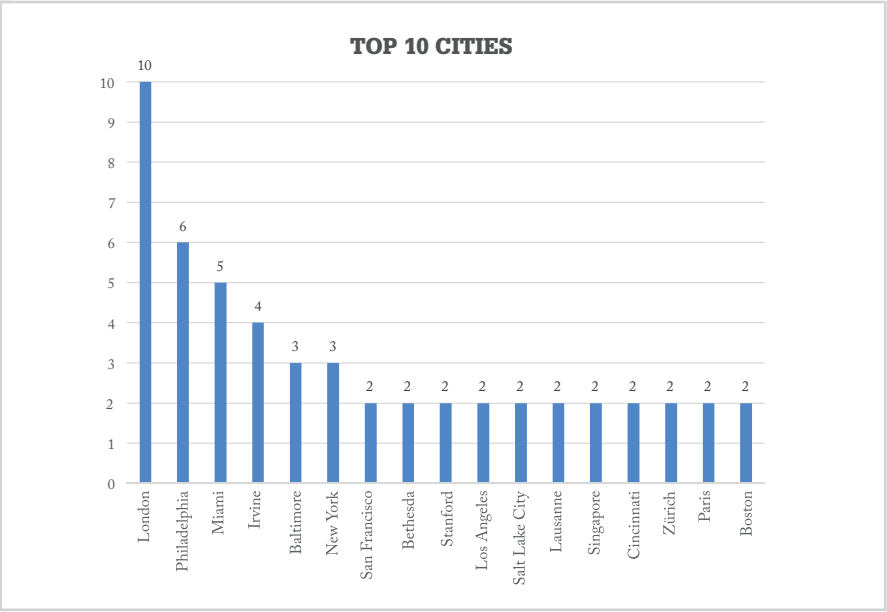


Here's what we found:

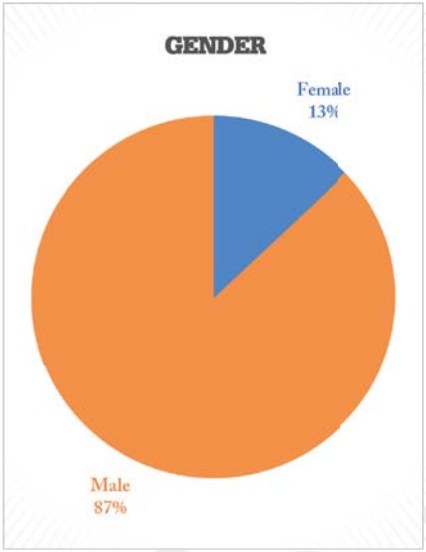
There's a global spread of Power Listers. Almost half hail from the US, and almost four in ten from Europe (although the status of the UK's 16 percent as 'European' might be up for debate soon). If we go by Power Listers per capita, the top three come out as Switzerland, Singapore then the UK. Let's examine the 47 Power Listers from the US. Where are they based?



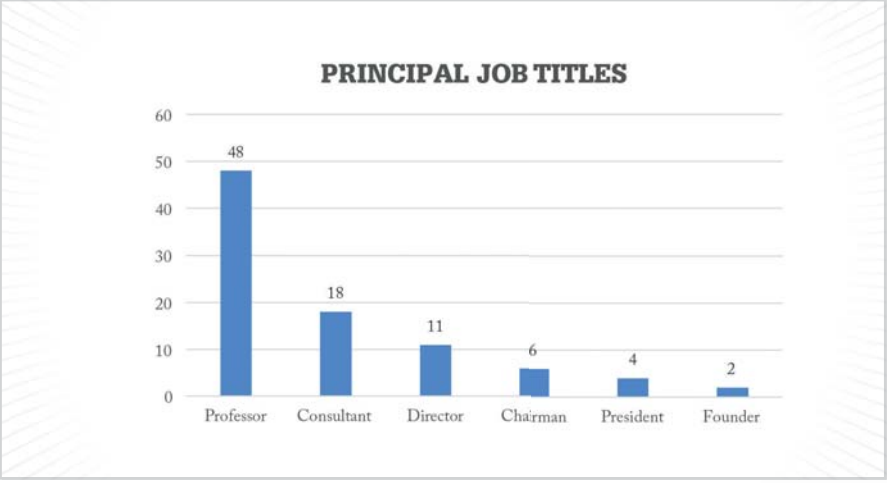
By state, we see that California, Pennsylvania, Maryland and Florida come in at 1, 2 and third equal.



Let's cut the data a different way. Which cities are the hottest in the world for Power Listers? Here, we see London leading the pack, followed by Philadelphia and Miami.



Let's visit gender balance. The first time we ran the Power List Top 100 in 2014, 13 percent of Power Listers were female. Four years later, that statistic is… 13 percent.



While many of those on the list have multiple job titles and affiliations and some work across multiple specialties, we decided to examine what their main "day job" was. What we found was that the vast majority had an academic affiliation – those with the principal job title "President" were relatively few, and of those who did, most were in industry.

What was the most common first name in the Power List this year? Robert, followed by Thomas, John and David. Surnames were a little more diverse – the only ones that popped up more than once were Chang and Shields.

So, what would the median, composite Power Lister look like? It would be a man with the title Professor, called either Robert Shields or Robert Chang, who lives in the United States, in the state of California, but somehow in London too.

This exploration of the Power List might be a bit of fun, but it's important to recognize the achievements of every single person on the list. Irrespective of their age, race, gender or location, our Power Listers have accomplished great things during their careers. They have all worked incredibly hard, be it in the clinic, OR, laboratory, boardroom or podium, and their achievements deserve to be celebrated – after all, every single one of them continues to work to improve people's vision each day. Thanks to you all.

Now You See Them, Now You Don't

Might temporary microglia depletion treat inflammatory retinal disease?

Microglia are curious cells. They're the retina's (and the central nervous system's) resident macrophages and when infection occurs, they're the first line of defense. But they're also central to keeping neurons healthy – in addition to looking for pathogens, they constantly scavenge for plaques and damaged neurons or synapses, always ready to transform into reactive phagocytes. But there's strong evidence that microglial reactivity is a hallmark of various retinal degenerative and inflammatory diseases, including both rare genetic disorders like retinitis pigmentosa (RP) and X-linked juvenile retinoschisis, and more common multifactorial retinal diseases such as AMD, diabetic retinopathy, glaucoma and uveitis. Why? It seems that retinal microglia, in disease states, can remove healthy cells too, contributing to vision loss. Studies have shown inhibiting or removing microglia in retinal degenerative disorders can help retain photoreceptors and slow vision loss. But then, they play an important role in maintaining a healthy retina. So, is their inhibition or removal ultimately bad news in the long-term too?

Wai Wong, chief of the US National Eye Institute's Section on Neuron-Glia Interactions in Retinal Disease, and his team set out to find out more about retinal microglia – and what happens to the retina if you eliminate them (in mice). To do this, Wong and his team used PLX5622, a drug that blocks the microglial cell survival receptor, CSF-1. Over a period of several days, CSF-1 inhibition strips microglia almost entirely from the retina, leaving just a few cells clustered around the optic nerve. Crucially, the loss of microglia doesn't affect nerve function. And, as Wong notes, "If we were to get rid of the microglia while a large, inappropriate immune response was happening, we might be able to miss the worst of the inflammation, but still come back into balance at a later point in time. We could hit pause on the immune system in the retina in a directed way."

What about when you press the play/pause button again? Figure 1 shows the answer. Thirty days after stopping the drug, Wong and his colleagues found that the microglia had repopulated the retina – and by 150 days, they had returned to their normal cell density. "The organization of these immune cells is quite elaborate, and all the organization comes right back," explains Wong: the returning microglia first started to regrow in clusters around the optic nerve head, then gradually, new microglia expanded outwards towards the edges of the retina. Over time, the cells re-established an even distribution across and through the various layers of the retina. As Wong put it: "We can actually image the eye and watch these cells divide and split and migrate as part of the repopulation response."

But were the new microglia in these mice fully functional? The researchers used a photoreceptor light injury model where photoreceptor cells are damaged by bright light. The new microglia were able to activate and migrate to the injury site normally, and the levels of pro-inflammatory cytokines following light injury were similar in retinas that contained endogenous microglia or repopulated microglia. Electroretinographic testing showed that the repopulated microglia were able to communicate with and fully maintain the function of neurons in the retina (especially when the depletion was short-lived). But significant challenges still remain before this approach can hit the clinic (not least, showing that this approach can actually work in humans). The biggest concern about the clinical use of such drugs is constraining their effect of these microglia-depleting drugs to the retina – as removal of microglia elsewhere in the central nervous system represents a maelstrom of potential side effects that are best avoided.

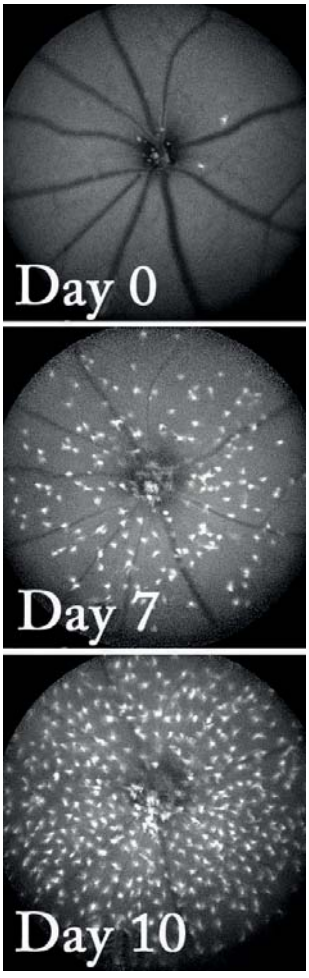


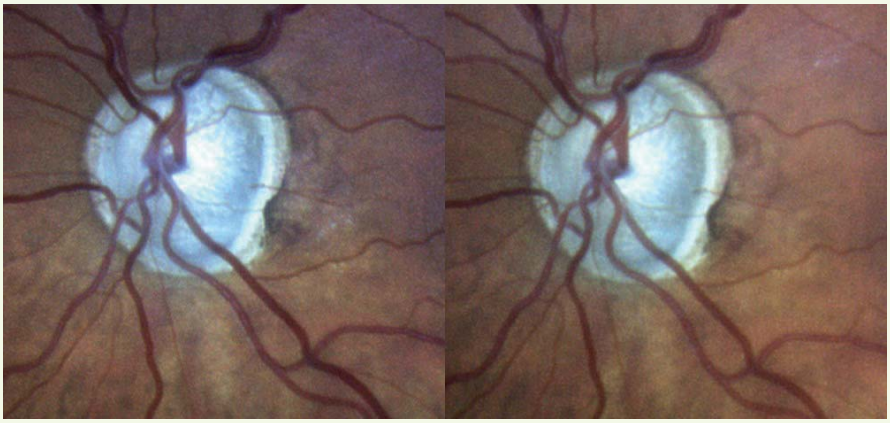
Figure 1. Fundus images of mouse retina after being treated with microglia-eliminating drug, PLX5622. When the drug was stopped (Day 0), nearly all of the microglia had gone, but by Day 7, microglia have started to migrate across the retina, and by day 10 they have increased in number.
Credit: Wai T. Wong, National Eye Institute.

Reference

1. *Y Zhang et al., "Repopulating microglia restore endogenous organization and function under CX3CL1-CX3CR1 regulation", Science Advances, 4, eaap8492 (2018).*

Navigating Glaucoma

Glaucoma needs better, faster and more accurate diagnostic and disease monitoring methods than the current gold standard, perimetry. Can a new technology combination, COMPASS Fundus Automated Perimetry (FAP), point the way to better outcomes? Francesco Oddone (Head of the Glaucoma Unit, IRCCS Fondazione G.B. Bietti, Rome, Italy) shares his experience.



High-tech imaging modalities may be all the rage, but don't forget the advantages – and longevity – of stereophotographic ONH imaging.

What are the main features of COMPASS?

Uniquely, COMPASS provides both confocal scanning ophthalmoscopy and automated perimetry capabilities in a single device. The combination offers significant advantages in the clinic: a single procedure yields both functional (quantitative) and anatomical (qualitative) information. Clearly, this is faster than doing such tests in series. Further, these data are of very high quality. The COMPASS real-time fundus tracker compensates for patients' face and eye movements by rapidly repositioning perimetric stimuli based on the current eye position. Finally, the instrument is fully automated, which minimizes the need for operator intervention; for example, the computer autonomously compensates for refractive error. Overall, COMPASS is designed to provide more and better information, in less time, and in a less onerous manner.

How do these features benefit glaucoma management?

As glaucoma is a progressive disease that affects the structure and the function of the optic nerve, we need both structural and functional information to accurately diagnose and monitor patient disease states. The COMPASS retinal tracking system permits more accurate correlation of functional measurements (retinal threshold sensitivity values) with retinal structure (fundus images). This greater accuracy is aimed at reducing test-retest variability, which in turn will mean that fewer tests will be required for the physician to confidently assess disease progression.

Furthermore, COMPASS' capabilities, together with other clinical information, facilitate the recognition of non-glaucoma retinal pathologies that could affect visual field, including pathological myopia changes, retinal scars and maculopathies. In such cases, the new technology considerably simplifies the differential diagnosis task faced by the clinician.

Finally, note that COMPASS provides high-quality, automatically acquired, confocal, high-definition, true-color stereophotographs of the optic nerve head (ONH). As glaucoma is associated with ONH changes, ONH evaluation is critical to diagnosis and monitoring. This aspect of COMPASS technology can be considered future-proofed: 30 years from now, the images COMPASS provides will still be useful in clinical settings, to identify structural changes over time. This may be considered an advantage in an era characterized by early obsolescence of imaging devices.

Will the patient notice a difference?

Given that COMPASS can help reduce the variability seen with functional tests, it holds the potential to improve the sensitivity of detecting progression. And if we are more confident about our assessments of progression, we may be able to provide better care for the patient. The benefit to patients' quality of life is clear.

What impact has COMPASS had on your practice?

Primarily, it aided our diagnostic process: the retinal tracker, which is the real heart of the FAP system, is designed to significantly reduce test-retest variability and improve the sensitivity of disease monitoring. Having a high-tech perimeter coupled to a confocal retinography system that can automatically produce high-quality, confocal, true-color, optic disc stereophotographs at the end of a perimetric test is a unique combination and is a great aid in my clinical life. Overall, these two key features of COMPASS make life easier for both operator and patient, and I hope that the results from ongoing multicenter clinical trials will provide evidence to make COMPASS the gold standard for functional testing in glaucoma.

In My View

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

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

Contact the editor at edit@theophthalmologist.com

No Smoke Without Fire

We need to reinforce the message to stop smoking

By Alan Mendelsohn, Eye Surgeons and Consultants, Fort Lauderdale and Miami, Florida, USA

I don't smoke. Neither did my parents and nor do my children. But that's not enough for me: I am on a mission to keep my patients from smoking. And I am looking for other ophthalmologists to do the same.

It is well known that smoking damages the entire body. The evidence is indisputable that smoking causes an epidemic of devastation, including markedly increased prevalence of multiple cancers, respiratory and cardiovascular diseases. Inexplicably, most people believe their eyesight is immune from the scourge of smoking. As ophthalmologists, we are acutely aware this is far from the truth. Smoking is associated with significantly increased prevalence and ocular pathology in the three leading causes of blindness in adults (macular degeneration, glaucoma, and diabetic retinopathy). Worse yet, smokers can be affected at a younger age and more severely than non-smokers. Yet many ophthalmologists are hesitant to bring up the topic of smoking, concerned the patient may not be receptive or will consider the subject off limits. Others may be frustrated by the lack of patient action and wary of investing time, effort and energy – or they may question whose role it is to bring up the hazards of smoking. Should it be a topic for a primary physician to broach or a social worker?

In my 30 years as an ophthalmologist, I have discovered a consistent pattern. Ninety-nine percent of my new patients are unaware of the effect of smoking on the eyes, and lack important information on how smoking causes an increased prevalence of eye disease. They are unaware that visual acuity impairments often occur at a younger age and in a more expedited fashion in smokers. When I explain about smokers having a significantly increased blood level of carboxyhemoglobin that causes retinal hypoxia – almost the equivalent of the smoker partially strangulating him or herself – I often hear audible gasps. I wish I had kept statistics on the number of patients who came into our office as smokers but no longer smoke. If I had to guess, the estimate would hover at the 50 percent mark. We think a very small percentage stop when they first hear the message, and others may wait until they have heard my 'doom and gloom' smoking statistics a few times. The best results take place when a family member is diagnosed with macular degeneration, glaucoma or diabetic eye disease. The most resistant are those who have been smoking for decades and still have excellent vision with no posterior segment pathology. They are far less likely to stop smoking, assuming incorrectly they are immune from ocular damage.

As a physician, I see my role not only as a diagnostician and treatment provider but also as an educator. My philosophy is the more your patients know about ocular health and preventative care, the greater your chances of reducing systemic and ocular morbidity as well as mortality. I also believe in persistence; if I do not succeed the first time, I keep trying as it is part and parcel of helping patients save their eyesight. Fellow ophthalmologists, I strongly encourage you to give the stop smoking push a new try. If one approach does not work, view it as a challenge and use a different one next time. Track the results, not over months but years, and watch the numbers plummet. It may not be dramatic, but it is enough to know that you did your best to change the course of eye disease in your patients.

Looking Beyond the Hospital Walls

Why it's vital for ophthalmologists to look outside the hospital environment to tackle today's capacity challenges

By Keith Austin, CEO, EMS Healthcare, Ellesmere Port, UK

The rising prevalence of eye disease is no secret. In the UK, where I'm based, it's predicted that we'll see an increase of 100,000 wet AMD cases in the 10 years to 2020, whereas the number of glaucoma cases will rise by almost 300,000 (1). Patients are already losing sight unnecessarily because of capacity problems in eye clinics (2), leading me to wonder what the situation will look like in another decade if nothing changes.

As demand heightens, so too does the level of funding required, yet the UK's Department of Health budget is currently increasing by just 0.6 percent on average each year, compared to a historic average of approximately four percent since the NHS began (3). The wider picture forms a negative impact on the economy, with fewer resources to treat sight loss having an acute impact on productivity. In fact, lower employment participation of people with impaired vision and unpaid care accounts for £5.65 billion in costs to the UK economy, whilst the reduction in wellbeing and health of those patients totals £19.47 billion (4). To put this in perspective, the total cost of sight loss in the adult population of the UK was £28.1 billion in 2013, compared to £22 billion in 2008 (5).

It begs the question; how are ophthalmologists expected to adhere to such an escalating demand – a demand that will not reduce so long as we have an aging population? With evening and weekend clinics already operating at full capacity, and hospital refurbishments often unaffordable, it's vital that clinicians consider more innovative and sustainable methods of delivering care.

A facility that is becoming increasingly popular amongst trusts looking to run clinics more efficiently is mobile medical units that provide fully independent assessment and treatment services right in the heart of community locations, complete with all the amenities expected in a modern clinic. The support for flexible infrastructure such as this extends across the NHS, with the Five Year Forward View highlighting out of hospital care as one of the main priorities for coping with today's healthcare landscape (6).

For ophthalmology, delivering care in more convenient locations rather than an often-hectic hospital environment is the single most effective method of dealing with rising patient numbers. Mobile ophthalmology units installed in easily-accessible sites can quickly create up to 250 more patient slots per week and can reduce the time spent waiting for and attending appointments by up to 50 minutes, which, ultimately, eliminates the need for evening and weekend clinics.

Being able to see more patients in a shorter period allows for a more efficient service and better planning management, freeing up resources to work towards greater operational savings. These savings can provide a practical and achievable step for trusts to contribute to the ambitious NHS commitment to £22 billion efficiency savings by 2020, a target based on productivity gains of two to three percent per year.

It's not just clinicians that reap the benefits of the delivery of care in the community. For patients, travelling to and from hospitals can be stressful and time-consuming when attending regular treatment, but the burden of travel is amplified for those with reduced vision. Mobile community-led care gives eye patients the option to receive assessment and treatment, including intravitreal injections and cataract surgery, within a nearby, easily-accessible location.

With more patients treated within target waiting times, whether for AMD, glaucoma, cataracts, or other time-critical eye conditions, more of the population will preserve healthy eyesight and require lower levels of both state-funded support and unpaid care. These people can then remain economically productive and enjoy a higher quality of life, whilst consultants can provide uncompromised care under circumstances alleviated from pressure.

This vision of convenient, efficient and flexible macula clinics will only materialize if decision makers collectively look beyond aging hospital estates to manage the continuous surge in eye health conditions set for the next 20 years.

References

1. *RNIB, "Saving money, losing sight" (2013). Available at online at: bit.ly/2vr9yNJ. Last accessed April 2018.*
2. *C MacEwen, "Increasing demand on hospital eye services risks patients losing vision" (2016). Available online at: bit.ly/2EQ8Sk4. Last accessed April 2018.*
3. *The King's Fund, "The NHS budget and how it has changed" (2009). https://bit.ly/2j2sE2g. Last accessed April 2018.*
4. *L Pezzullo et al., "The economic impact of sight loss and blindness in the UK adult population", BMC Health Serv Res, 18, 63 (2016). PMID: 29382329.*
5. *RNIB, "Future Sight Loss UK 1: The economic impact of partial sight and blindness in the UK adult population" (2009). Available at: https://bit.ly/2qAQhne. Last accessed April 2018.*
6. *NHS England, "Next Steps on the NHS Five Year Forward View" (2017). Available at: https://bit.ly/2wPmJYG. Last accessed April 2018.*

TURNING *Back* TIME

Gene therapy has traditionally focused on correcting one defect at a time. But what if you could do more with the tools of the trade? How about reprogramming cells to sidestep disease – or turning back the clock on senescent cells in age-related disease? Here's what we can do today – and what's on the horizon.

By Kang Zhang

The Neural Retina Leucine Zipper gene (*Nrl*) plays a fascinating role in retinal development. It encodes a transcription factor that acts as a master control switch for rod photoreceptor differentiation by regulating the expression of important rod-specific genes. These include the rhodopsin-encoding *RHO*, and *PDE6B* – a subunit of the cGMP-PDE protein complex, which is essential to light-mediated neurotransmission in the retina. The interplay between the various developmental morphogens and signaling cascades is nuanced and complex… What you really need to know is that all photoreceptor precursor cells develop into cones in the absence of *Nrl*. But what's really interesting about *Nrl*? Its action is reversible. Inactivate it, and rods become reprogrammed and turn into cones.

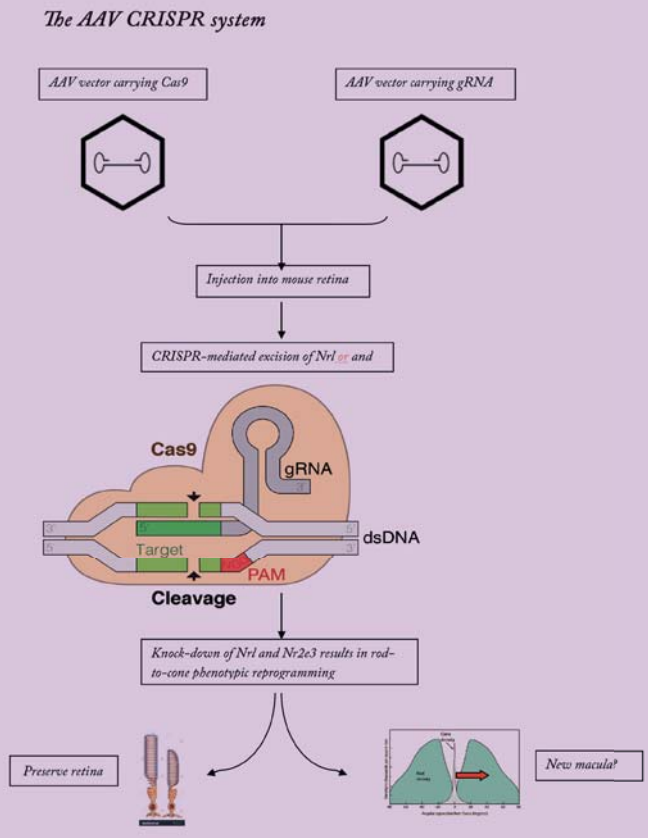
We've known for many years that retinitis pigmentosa (RP) is caused by mutations in genes that are expressed in rods, not cones, and it results in a progressive sequence of rod cell death followed by cone loss. Rod degeneration results in the collapse of the outer nuclear layer (ONL) of the retina, and this generates an oxidative, nutrient-deficient environment that is toxic to cones. It's actually the cone loss that's the most debilitating. Think about it: rods are absent from the all-cone fovea centralis, and it's hard to find an environment where rod-mediated vision is actually used – particularly in urban settings, where artificial light is endemic and most bedside tables have a lamp.

So, if you spare the rod, you save the cone? That's the conclusion most of us have reached and a number of therapeutic approaches under investigation are trying to achieve this. In some ways, RP is an attractive candidate for gene therapy; the eye is accessible, and efficacy is easily tested through imaging, eletroretinography (ERG) and even standard visual acuity testing, and the genetic defects are well understood. It's why there are a number of gene therapies currently in Phase I/II clinical trials, with more in preclinical stages. But there are about 200 genes that, if defective, can cause RP – so to treat all RP patients by gene therapy, we would need as many therapies as there are defective genes. Having done an early gene therapy trial (1) on a rare RP condition caused by a *Mertk* mutation (which has only less than 40 patients in the entire world), and given what we know about *Nrl*, its inactivation and cell fate, might there be a better way – one treatment to cure them all? I wanted to answer two big questions: could we make photoreceptor cells insensitive to inherited mutations by reprogramming them such that they switch from a vulnerable to an invulnerable state? And could this – potentially universal

– RP therapy work in the clinic to preserve cone-mediated, high-acuity daytime color vision?

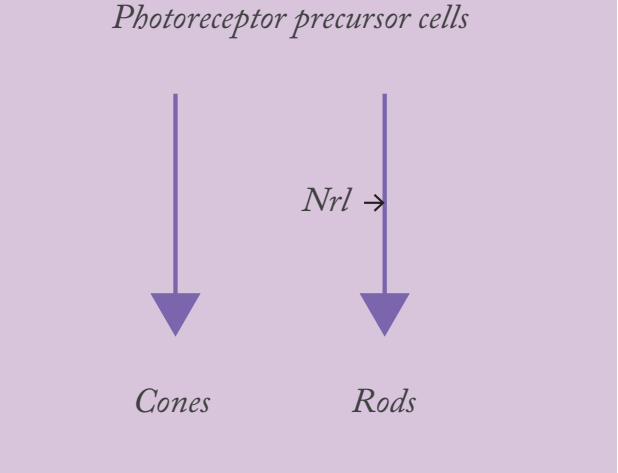
The first hurdle that needed to be cleared in taking this approach was a practical one. It's all well and good using germline techniques to make conditional *Nrl* knock-out mice as part of an experiment to understand that gene's function. But that's not an approach that can be taken in patients. For a clinically relevant approach, you first need a method capable of inactivating *Nrl* in post-mitotic cells – and these are notoriously resistant to genetic manipulation. Our approach was to use a homology-independent targeted integration (HITI) strategy based on the revolutionary CRISPR/Cas9 technology. The CRISPR/Cas9 guide RNAs are carefully designed to permit precise sequences of host cell DNA to be excised and replaced with transgene sequences, which we deliver to the cells with a vector based on adeno-associated virus (AAV).

In fact, we had already developed an HITI-AAV toolkit and had successfully used it to integrate a transgene (green fluorescent protein) into the DNA of post-mitotic, cultured primary neurons (1). We then went on to use our toolkit on Royal College of Surgeons (RCS) rats, which express a RP-like phenotype (thanks to mutations in the second exon of the *Mertk* gene). We were able to perform a CRISPR/Cas9-mediated replacement of the mutated gene in three-week-old animals, which not only preserved outer nerve layer (ONL) thickness, but also improved electroretinographic (ERG) responses to light (2), validating a new CRISPR approach for gene therapy.



Two AAV vectors are employed, one expressing Cas9, and the other carrying guide RNAs targeting *Nr1* and *Nr2e3*,. The gRNAS target Cas9 nuclease to genomic *Nrl* and *Nr2e3*, resulting in knock-down of these transcription factors. (3)

"Could we make photoreceptor cells insensitive to inherited mutations by reprogramming them... from a vulnerable to an invulnerable state?"



So, we can successfully transfect post-mitotic photoreceptors with our HITI-AAV system. It's all great work; however, it isn't cell-fate switching, nor is it the universal RP treatment I've proposed. What it did show was that our CRISPR toolkit could work in patients with RP, and that encouraged us to take the first steps towards using cell-fate switching to treat RP. Now, we have developed an HITI-AAV system that

incorporates two guide RNAs targeting *Nrl* or *Nr2e3*. You already know why we're targeting *Nrl*, so why *Nr2e3*? It's a key transcription factor that's activated by *Nrl*, and in turn up-regulates the rod-specific gene transcription network – and targeting either or both transcription factors should reprogram rods to cones.

"This approach could provide end-stage AMD patients with a new "macula" and potentially reverse some of their vision loss."

Just like our *Mertk* work, we first had to demonstrate that the system can switch rods to cones in mice. Long story short: subretinal administration of CRISPR-AAV-nrl at postnatal day 7 in wild-type mice resulted in substantially increased numbers of cone-like cells in the retina (as determined by the presence of the cone cell marker, MCAR), and quantitative PCR demonstrated down-regulation of rod-specific genes and up-regulation of cone-specific genes. The next step was to see if our CRISPR-AAV-nrl system worked across multiple murine RP models with different mutations, so we tested it in *Rd10* and *FVB/N* mice. Again, we saw similar, encouraging results. Treated *Rd10* mice showed improvements in vision and photopic b-wave amplitude under ERG testing, suggesting that cone function had improved. The treatment also appeared to preserve cells expressing cone proteins, maintain ONL thickness, and protect S-opsin and PNA expressing cells – cones, in other words. In the FVB/N mouse, treated animals showed preservation of mCAR+ cone cells and maintenance of ONL thickness and, again, displayed improved vision and photopic b-wave values.

So, another hurdle has been cleared: the data effectively show that our CRISPR genome editing approach can reprogram rods to cone-like photoreceptors in post-mitotic tissues, interrupt retinal degeneration and restore visual function – all in at least two different mouse models of RP.

Next, we constructed a CRISPR-AAV-Nrl vector to target the exact same *Nrl* gene sequence shared by humans and monkeys, which allowed us to use the same AAV vector in both non-human primate (NHP) safety studies and human clinical trials. The preliminary NHP results have been extremely promising: our three-month follow-up data suggest that our approach converts rods to cones in monkeys without any significant toxicity, and we expect to progress to clinical trials later this year.

SEEING THE BIGGER PICTURE

The application of rod to cone cellular reprogramming extends far beyond RP; this approach holds the potential to provide a new treatment option for age-related macular degeneration (AMD). People with advanced AMD suffer progressive vision deterioration and loss due to choroidal neovascularization or geographic atrophy, both of which destroy an increasing proportion of cones in the macula. My proposal is that, given the retina contains 200 million rods and 5 million cones, we should be able to employ a cellular reprogramming strategy to switch a patch of rods into cones in a perifoveal area where retina is unaffected by AMD. This approach could provide end-stage AMD patients with a new "macula" and potentially reverse some of their vision loss. For younger people, however, who are at risk of developing AMD but who have not yet progressed to overt damage, a different approach would be required; for these patients, we are investigating a synthetic biology route (Box 1).

BOX 1: SYNTHESIS OF SCIENCE AND HOPE

What do you offer a young patient at high risk of AMD? Historically, very little – but novel options are now offered by the combination of new synthetic biology techniques and the increasingly detailed understanding of AMD's genetic basis.

- Nearly 70 percent of AMD cases are associated with just three genes, *Htra1/ARMS2*, *CFH* and *C3* – why not remove any inherited risk by employing gene-directed approaches?
- One issue is that AMD risk alleles are spread over stretches of DNA comprising hundreds of kilobases – the affected sequences are too long for conventional gene therapy approaches
- Advances in synthetic biology, however, now allow the construction of entire chromosomes, or even – in the case of simple organisms such as yeast – of entire genomes
- By combining gene editing and synthetic biology, it may be possible to excise the entire range of AMD-associated alleles and replace them with normal alleles, in vivo
- Just a few interventions at the genome level would very substantially reduce the AMD risk for an individual.

What about people with late-stage glaucoma who have lost a significant proportion of their retinal ganglion cells (RGCs), compromising their optic nerve? Could we address these situations simply by reprogramming neuroglial cells into retinal neurons? There's some precedent for this concept. We know that Müller glial cells from the retina of non-mammalian vertebrates produce new retinal neurons in response to injury. And we know that these new cells can structurally and functionally integrate with existing visual circuitry, thereby repairing the retina. Mysteriously, however, mammalian Müller cells appear to have lost this capacity for retinal regeneration. Why?

At last, we have at least one answer: it's due to p53 function (4). By knocking out *p53* in mouse Müller glia, we restore their ability to rapidly and efficiently differentiate into photoreceptor precursors in culture. Further, these Müller glia-derived progenitors can incorporate themselves into the host retina after transplantation, and express markers for either retinal ganglion cells (Islet1 and Brn3) or photoreceptors (rhodopsin and IRBP). Importantly – after all, *p53* is a classic tumor-suppressor gene – we observed no tumor formation after transplantation of the precursors.

Reprogramming cells isn't limited to ophthalmology – there's a clear rationale for its use in leukemia too. As macrophages are not susceptible to the cancer transformation processes associated with the oncogenic mutations that drive leukemia, we could design a reprogramming strategy that will treat leukemia by switching malignant leukemic cells into benign macrophages. Similarly, cells of glioblastoma multiforme (GBM) – a very aggressive glial cell lineage tumor – could be switched into a neural cell type in which the oncogenes or mutations underlying GBM will no longer be effective.

"It's clear to me that cellular reprogramming techniques will have a significant therapeutic impact across many disease areas."

REMEMBER THE VULNERABLE

It's clear to me that cellular reprogramming techniques will have a significant therapeutic impact across many disease areas. And as these techniques rely on modulating the patient's own cells, they are likely to be less risky than modalities based on exogenous stem cells, where there may be a concern of tumorigenesis or immune rejection. Add the fact that reprogramming therapies are not restricted to genetic subtypes and are applicable to very broad range of patients, and we anticipate a broad application of this approach.

That said, there will be big challenges getting these kinds of advanced therapies to everybody who needs them. It's one thing to develop a technology that can address a medical need – quite another to ensure that it is broadly accessible to patients at low cost. There are still many patients with treatable diseases who go untreated, particularly in rural areas of developing countries. Changing this situation may take decades, and will need a concerted effort by the global community. It will also require the employment of many different tools, not least artificial intelligence, which I believe will have a key role in allowing

Cell fate – re-determining the predetermined

Disorder	*Fate switch*	*Therapeutic outcome*
RP	Rods – Cones	Halts the deleterious effects of rod degeneration on the retina
AMD	Rods – Cones	Turn rods into cones in an unaffected perifoveal area, generating a new "macula"
Late-stage glaucoma	Müller glia – RGCs	Knock out *p53,* de-differentiate Müller glia, culture, transplant, differentiate into RGCs
Leukemia Glioblastoma	Leukemic cells – macrophages Glial – neuronal cell type	Convert malignant cells to a benign cell type

Turning back time
Understand what each component in aging does – and the consequences of manipulating them

Patient, heal thyself:
Wake your own stem endogenous stem cells and direct them to repair damaged tissue in situ.

broad patient access to new therapies (for example, by enabling remote diagnosis via smartphones and the Internet).

Development of simpler and cheaper administration methods also would help: at present, the best way to deliver reprogramming therapy to RPE or photoreceptor cells is to inject vector into the sub-retinal space, but this is costly, inconvenient and requires considerable surgical skill. In the future, however, we hope to administer the treatment as an in-office procedure, just like intravitreal injections (but using robotic devices). And maybe one day, we will be able to eliminate the burden of injections altogether. For example, we've been working on a topical eyedrop for wet AMD for the last five years, and expect it to move into clinical trials in the US and China early next year. Replacing intravitreal injections with eyedrops would be of great benefit.

"I expect, within my lifetime, to see human beings enjoying a longevity of 150–200 years."

TURNING BACK TIME IS THE FUTURE

In my research, I always try to consider broad themes that are applicable across different areas of medicine. As a consequence, although I work within ophthalmology, I increasingly find that I am thinking outside the eye field. You could say I'm using ophthalmology as a model to address broad medical needs rather than conditions that are limited to the eye. In particular, one of my overarching goals is to combat age-related

BOX 2: DON'T REPLACE – REGENERATE

Will slow, natural lens regeneration relegate current methods of cataract treatment to the 'quick and dirty' category of care?

The Need

- Cataracts are normally treated by replacing the occluded lens with an artificial intraocular lens (IOL)
- This highly successful procedure normally results in improved vision within a few hours
- However, IOL implantation carries a risk of complications, and current IOLs cannot accommodate in the same way as young crystalline lenses

Our Solution

- We developed a method for regenerating a new lens in situ (5), which required:
  - development of a cataract removal method that preserves endogenous lens epithelial stem/progenitor cells (LECs)
  - identification of factors (Pax6 and Bmi1) required for lens epithelial cells (LECs) to participate in lens regeneration
- Using this method, we regenerated functional lenses in rabbits, macaques and human infants
- The approach may also restore accommodative power, at least where accommodative loss is mainly due to lens sclerosis

What's Next?

- Modifications to the basic method are in progress:
  - Injection of a 3D-printed scaffold, impregnated with appropriate growth factors, is expected to stimulate and guide LECS during lens regeneration
  - The intent of this device is to decrease the time required for functional lens regeneration from 6–8 months to 2–3 months, improve refractive outcomes, and allow customization of the lens' final form to the specific requirements of the patient's eye

diseases – and perhaps to address ageing itself! Indeed, I believe that if we work out how to stop ocular diseases of ageing – such as macular degeneration, glaucoma and cataract – we will also be able to prevent other age-related conditions: Parkinson's, Alzheimer's, and so on.

But what's critical to the development of anti-ageing therapies is achieving a full understanding of the biological clock – we were the first to identify an epigenetic gene modification mechanism that drives the ageing process in every single tissue and cell, including those in the eye. We've been working extensively on understanding how this clock ticks – and what makes it tick. In particular, we have been trying to identify and understand the upstream factors that make the clock run faster or slower, and their downstream consequences. Ultimately, this research will enable us to devise treatments that inhibit the ageing process – in fact, we have evidence to suggest that we can even reverse it! I expect – within my lifetime – to see human beings enjoying a longevity of 150–200 years. And this extended lifetime would not be burdened by the frailties of age; centenarians would function as though they were healthy 40–50-year-olds.

Finally, I believe that the best approach to these age-related conditions is to harness the regenerative power contained within our own cells and tissues. I am convinced that the next phase of regenerative medicine will focus on waking up our endogenous stem cells and directing them to repair or regenerate the damaged tissue in situ – another overarching theme of my work. We've already seen this happening in cardiac cell regeneration, where you can guide cardiac fibroblasts to differentiate into beating cardiomyocytes; one day, we will see the same principles used to address diseases of old age – for example, to reprogram glial cells into functional neurons as part of an Alzheimer's treatment. I foresee a wave of innovative therapies in this field over the next 10 years – and I hope our technique for regenerating lenses (Box 2) is just the first of them!

References

1. *NG Ghazi et al., "Treatment of retinitis pigmentosa due to MERTK mutations by ocular subretinal injection of adeno-associated virus gene vector: results of a phase I trial", Hum Genet 135, 327–343 (2016). PMID: 26825853.*
2. *K Suzuki et al., "In vivo genome editing via CRISPR/Cas9 mediated homology-independent targeted integration", Nature, 540, 144–149 (2016). PMID: 27851729.*
3. *J Zhu et al., "Gene and mutation independent therapy via CRISPR-Cas9 mediated cellular reprogramming in rod photoreceptors", Cell Res 27, 830–833 (2017). PMID: 28429769.*
4. *JJ Zhao et al., "Induction of retinal progenitors and neurons from mammalian Müller glia under defined conditions", J Biol Chem, 289, 11945–11951 (2014). PMID: 24523410.*
5. *H Lin et al., "Lens regeneration using endogenous stem cells with gain of visual function", Nature, 53, 323–328 (2016). PMID: 26958831.*

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In Practice

Surgical Procedures
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28–33
Not the Usual Suspects
Irregular astigmatism in patients presenting for cataract surgery or RLE can cause the surgeon a lot of grief. Sheraz Daya shares his quarter of a century's worth of experience of dealing with these "irregulars", and shows how he deals with such corneas.

Not the Usual Suspects

The secret to managing irregular astigmatism during cataract surgery? Tackling the problem at its source

By Sheraz Daya

When people talk about astigmatism and intraoperative aberrometry, the conversation is often made with the assumption that the cornea is normal and regular. When it isn't normal and regular… well, you have a problem. I have been dealing with some pretty difficult corneas for a quarter of a century now, so let me share with you what I have learned over the years.

Irregular astigmatism in patients presenting for cataract surgery (or refractive lens exchange; RLE) can have consequences: poor vision. For the surgeon, this is partly because the biometry can be challenging, which makes accurate IOL calculations difficult. Any error results in a refractive miss, causing both the patient and surgeon grief.

At a Glance

- *A lot of talk about astigmatism and intraoperative aberrometry is made on the assumption that the cornea is normal and regular. But what if it isn't?*
- *Biometry becomes far more difficult, as does IOL power calculation. Get it wrong, and there's grief all round*
- *Understanding the causes of irregular astigmatism – and how to deal with them – is key*
- *Here, I offer general principles of how to manage these 'irregulars' and give a few case examples of my own.*

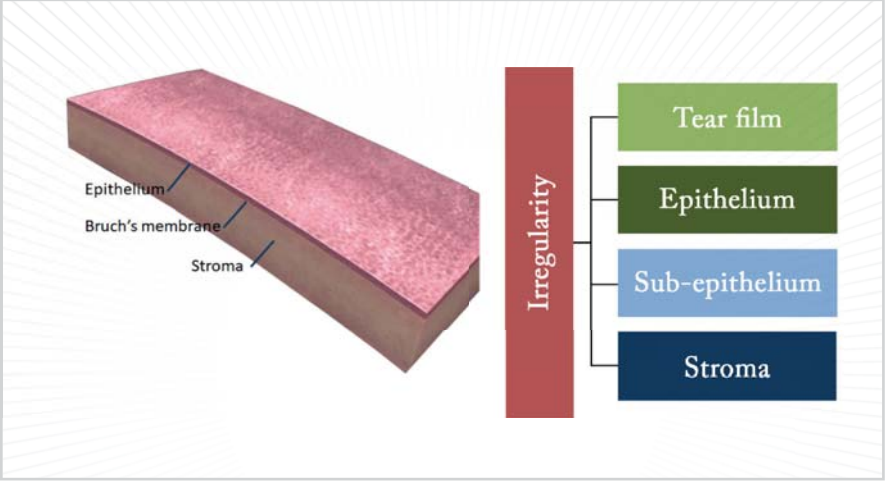


Figure 1. Disorders of the tear film, or any one of three corneal layers – the epithelium, sub-epithelium or the stroma – can all cause irregular astigmatism.

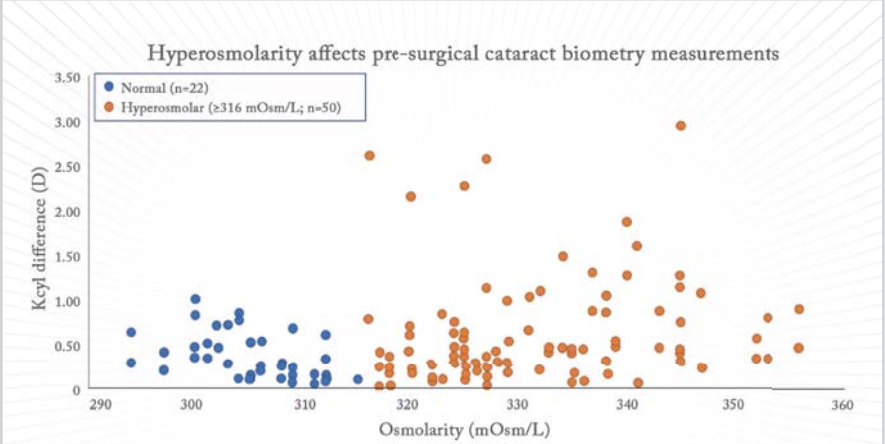


Figure 2. Keratometry cylinder (1). Seventeen percent of hyperosmolar eyes had at least 1.00 D of change in keratometric cylinder values between two visits. The hyperosmolar group demonstrates a wider variation in keratometric cylinder between visits relative to the normal group (p=0.013).

To deal with irregular astigmatism, we first have to understand its cause.

Why corneas become irregular

Let's look at the cornea systematically from front to back. There are five layers and three of them are responsible for irregular astigmatism (Figure 1). The tear film sits atop the cornea, and needs to be regular in its consistency to provide regularity of the corneal surface. The epithelium translates to the tear film and, if that is irregular then, once again, we have irregular astigmatism. You cannot forget the subepithelial area; there are conditions that affect this region and they also translate right across to the front surface of the cornea. And then there is the stroma; if it is scarred, ectatic or abnormal in in terms of shape that may also cause irregular astigmatism.

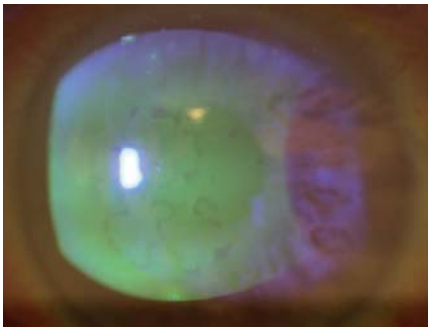


Figure 3. Anterior basement membrane dystrophy – also known as epithelial basement membrane dystrophy, Cogan's dystrophy or Map-dot-fingerprint dystrophy – results in irregular astigmatism.

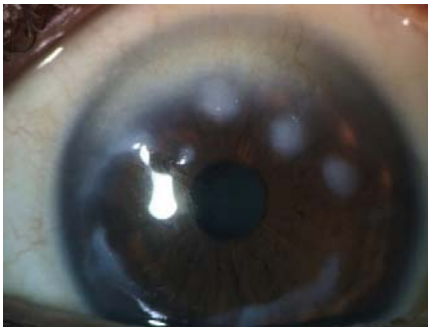


Figure 4. An example of a sub-epithelial disorder, Salzmann's nodular degeneration, that causes irregular astigmatism. Other disorders include scarring of Bowman's layer and Reiss-Bücklers corneal dystrophy.

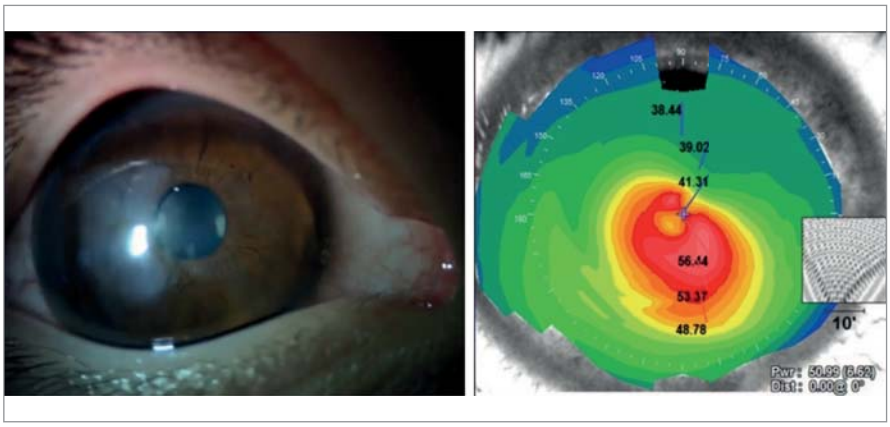


Figure 5. An eye with keratoglobus, scarring and an extremely thin cornea (left) – and a very unusual topographic map (right).

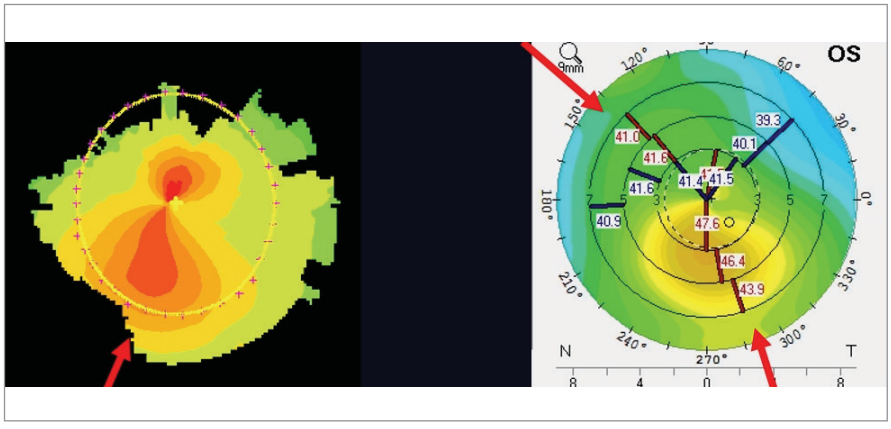


Figure 6. Irregular astigmatism: corneal shape. Asymmetric (left) and non-orthogonal astigmatism (right).

Dry eye

Dry eye is probably the single biggest cause of irregular astigmatism. It's something that cannot be dismissed – and, in this age of refractive lens exchange and refractive cataract surgery, we are appropriately giving this topic a great deal of attention. We all know the causes of dry eye: underproductive, evaporative and inflammatory, but remember, an irregular tear film can exist in asymptomatic patients.

Tear osmolarity can be used as a measure of dry eye, and Epitropoulos et al. (1) showed that patients with hyperosmolar tear film occasionally display great variation in terms of their keratometric cylinder (Figure 2) – plus, their IOL calculations varied by 0.5 D in 10 percent of cases. Dry eye really is not a trivial disorder, and it certainly does not have a trivial impact on IOL calculations.

Epithelium-induced irregular astigmatism

Figure 3 shows a case of anterior basement membrane dystrophy – also known as epithelial base membrane dystrophy, Cogan's dystrophy, map-dot-fingerprint dystrophy... Whatever you call it, the irregularity caused in the cornea makes accurate calculation very difficult.

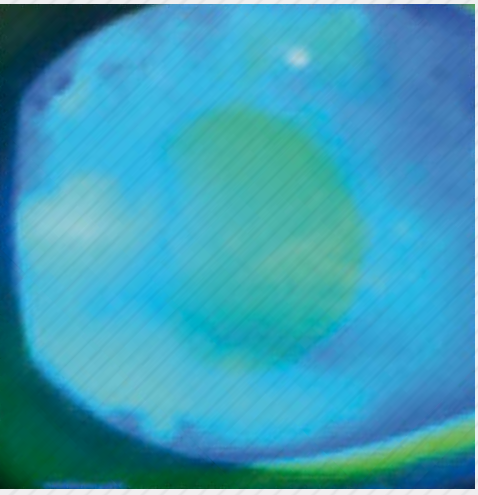
Irregular astigmatism arising from the sub-epithelium

Salzmann's nodular degeneration (Figure 4) can also cause problems. Even if the degenerative nodule is peripheral, it can influence central keratometry and regularity. You may be able to risk performing a cataract operation on this patient – but, if the nodules progress and eventually need removal, you have got a whole new keratometry to deal with; each case needs to be carefully considered.

Stromal irregular astigmatism

Both scarring and ectatic disorders can cause irregular corneal astigmatism from the stroma. The patient in Figure 5 actually has a combination of both: keratoglobus with scarring and an extremely thin cornea, which has resulted in a very unusual topographic map. Such patients are not easy to deal with.

Corneal shape changes can commonly cause irregular astigmatism. They often present as asymmetric bow ties; if they're orthogonal, then they are on the correct axis, the cornea is just steeper inferiorly than above (Figure 6) – and that's not bad, because the overall astigmatism is fine – it's when they're non-orthogonal that it's a problem. If you're going to use a toric lens in a non-orthogonal astigmatic patient, then the biggest question is: where do I orientate the implant? I shall address this later in this article.



The RLE-requesting web developer with terrible tear films

This video depicts the eye of a patient who came to see me for RLE. He was adamant that he wanted trifocal lenses implanted; however, after examination, I had to tell him, the bad news "Your tear film is terrible and you have got a whole load of other problems that need attention (punctate epithelial keratopathy and anterior basement membrane dystrophy)!" He even had an acute chalazion in his fellow eye! My patient was certainly not ready for refractive lens exchange.

His tear film was streaky, so no surprise by his report of fluctuating vision – which he thought it was from his cataracts. There was no way that I was going to operate on him until I fixed his ocular surface, a process that took about three months, whereupon we proceeded with the RLE, successfully implanting trifocal IOLs.

Video available at top.txp.to/issues/0518/501.

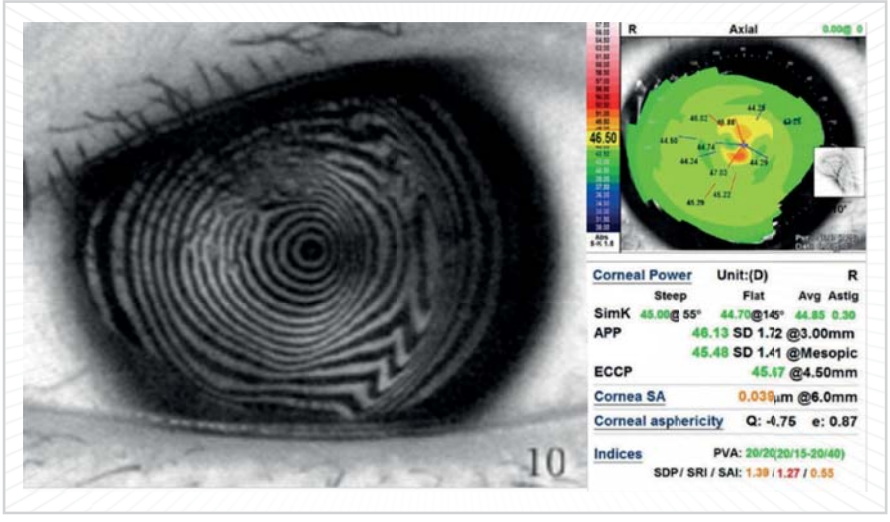


Figure 7. Placido disk-based diagnostic systems are a great way of evaluating the extent of corneal irregularity.

Diagnostics of irregular astigmatism

We are doctors – and one of the most fundamental aspects of the profession is evaluating patents clinically. A comprehensive clinical evaluation is vital in diagnosing irregular astigmatism, but we do also have a number of diagnostic instruments available to help us. And they can also be used to monitor disease progression (and improvement) of patients. When we look at a patient, going from front to back; first, we look at the tear film, then look at the shape, clarity and surface of the cornea to see if there is anything that might influence things. Next comes a fluorescein stain to check lid action and the distribution of the fluorescein dye. If patients are not closing their eyelids properly and have exposure, then they may need to be seen by an oculoplastic surgeon before proceeding to cataract surgery.

What tools do we have at our disposal, if we suspect there is a problem and want to know the magnitude of that problem?

First, you need a Placido-based reflective topographic system (Figure 7), and there are some great markers devised by Steve Klyce that can be used to flag irregular corneas: the Surface Regularity Index (SRI) is used a lot; the Standard Deviation of (corneal) Power is also a good one. In Figure 7, the SRI value is colored in red – and that indicates there is something going on with this patient's eye – anterior basement membrane dystrophy in this case.

Some Placido systems are combined with aberrometry systems (such as the Nidek OPD 3, Tracey Technologies' iTrace and Topcon's KR1W). They all work in slightly different ways, but all are excellent at providing truly useful information about the surface and overall aberrometry, and by subtracting corneal-derived aberrations from the overall aberrations, internal aberrations can be calculated. Three-dimensional diagnostic instruments (for example, the Orbscan [B+L] with its scanning slit approach or the Scheimpflug-based systems: Oculus' Pentacam, Ziemer's Galilei or Visionix's VX120 family) offer shape analysis – elevation, posterior cornea and corneal thickness, which is really useful information when it comes to dealing with the corneal shape. Anterior segment OCT is now coming into vogue and I suspect will displace some of the current "gold standard" devices being used.

Management strategies

The principles of management are simple: eliminate and reduce corneal irregularity by addressing the source of the problem by either medical therapy (for example, when the cause is dry eye) or surgical intervention. Follow-up is important; the cornea needs to be evaluated to see how the patient's eye is progressing. Has the surface got smoother; has the tear film improved? Has the surface stabilized?

If a patient presents with dry eye,

Figure 8. Anterior basement membrane dystrophy is commonly associated with meibomian gland dysfunction and may be related to inflammation. The pathology is a duplication of the basement membrane. The irregularity it imparts onto the cornea is best removed either by epithelial cell debridement (see the video at top.txp.to/issues/0518/501) or phototherapeutic keratectomy.

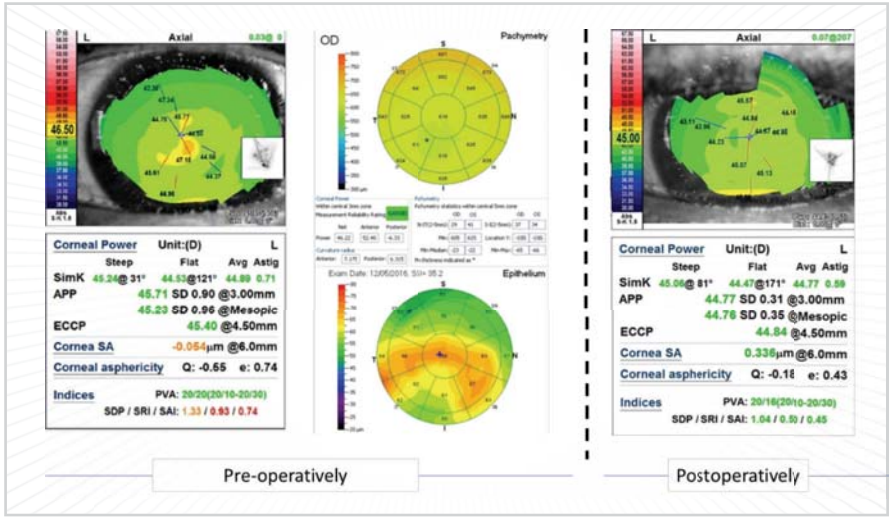


Figure 9. The difference epithelial debridement has on corneas with anterior basement membrane dystrophy.

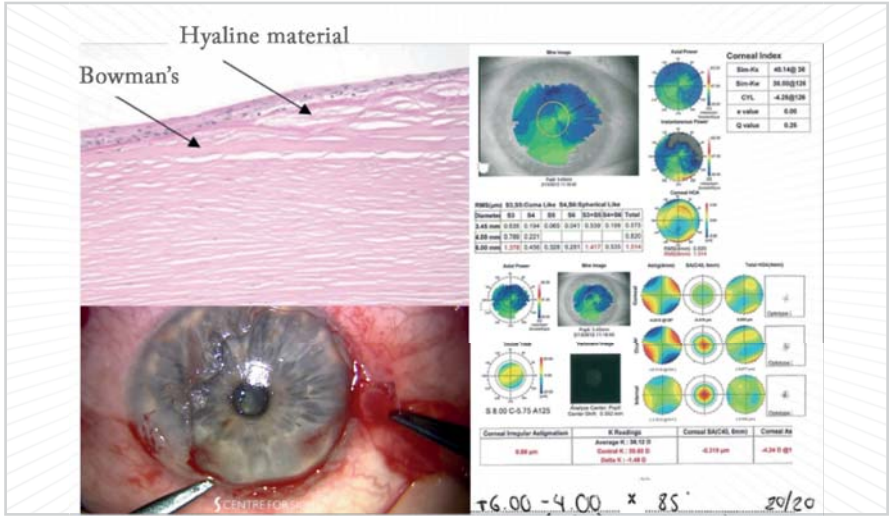


Figure 10. Clockwise: the corneal pathology of Salzmann's nodular degeneration (SND), keratometry, axial power and HOA maps, and a still from a video of a superficial keratectomy procedure performed on the most extensive SND patient I have ever seen. The video is available at: top.txp.to/issues/0518/501.

evaluate the cause and treat it. Once the tear film is stable, biometry and IOL calculations can be performed with some confidence. The key is to proceed from stable foundations, rather than highly fluctuating ones. But what about the aforementioned corneal disorders?

Anterior basement membrane dystrophy

Anterior basement membrane dystrophy results from a duplication of basement membrane, which causes an irregularity you can see on the fundus retroillumination picture (Figure 8). Typically, epithelial debridement (even at the slit lamp) followed by a bandage contact lens is sufficient in such cases – occasionally we'll add phototherapeutic keratectomy (PTK) – 5–10 µm laser ablation in PTK mode – to promote good healing and adherence.

The patient in Figure 8 had quite a high SRI; the OCT-based epithelial maps show the difference between corneal irregularity before and after epithelial debridement (Figure 9). His keratometry changed from 45.71 D to 44.77 D – just over 1 D change – and his irregularity index went from orange and red values to green ones. The cornea became more regular with better potential vision. Six weeks later, these values remained stable, which meant we felt comfortable enough to perform ocular biometry and IOL calculations.

Salzmann's nodular degeneration

A patient presented for a second opinion to the Centre for Sight for RLE with a refractive error (+8.00 D). He became worried, when he realized his original surgeon was a little hesitant. When I examined him, I saw marked 360° nodular degeneration and an irregular cornea. Salzmann's nodular degeneration is caused by hyaline that sprouts out from breaks in Bowman's layer and goes on to the surface (Figure 10). In terms of removal typically the edge can be found and elevated and removed as in the image.

Postoperatively, he had a smooth regular cornea that was steeper; his refraction changed considerably and Figure 11 shows his keratometry: he was going to have a 28.5 D lens placed in his left eye (with flat

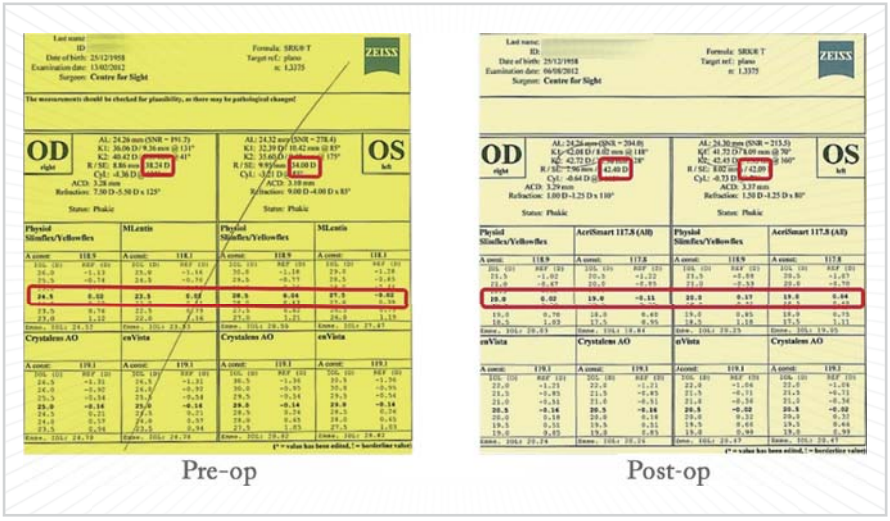


Figure 11. Pre- and post-op keratometry of a patient with Salzmann's nodular degeneration who underwent superficial keratectomy.

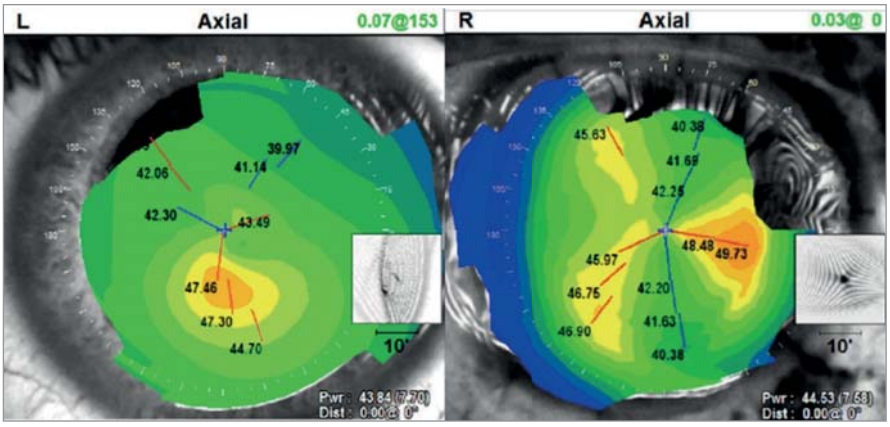


Figure 12. An illustration of a patient with non-orthogonal astigmatism.

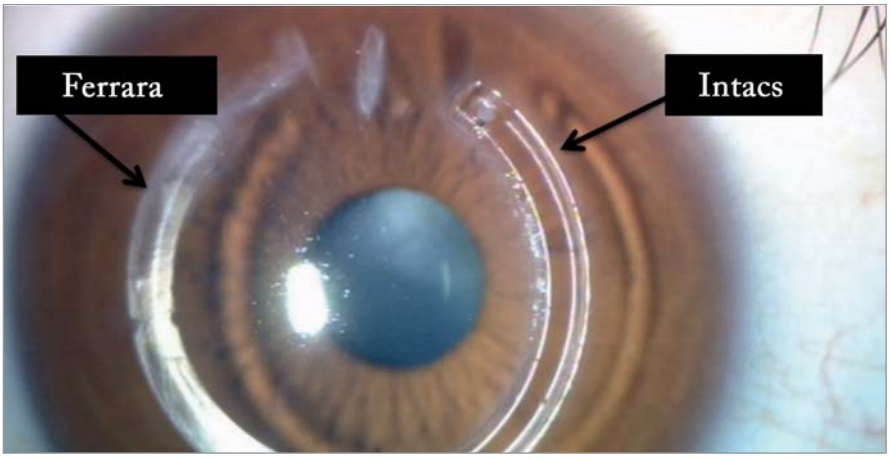


Figure 13. A Ferrara and an Intacs ring (CorneaGen) in the same eye of a patient.

Ks), but after the procedure he only needed a 20 D lens – an 8 D difference (there was a 4.5 D difference in the right eye).

Non-orthogonal astigmatism

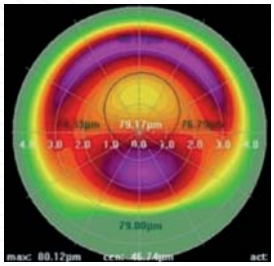
What causes non-orthogonal astigmatism (Figure 12)? Ectatic disorders like keratoconus mostly, but it can also occur in post-corneal graft patients. So how does one deal with those patients who have got corneal ectasia or keratoconus?

I always try and find out from the optometrist what the BSCVA was before the cataract. If it was 6/12 or better I'd probably go ahead and do a lens calculation and put a toric lens in. If it was less than 6/12, then I'd have to try and find a way to regularize the corneal shape either by use of intracorneal rings (Figure 13) or corneal cross-linking (CXL) with topo-guided PRK. The last resort would be corneal transplantation.

Arthur Cummings of the Wellington Eye Clinic, in Dublin, Ireland, shared the details of another case with me – a patient who underwent CXL and topo-guided PRK (Figure 14). He had a pre-op I-S ratio of 52.1 – but, after the procedure, the ratio had reduced to 6.9; similarly, UVCA was 6/60 before surgery, and 6/18 afterward, and – importantly – the patient was now ready for ocular biometry, lens calculation, and a toric IOL implantation.

Which axis do you use non-orthogonal astigmatism?

In Figure 15, the Pentacam shows 73° simulated steepening; the OPD (on refraction) shows in the 90° axis, and on topography, 97°. Which axis does one use? Well, to confound this further, I prefer to use the corneal-derived Z2-derived aberrometry polynomial for astigmatism. We've been doing this for quite some time now, and we've found that it very accurately averages out the actual axis. In this particular case, 102°



	Post-op	Pre-op
I-S ratio	6.9	52.1
SE	-2.25 DS	-0.75
Cyl	2350 D	3.50
UCVA	6/18	6/60

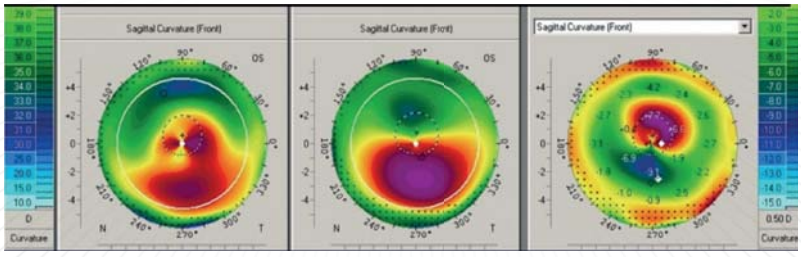


Figure 14. CXL and topo-guided PRK. Case courtesy of Arthur Cummings.

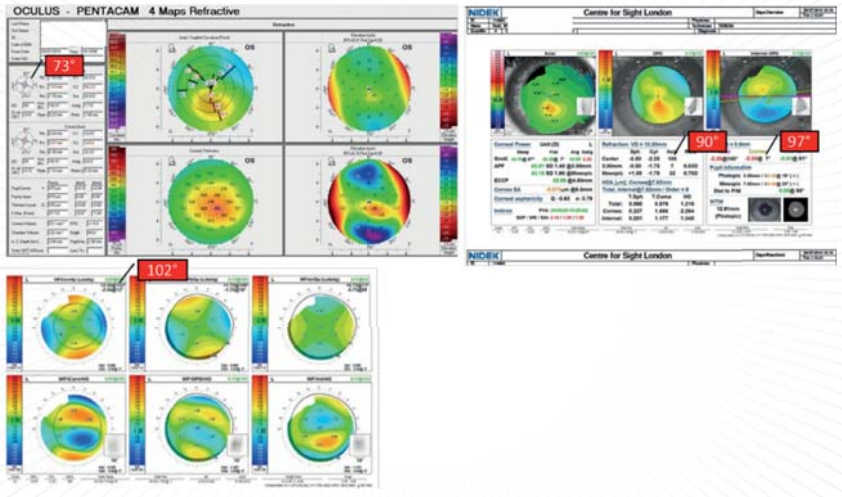


Figure 16. Surface maps and aberrometry of a patient with a prior corneal transplant.

Figure 15. Non-orthogonal astigmatism: which axis to use? The Pentacam says 73°; OPD indicates (by refraction) 90° and (topography) 97°, and the corneal-derived Z2-derived aberrometry polynomial for astigmatism (Z2±2 S2±2) indicates 102°!

is the axis that needs to be used.

These diagnostic devices can also provide a good indication of orientation of the toric lens postoperatively without dilation. Figure 16 shows the surface maps and aberrometry of a patient who had a corneal transplant before I had implanted a toric IOL. Before the procedure, I had intended to place the lens at a 121° axis – but it turned out it was actually placed at 127°, giving the patient a residual refraction of 2 D. I always aim for emmetropia – but it's not always possible in these types of patients – and so they need to be counseled in advance about this possibility.

The bottom line

As noted, the principles of managing irregular astigmatism cataract surgery are actually pretty simple: find the source of the problem, address it as best as you can, then only proceed to ocular biometry, IOL calculations, and surgery when the astigmatism is compatible with potentially good vision. If you can follow those rules, then you needn't fear irregular astigmatism in cataract surgery: you can embrace it instead!

Sheraz Daya is the Medical Director of the Centre for Sight, East Grinstead, Sussex UK, is a member of The Ophthalmologist's Power List 2018 Top 100, is internationally renowned for his work in laser eye surgery, lens replacement, stem cell transplantation, corneal transplantation and refractive cataract surgery, and was recently awarded the Fyodorov Medal by the Hellenic Society of Intraocular Implant and Refractive Surgery.
He reports that he has consulted for Bausch + Lomb, Carl Zeiss Meditec, Excellens, LinCor Biosciences, Medicem, Nidek, STAAR Surgical, Scope Pharmaceuticals, and Rayner, is an equity owner in Excellens, PRN and Strathspey Crown, has received grant support from Johnson and Johnson Vision, and lecture fees from Bausch + Lomb and Nidek.

Reference

1. *AT Epitropoulos et al., "Effect of tear osmolarity on repeatability of keratometry for cataract surgery planning", J Cataract Refract Surg, 41, 1672–1677 (2015). PMID: 26432124.*

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36–38
Great Minds Look Ahead
The 2018 Power List cadre offer their thoughts on the future of ophthalmology.

39–41
Enter the Exosome
Ben Meade discusses stem cell exosomes, and how they could be the answer to our retinal degeneration needs...

Great Minds Look Ahead

The 2018 Power Listers offer a glimpse of ophthalmology's future

Ophthalmology is an ever-changing field with a pioneering attitude – it's why so many breakthroughs and innovations in medicine and technology are made in eyecare first. For 2018, we asked the influential leaders making up the Power List for their vision of where ophthalmology is heading.

The future of cornea

"I'm currently trying to solve the surgical challenges in Descemet's membrane endothelial keratoplasty (DMEK) surgery, which is probably one of our most difficult surgical procedures in corneal transplantation today. The current surgical approach to DMEK makes it generally inappropriate for complex or high-risk cases, where it is needed most – especially as it has the lowest rejection risk. I'm currently evaluating a completely new surgical approach to this procedure."

Donald Tan, Professor at the Singapore National Eye Centre and Duke–National University of Singapore Medical School, Singapore.

At a Glance

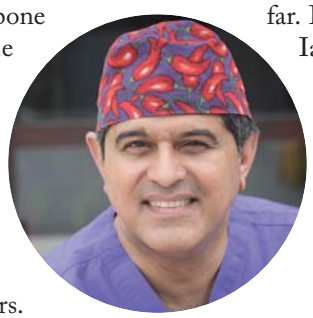
- *Ophthalmology is an incredibly innovative field – and often the forefront of medical breakthroughs*
- *But what's next, and where might the field be heading in the future?*
- *We asked members of our 2018 Power List about the future of cataract, cornea, glaucoma, refractive surgery and retina*
- *Here, we share their thoughts…*

"It is exciting to see how the discovery of the pre-Descemet's layer has evolved into direct clinical applications, both from our own research but more importantly from research by other independent groups around the world. We have made new discoveries in relation to this and other aspects of corneal transplantation, which are either in press or submitted to reputed journals."

Harminder Dua, Head of the Division of Ophthalmology and Visual Sciences, University of Nottingham, Nottingham, UK.

"Corneal transplantation has changed considerably over the last 15 years and many of those changes are thanks to technology derived from refractive surgery! Microkeratomes enabled Descemet's stripping endothelial keratoplasty (DSAEK), which ended up evolving into DMEK. I expect both procedures will be replaced by therapeutic modalities, such as corneal cell therapies with Rho Kinase inhibitors. Stromal substitutes are already in development and I expect synthetic corneas will become more commonplace. Stem cell treatments will have a role, so long as the correct concoction of cytokines and growth factors can be found to get stem cells recruited from the bone marrow and provide the necessary repairs required."

Sheraz Daya, Medical Director, Centre for Sight, East Grinstead, UK.



"I have been pursuing new modalities for corneal and ocular surface disorders. In the future, I would like to establish cultured corneal endothelial cell injection therapy for bullous keratopathy."

Shigeru Kinoshita, Professor and Chair of Frontier Medical Science and Technology for Ophthalmology, at Kyoto Prefectural University of Medicine, Kyoto, Japan.

Ten-year goal: "To develop direct evaluation technology to evaluate corneal biomechanical properties to screen for keratoconus in its earliest manifestations, and predictive models for corneal interventions, such as laser ablation and cross-linking to individualize treatment parameters."

J. Bradley Randleman, Professor of Ophthalmology at the Keck School of Medicine, University of Southern California, and Medical Director of Beverly Hills Clinic, USC Gayle and Edward Roski Eye Institute, Los Angeles, CA, USA.

The future of cataract and refractive surgery

"As a profession, our biggest challenge is the growing backlog of cataract blindness in the developing world. Though our own patients are beneficiaries of increasingly sophisticated technology, cataract blindness will not be solved by refractive IOLs and femtosecond lasers. Different innovations that are low tech, affordable, and more easily mastered than phacoemulsification are needed. Manual small incision cataract surgery (MSICS) is the most important innovation so far. I work with a group within Iantech, which is devoting resources to developing





a low-cost iteration of its miLOOP that could be used for MSICS in resource-limited countries. I am also working with a team that is developing a promising topical medication that could prevent or potentially reverse cataract formation. A non-surgical way to halt or delay cataract blindness will have a far wider global impact than any surgical intervention ever could."
David Chang, Clinical Professor, University of California, San Francisco, CA, USA.

"In lens-based procedures, I believe the future lies in the ability to modify the IOL power after implantation, as well as the development of the types of accommodative IOLs. Surgery-wise, the future lies in the field of increased precision of surgical procedures given to us by robotic systems and lasers. As for corneal refractive procedures, I consider refractive index shaping with intra-stromal laser application very promising."
Boris Malyugin, Deputy Director General at S. Fyodorov Eye Microsurgery Institution, Moscow, Russia.

"I believe the future is now, and there are great ideas out there that just have to be filtered and put into clinical practice. The future is what we make out of it, and I believe it is very important that we, as specialists, come together with the industry to design our own future in the best interest of our patients."
Florian Kretz, CEO of Augenärzte Gerl, Kretz & Kollegen; Lead Surgeon, Augentageskliniken Rheine & Greven; Consultant & Research Coordinator of the International Vision Correction Research Center Network (IVCRC.net), University of Heidelberg; and CEO of the NGO Augenärzte für die Welt GmbH, Germany.

"I believe [the future] will be focused on three major areas. One will be for non-accommodative patients where the use of a new generation of IOL will restore accommodation; the lens capsule will be the key to this technology. The second will focus on the younger patient group and include more advanced – and more customized – corneal-based corrections. The third will be for irregular and unstable corneas, for instance with keratoconus, which will likely use tissue addition and in situ molding of the cornea with biomaterials."
Ioannis Pallikaris, Founder and Director of the Institute of Vision and Optics, University of Crete, Greece.

The future of glaucoma

"There's definitely a tide change. We have so many treatment options (some could say too many at the moment, as we try to make sense of them all!). What I see coming is data increasingly driving our decision making and becoming more integrated; AI-assisted systems pulling together IOP, retinal nerve fiber layer (RNFL)/ ganglion cell layer (GCL) analyses with (better measures of) visual field function and possibly newer variables like outflow resistance, episcleral venous pressure and methods of predicting conjunctival fibrotic response to surgery. We'll be able to detect smaller rates of change and more accurately predict future risk. With this comes tailored management of need versus risk which is constantly appraised."
Dan Lindfield, Consultant Ophthalmologist and Glaucoma Director, Royal Surrey County Hospital, Guildford, UK.

"We will move to more remote monitoring of care and will increasingly have access to more effective treatments. Blindness rates will be greatly reduced."
David Friedman, Professor and Director of the Dana Center for Preventive Ophthalmology, Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore, MD, USA

Future goals: "Collaborating with scientists, industry and regulatory agencies to develop the first neuroprotective agent (to protect the optic nerve independent of lowering IOP)."
Robert Weinreb, Director of the Shiley Eye Institute and Hamilton Glaucoma Center, University of California, San Diego, CA, USA.

The future of retina

"Breakthroughs in gene and stem cell therapy will provide immense opportunity for advancing medical and surgical

approaches to eye disease, and fighting degenerative retinal disease, while big data, telemedicine, and analytical advancements in AI and deep learning will enhance public health and lift our level of evidence-based medicine."

Julia Haller, Ophthalmologist-in-Chief, Wills Eye Hospital; William Tasman Endowed Chair, Professor and Chair of Ophthalmology, Thomas Jefferson University, Philadelphia, PA, USA.

The Future? "Retinal prosthesis implants with much smaller pixels. Ultimately, we hope to achieve single-cell resolution, which might restore visual acuity at a level better than 20/80. In addition to photovoltaic restoration of sight, we are working on transplantation of photoreceptors, and the results are extremely encouraging!"

Daniel Palanker, Professor, Department of Ophthalmology and Director of the Hansen Experimental Physics Laboratory at Stanford University, Stanford, CA, USA.

"Argus II is just the beginning. I hope to restore color vision and enhance reading vision so that patients can read small print and watch television. Through the support of the California Institute for Regenerative Medicine, I've also developed a novel minimally invasive stem cell-based treatment, CPCB-RPE1, for patients with an advanced form of dry AMD, which is in a Phase I/IIa clinical trial. The implanted scaffold of RPE are localized, and can function to support and replenish dying photoreceptors of the retina, which would help restore and prevent vision loss in patients with AMD."

Mark Humayun, Cornelius J. Pings Chair in Biomedical Sciences, Professor of Ophthalmology, Biomedical Engineering, and Integrative Anatomical Sciences; Director, USC Institute for Biomedical Therapeutics; Co-Director, USC Roski Eye Institute at the University of Southern California, Los Angeles, CA, USA.

"Once we have regulatory approval for [Nightstar's] gene therapy programs for recessive diseases, we will need to look at other technologies for dominant diseases and we have exciting CRISPR projects in the pipeline."

Robert MacLaren, Professor of Ophthalmology at the University of Oxford, UK; and Founder of Nightstar.

The future? "Improved recovery of vision after retinal detachment repair, gene therapy and stem cell treatments."

Stanley Chang, Former Edward S. Harkness Professor and Chairman of the Department of Ophthalmology and K.K. Tse and Ku Teh Ying Professor of Ophthalmology, Columbia University Medical Center, New York Presbyterian, New York, NY, USA.

Exciting developments? "The increasing awareness of the importance of neural cell health and not just the amelioration of exudative manifestations of AMD and diabetes, as well as the consideration of combined therapies to reduce neural cell loss."

Usha Chakravarthy, Professor, Ophthalmology and Vision Sciences, Royal Victoria Hospital (The Belfast Trust) and Queens University of Belfast, Northern Ireland.

Outside the OR…

"I believe that healthcare will be transformed in the next 10 years by the introduction of AI, in particular a technique known as "deep learning". I would like ophthalmology to be the medical specialty leading the way in this regard (and I would like my institution, Moorfields Eye Hospital, to be playing a key role in this). In the short term, I believe that AI will greatly increase our knowledge of ophthalmic disease using imaging techniques that are already widely available. In the longer term, I think there will be much closer integration between imaging data and omics data – 'AI-assisted science' will be required to facilitate this."

Pearse Keane, Consultant Ophthalmologist, Moorfields Eye Hospital, London; NIHR Clinician Scientist at Institute of Ophthalmology, University College London, UK.

We've shared only a handful of responses here – for the full Power List and more insight, visit www.theophthalmologist. com/power-list/2018.

Enter the Exosome

Simpler to produce and easier to administer than stem cell therapies – are exosomes the answer to our retinal regeneration needs?

By Ben Mead

Retinal stem cell therapy works – but the cells aren't really working in the way you were promised they would back in college. It turns out that they protect the retina not by differentiating into and replacing damaged neurons, but by rescuing existing, compromised cells. But how?

Ten years ago, few would have guessed that exosomes – small extracellular vesicles that are known to assist the elimination of the by-products of cellular metabolism – had any function beyond waste management. But today, the evidence suggests that these humble structures have significant and beneficial effects in terminally differentiated neural tissues.

At a Glance

- *Until recently, exosomes were thought to function only as waste product excretion vehicles; in fact, they contain functional molecules that can alter the phenotype of non-cognate cells*
- *In particular, the ocular neuroprotective effect of stem cells – which depends on preservation of existing neurons rather than on neuroregeneration – is mediated by stem cell exosomes*
- *Current work demonstrates this effect in the optic crush model, where exosome-vectored microRNAs eliminate about two-thirds of the RGC death seen in untreated animals*
- *Stem cell-derived exosomes may form the basis for a novel, cell-free neuroprotective glaucoma therapy*

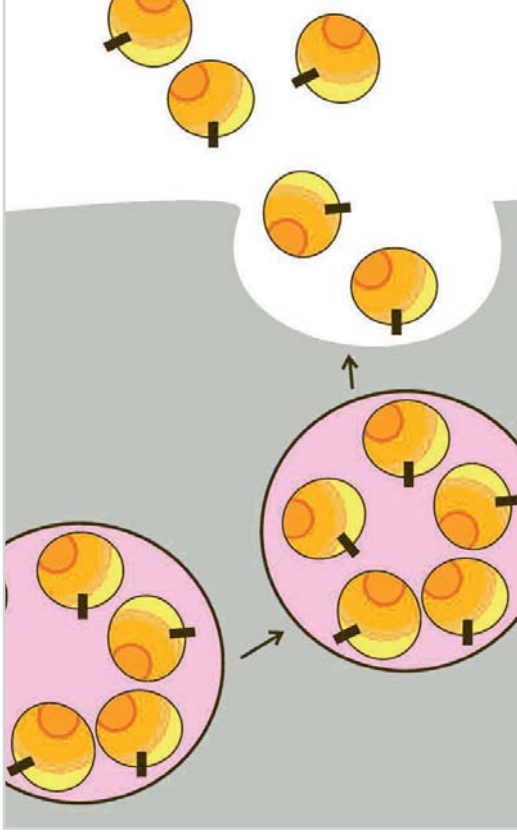
Waste not

The surge of interest in exosomes over the last decade was triggered by the demonstration that exosomes contain functional mRNA and microRNA (1). Furthermore, exosomes can mediate transport of these RNAs to entirely different cell types where the exogenous messenger is translated into protein, and the microRNAs modulate endogenous gene expression. In other words, exosomes enable one cell to modulate the protein phenotype of another.

After this (unprecedented) observation, researchers began to postulate functional roles for exosomes. One hypothesis was that malignancy-derived exosomes may contribute to malignant transformation of previously healthy cells, but a happier hypothesis was also made: the therapeutic potential of exosomes. In heart disease, for example, the administration of mesenchymal stem cell-derived exosomes mediates a cardioprotective effect similar to that of the stem cells themselves. Why use a cell therapy approach – with all the potential issues of unwanted proliferation, differentiation (and de-differentiation) and migration – when secreted factors give the same effect? This rationale was behind our decision to investigate the use of isolated exosomes for retinal therapy.

Ways and means

Cells expel many extracellular vesicles; the first step in developing an exosome therapy is to remove all unwanted vesicles. Fortunately, this is simply a question of ultracentrifugation. In brief, we expand stem cells in a vat and harvest the culture medium; spin it at low speed to remove cell debris; spin at high speed



to pellet the exosomes, and then wash off the supernatant. This simplicity is one of the great advantages of the exosome approach – it's so much easier than isolating specific proteins from cell culture medium. Another advantage is the stability of the preparation: unlike cells, which must be maintained at 37°C with appropriate nutrition, exosomes are stable at -20°C for extended periods (up to a year, according to some reports). Furthermore, they are easier to administer than cells: dense cell suspensions are too viscous to easily inject, which constrains the number of cells you can administer. Exosomes, by contrast, can be easily injected in huge numbers. Finally, it's easy to get robustly quantifiable data with exosomes, whereas cell delivery counts require guesswork – the vitreous isn't a great substrate for stem cells, and cell survival rates are unclear, even a few hours after injection.

But does it work?

We decided to investigate the therapeutic potential of stem cell exosomes in the optic nerve crush model (2). This a good model to test neuroprotective strategies for retinal

"The great majority of exosome-mediated neuroprotection can be attributed to their microRNA component."

ganglion cells (RGCs): traumatizing the optic nerve (with a crush) destroys RGCs within about three weeks while leaving all other retinal cell types intact. In our study, we administered intravitreal injections of 3×10^9 exosomes at the same time as the crush. Three weeks later, we sacrificed the animals, retrieved the retinal tissue and stained the cells for microscopy. When we compared the number of RGCs surviving in treated and untreated animals, we saw a clear difference: untreated rats lost about 90 percent of their RGCs, while treated rats lost only about 30 percent (Figures 1 and 2). Furthermore, the exosome-treated RGCs maintained function as measured by electroretinography (Figure 3).

We also investigated the mechanism by which exosomes might mediate this pronounced protective effect, and found that down-regulating stem cell microRNA results in exosomes that displayed a reduced protective effect (Figure 2). This finding strongly suggests that the great majority of exosome-mediated neuroprotection can be attributed to their microRNA component.

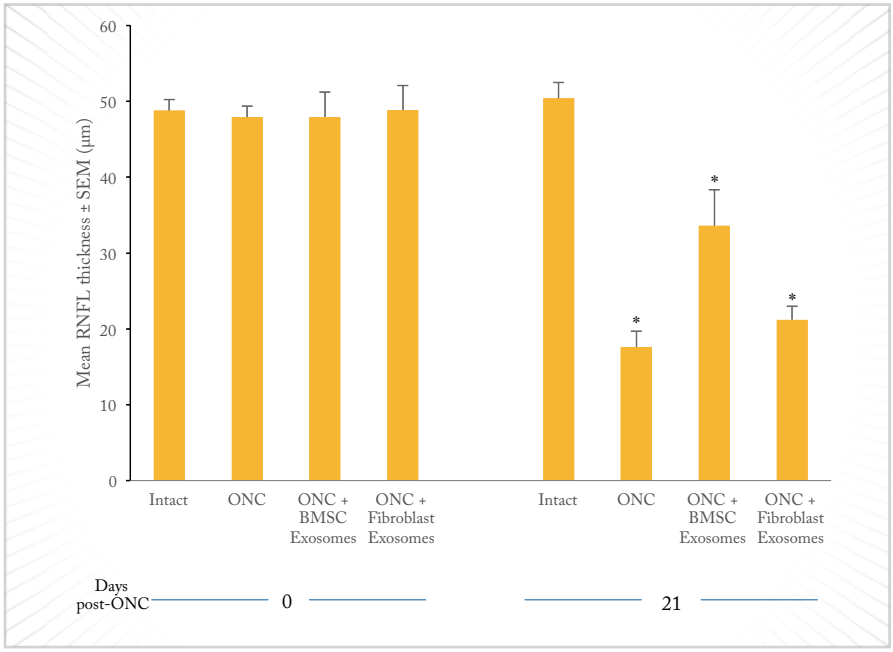


Figure 1. RNFL thickness in rat eye after optic nerve crush (ONC) and exosome treatment (2).
Note that ONC eyes lose well over half of the RNFL thickness; in bone marrow-derived stem cell (BMSC) exosome-treated eyes, the loss is reduced by about 50 percent. Fibroblast exosomes confer much lower protection.

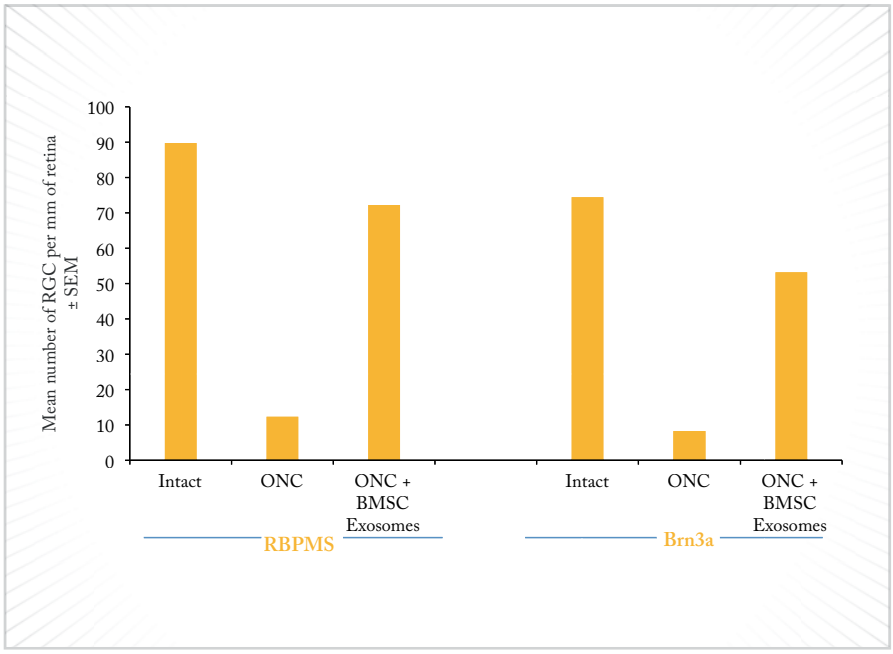


Figure 2. Mean number of RGC per mm of retina in rat eye after optic nerve crush (ONC) and exosome treatment.
Note that the ONC results in loss of approximately 85 percent of RGCs in untreated rats, but rats treated with bone marrow-derived stem cell (BMSC) exosomes lose only about 20 percent of their RGCs. This protective effect is largely eliminated by using exosomes from stem cells in which microRNA production has been downregulated (2).

Time to translate?

Our work indicates that stem cell exosomes may represent the basis of an entirely new therapeutic modality: one that uses stem cells not as a tissue replacement product,

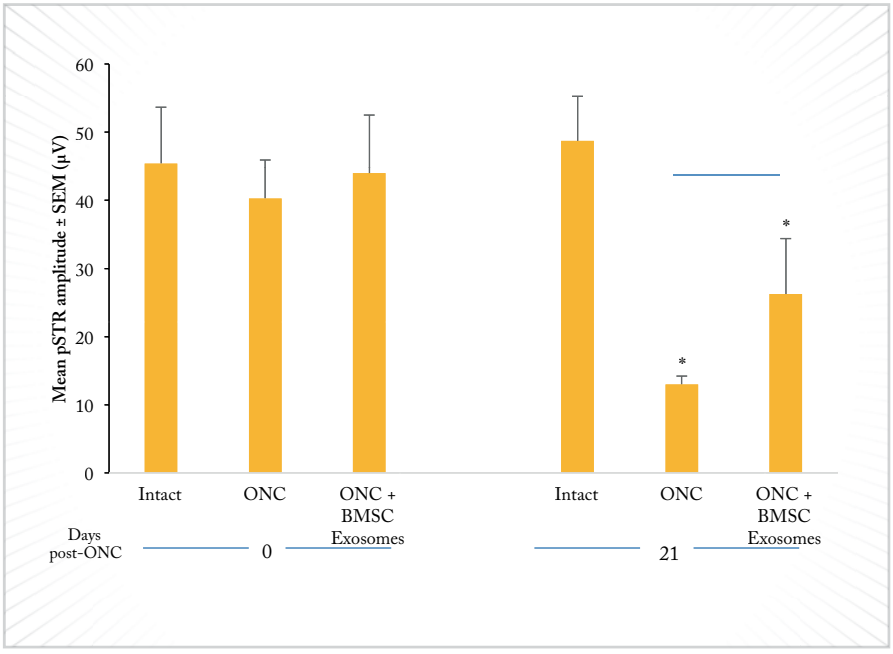


Figure 3. Positive scotopic threshold response (pSTR) in treated and untreated rats after ONC (2). ONC results in a ~70 percent reduction in mean pSTR amplitude in untreated rats; exosome treatment cuts this loss of function by about half.

but as a source of sub-cellular protective factors that mediate their effect through the target cells themselves. Exosomes have similarities to viral and liposomal gene therapy vectors – but are far easier to produce. They are also extremely straightforward to administer: intravitreal injection is already standard clinical practice and is already received by millions of patients a year.

There are other reasons to believe that the clinical pathway for exosome-based glaucoma therapies will be straightforward. In particular, stem cell therapies are already in trials for the treatment of retinal disorders, including glaucoma and optic nerve injury – for example, the SCOTS trial (3), which is testing autologous bone marrow stem cells in retinal and optic nerve damage and disease. Given that these cells are secreting exosomes, you could say that exosomes are already in the clinic! All we are proposing is a more efficient way of delivering the vesicles – one that avoids the risks, such as retinal detachment, associated with ocular cell therapies.

A possible issue is the fact that exosomes contain thousands of different microRNAs, which in theory could modulate thousands of different genes – a potential source of off-target effects.

"Given that these [stem] cells are secreting exosomes, you could say that exosomes are already in the clinic!"

But again, the same could be said of whole cell therapies, and so far, there are no data to suggest that these have safety issues related to exosome activity. Maybe in the future, we will identify the microRNA subset responsible for the exosome therapeutic effect, and build a therapy based on that alone. That said, it may be simpler to use naturally occurring vesicles, especially given that they are so easy to isolate, store and administer.

Looking ahead, we envisage exosome-mediated therapy not just for glaucoma but also for conditions, such as AMD. Identifying all possible applications will require us to address various fundamental questions, such as optimal dosing and required dosing frequency. And that means there's plenty to keep us busy!

Ben Mead received his PhD from the University of Birmingham (UK) for work on the use of stem cells to treat retinal disease and to prevent the death of retinal ganglion cells. Currently, he is a post-doctoral fellow at the Section of Retinal Ganglion Cell Biology of the National Eye Institute, Bethesda, MD, USA, where he is investigating the neuroprotective potential of stem cell factors. His current position is funded by the Marie Skłodowska-Curie Fellowship Scheme

References

1. *H Valadi, et al., "Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells", Nat Cell Biol, 9, 654–659 (2007). PMID: 17486113*
2. *B Mead and S Tomarev, "Bone marrow-derived mesenchymal stem cell-derived exosomes promote survival of retinal ganglion cells through miRNA-dependent mechanisms", Stem Cells Translational Medicine, 6, 1273–1285 (2017). PMID: 28198592*
3. *https://clinicaltrials.gov/ct2/show/NCT01920867*

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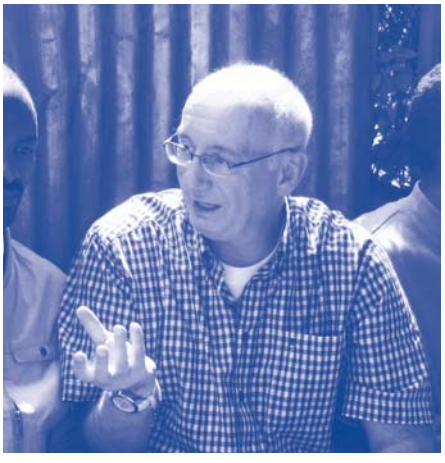
the Analytical Scientist

2015

Peter Seeberger & Andreas Seidel-Morgenstern, Directors at two collaborating Max Planck institutes in Germany, developed an innovative process to manufacture the most effective drugs to treat malaria from plant waste material, air and light.

2016

Waseem Asghar, Assistant Professor at Florida Atlantic University, developed flexible sensors for the rapid and cost-effective diagnosis of HIV – and other infectious diseases – in point-of-care settings.



2017

Richard Jähnke, Global Pharma Health Fund (GPHF), developed and continuously improved GPHF Minilab – a "lab in a suitcase," enabling resource poor countries to rapidly identify substandard and falsified medicines.

Nominations will open soon for the 2018/2019 Humanity in Science Award

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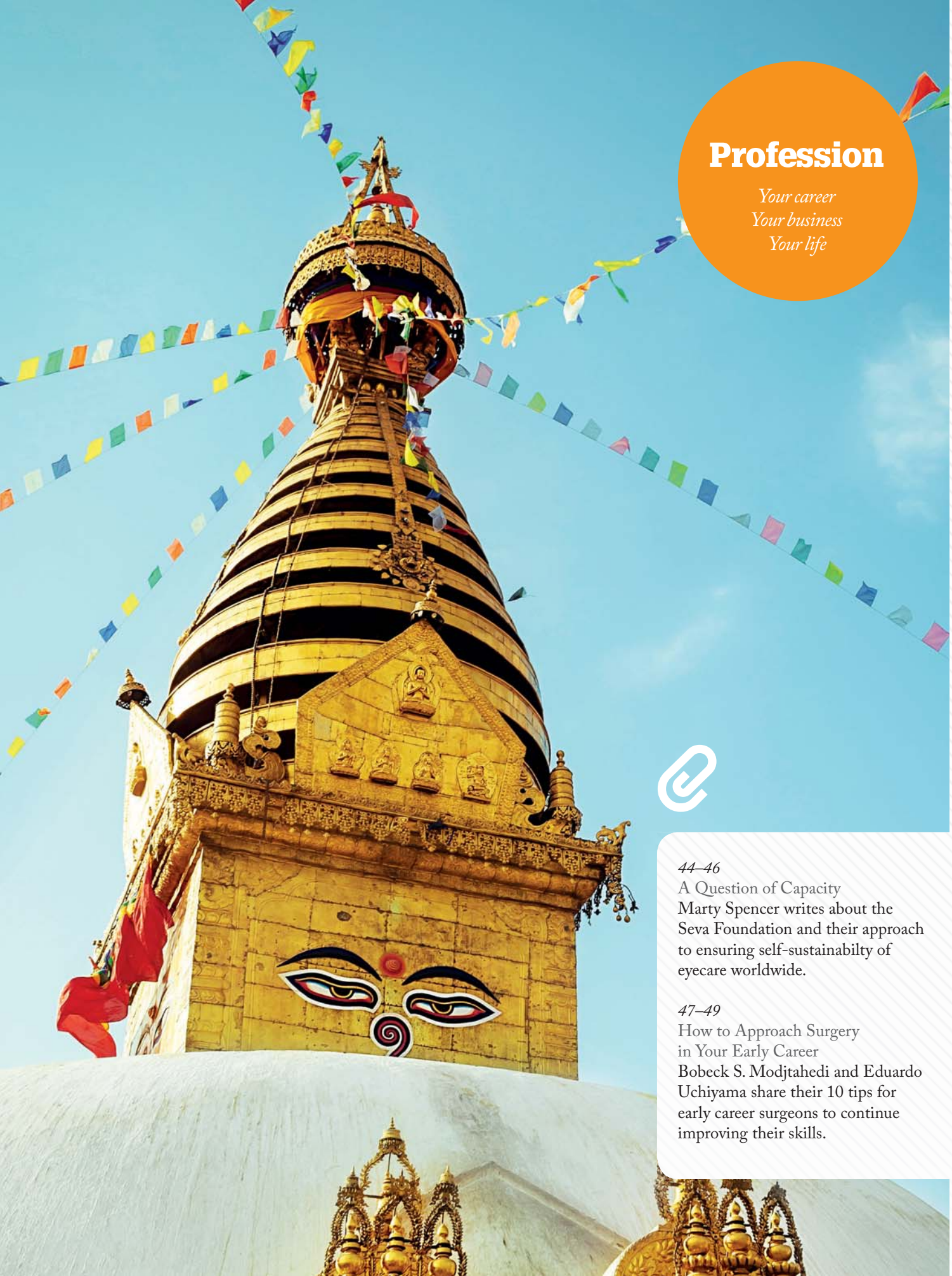

Profession

Your career
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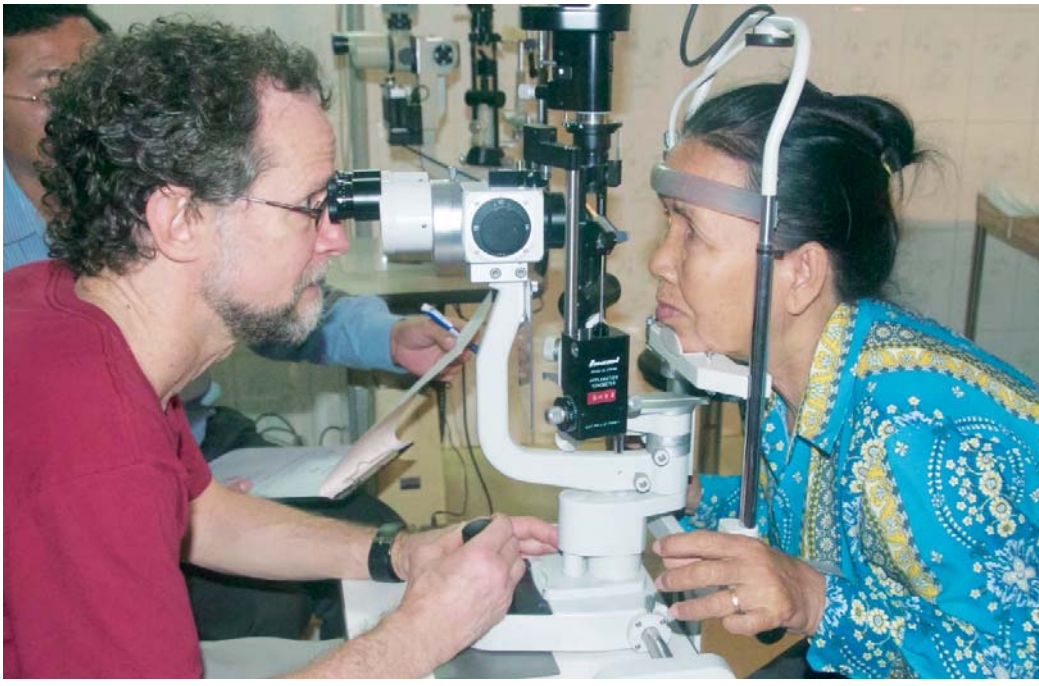
44–46
A Question of Capacity
Marty Spencer writes about the Seva Foundation and their approach to ensuring self-sustainabilty of eyecare worldwide.

47–49
How to Approach Surgery in Your Early Career
Bobeck S. Modjtahedi and Eduardo Uchiyama share their 10 tips for early career surgeons to continue improving their skills.

A Question of Capacity

How Seva plans to add another million sight-saving surgeries in developing countries per year by 2020

By Marty Spencer



Marty Spencer in the field with Seva.

A recent paper in the Lancet from the Vision Loss Expert Group (VLEG) conveys sobering data about the projected increase in blindness worldwide over the next 30 years. "Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis," (1) found that there are 253 million people worldwide with vision impairment, including 36 million who are blind and 217 million with moderate or severe visual impairment (MSVI). A full 89 percent of visually-impaired people live in low and middle-income countries.

The authors of the study estimated that 81 percent of visual impairment (blindness and MSVI combined) is avoidable. In this case, "avoidable" includes cataract and uncorrected refractive error, the two conditions included in the World Health Organization's Global Action Plan. It also encompasses trachoma, glaucoma, diabetic retinopathy and corneal opacity.

Additionally, the VLEG study found that the prevalence of visual impairment has been dropping over the last 25 years, from 4.6 percent in 1990 to 3.4 percent in 2015. That's the good news. But there's also bad news; the study forecasts that various global trends, including population increase and ageing, threaten to overwhelm our existing efforts. Applying the new VLEG data, the International Agency for the Prevention of Blindness (IAPB)'s new Vision Atlas (2) projects a threefold increase in avoidable vision impairment by 2050.

These trends can seem discouraging, but within them is a kernel of hope. Because so many of the vision-related challenges are treatable or preventable, there are clear and specific actions that can be taken to change the trajectory. I have volunteered for many years with the Seva Foundation, delivering cataract surgery training and technology to underserved regions of the globe. Groups like Seva are pioneering cost-effective and sustainable solutions that will bring us much closer to a world free of avoidable blindness, perhaps someday much closer than we might imagine.

Seva was founded 40 years ago to address the problem of preventable and curable blindness. Since that time, the foundation has been developing and perfecting the technological, capacity-building and outreach methodologies for delivering sight-saving and sight-restoring services in underserved regions throughout the world. Through its Global Sight Initiative (GSI), Seva plans to increase capacity in eye care facilities around the world so that an additional

At a Glance

- *Preventable blindness is on the rise globally, according to new data from the Vision Loss Expert Group; there are clear and specific actions that can be taken to change this trajectory*
- *Approaching its fortieth anniversary, Seva Foundation is increasing capacity in eye care facilities around the world through its Global Sight Initiative (GSI), so that an additional one million people will receive sight-restoring surgery every year by 2020*
- *Ophthalmologist Marty Spencer, long-time Seva board member, talks about his volunteer work with Seva, training local eye care professionals and introducing new technologies to eye care facilities in developing countries*
- *Seva's cultural competence model of building local capacity where cataract surgery takes 15 minutes, costs $50, and is offered on a sliding scale to patients should help local eye care facilities become self-sustainable within 5 to 10 years.*

one million people annually will receive sight-saving surgery by 2020.

A sustainable model

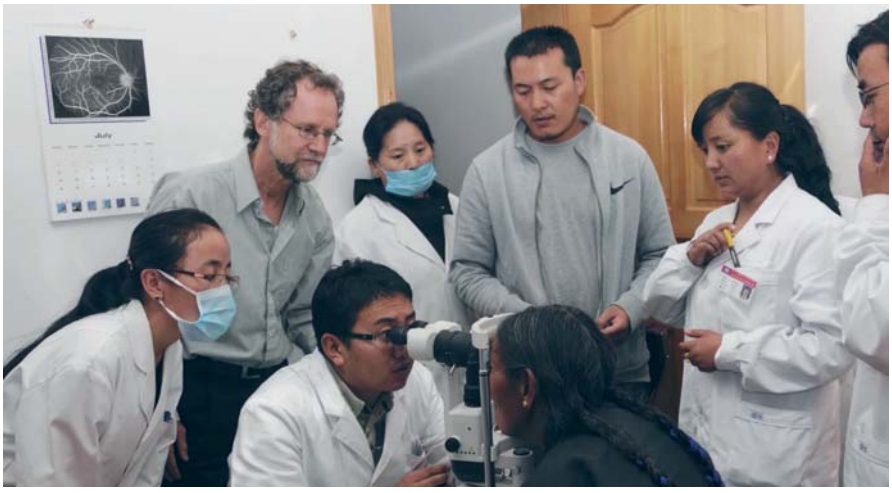
GSI pairs established, successful mentor eye hospitals with mentee hospitals in need of training and support. Through this support, one mentee hospital in the GSI network has increased its annual capacity for performing cataract surgeries from 4,000 nine years ago to 10,000 today. If the 94 hospitals currently receiving mentorship match that output – which is a feasible goal, based on past performance – together they would get us more than halfway to the global goal of one-million additional cataract surgeries a year.

There's cause for more hope. These current GSI mentee hospitals only cover a small portion of the low- and middle-income countries of the world: a handful in Central America and the Caribbean, fewer than ten in Africa, several in Nepal, and the bulk of them in various locations in India. An expansion of this network of mentor and mentee eye hospitals could exponentially increase the number of people receiving eye care.

Along with GSI's hospital network, Seva provides funding, support, and critical capacity-building to eye care centers in numerous locations around the world. This "teach a man to fish" model has proved enormously successful. The locally-run eye care programs Seva partners with generally become self-sustaining within five to ten years. In many cases, this is done by using multi-tier payments systems, where one-third of a facility's patients subsidize care for the other two-thirds.

The role of volunteers

A key aspect of this model is access to low-cost, but still high-quality, materials and techniques. Seva has played a crucial role in the development of several innovations in eye care delivery in underserved regions. Volunteer ophthalmologists and other eye care providers play a key role in keeping local providers aware of and trained in the latest medical innovations.

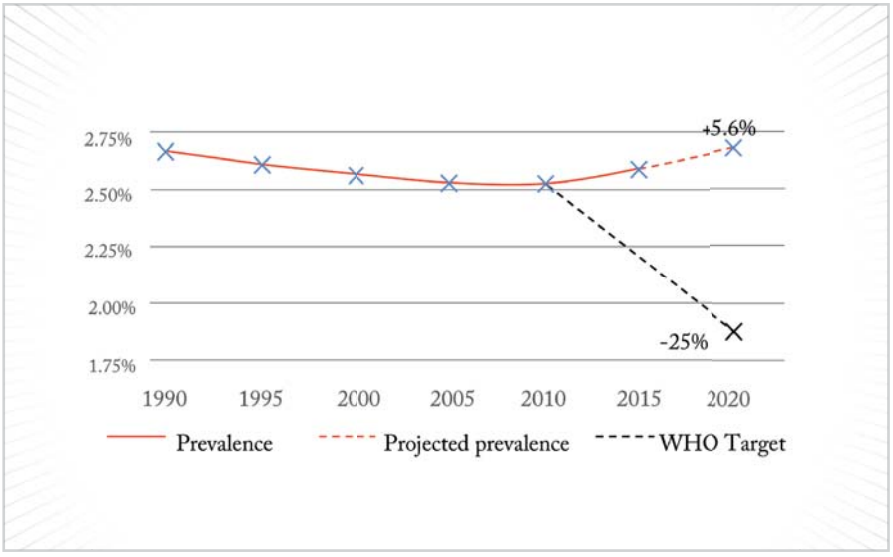


Marty Spencer (top left) training eye care professionals at a Seva partner facility.

Marty (center) with his daughters Laura (left), Chair of the Board of Seva Canada and Justine, a volunteer for Seva Canada.

For example, I introduced manual sutureless cataract surgery in several countries over the past 20 years. Another Seva board member, Dick Litwin, introduced the use of intraocular lenses (IOLs) for cataract surgery in India back in the early 1980s. At first, as IOLs were going through developmental iterations in the West, Seva obtained the outdated models – which were still perfectly viable – for their partner eye hospitals in India and Nepal. Each lens cost $300 at that time in the U.S., but came free to Seva, enabling their partners to offer free cataract surgery to those in need.

As IOL technology stabilized, the supply of free lenses dried up, and so Seva and its sister organization, Seva Canada, provided the impetus for what eventually became Aurolab. Now the manufacturing division of Aravind Eye Hospital in Tamil Nadu, India, Aurolab makes IOLs and other ophthalmic consumables, such as surgical sutures, pharmaceutical products, surgical



Changes in the global prevalence of avoidable visual impairment, 1990–2015 and projections to 2020 (2).

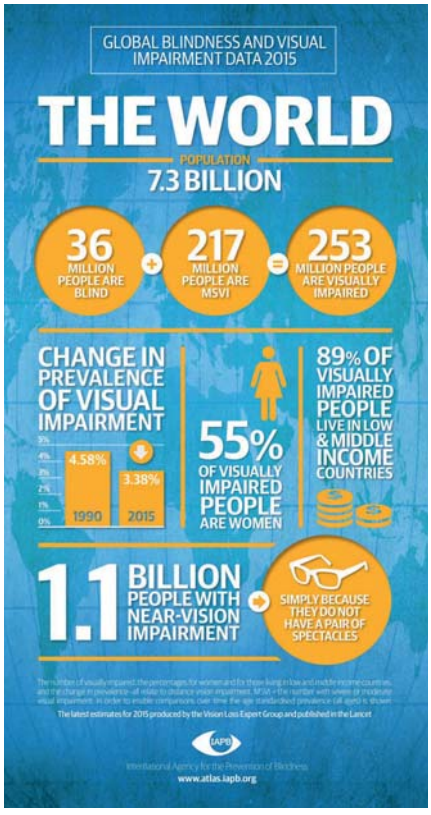
blades and other equipment. Producing high-quality supplies in-country, with quality and cost controls, has been a major factor in the spread of free cataract surgery to people in need. The current cost of sight-restoring cataract surgery performed at Seva-partner eye camps and hospitals is only $50 – and that price includes both materials and surgical staff required to perform the procedure.

Cultural competence

Adapting teaching and service techniques to the particular needs and cultures of various developing nations has also contributed immensely to expanding the volume and quality of eye care worldwide. When Litwin first traveled to India, the person he shared those IOL prototypes with was Venkataswamy, a founding board member of Seva and the force behind Aravind Eye Hospital. At that time, Aravind had already created a successful model of delivering high-volume, high-quality, low-cost eye care in rural regions of India. Seva's founders realized this model could be adapted to different countries in culturally-appropriate ways.

Seva has a long history of connecting ophthalmologists and other eye care medical professionals with their newly-discovered life's calling of helping people to see. This was certainly the case for me. My avocation for the past 30 years has been alleviating and preventing blindness in developing countries – work that has been extremely meaningful to me. I invite everyone working in the field of eye health to consider contributing their time and talents to this global effort. There are myriad opportunities to do so. For example, I recently volunteered a week's time training at a center in Latin America and traveled to provide and demonstrate services in rural Nepal.

With its global network, volunteer force of ophthalmologists, eye care nurses and other medical professionals, and its strong donor base, Seva Foundation is strongly positioned to provide sight-saving and sight-restoring services to more people in more places around the globe in the decades to come. The challenges, as evidenced by the latest data from VLEG, are daunting. But Seva and their governmental and non-profit compatriots in the field of reducing global blindness have made enormous strides. Seva's four decades of experience



Global blindness and visual impairment data 2015 (Source: IAPB Vision Atlas)

are serving as a hopeful springboard to launch the next phase of the work. We go forward with a 20/20 vision of a world where all can see.

Marty Spencer sits on the Board of Directors of Seva Foundation and Seva Canada. He has received the Governor General's Medal for Volunteers Award from the Canadian Government for his commitment and service to prevent blindness and restore sight around the world.

References

1. *SR Flaxman et al., "Global causes of blindness and distance vision impairment 1990–202: a systematic review and meta-analysis", Lancet Global Health, 5, e1221–e1234 (2017). PMID: 29032195.*
2. *International Agency for the Prevention of Blindness, Vision Atlas, Available at http://atlas.iapb.org/. Last accessed February 21, 2018.*

How to Approach Surgery in Your Early Career

Ten tips for being a better retina surgeon, after you've completed your fellowship

By Bobeck S. Modjtahedi and Eduardo Uchiyama

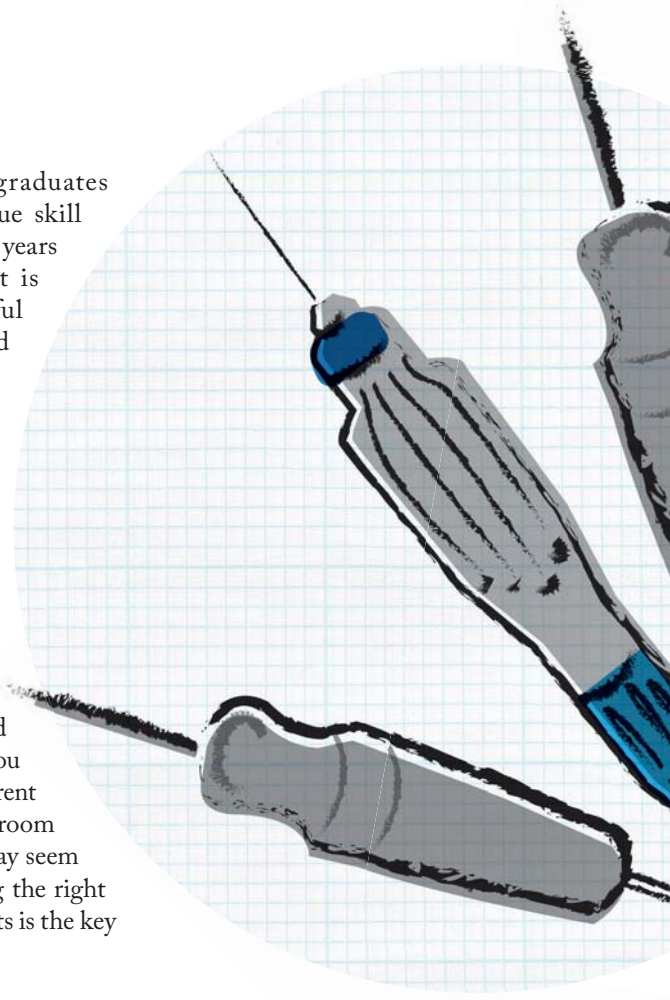
The beginning of your post-fellowship career is fraught with multiple perilous transitions. Perhaps the most daunting is assuming the role of primary surgeon. The first three-to-five years after training can be thought of as a second fellowship where you will: hone your skills as a surgeon and improve your efficiency, determine what approaches work best for you, and define your threshold to operate for different conditions. The patients you operate on now will be seeing you for years to come – you want to make sure to put yourself in the best position for success, as you will be reminded of that surgical effort every time you examine that retina.

At a Glance

- *You are not done with learning after you've made it past fellowship*
- *The patients you see operate on now will be the patients you see for years to come – every retina examination will be a reminder of how that surgery went*
- *You need to be mindful of your limitations and biases – and always work to improve yourself as a surgeon*
- *Here, we share what we've learned from our experiences as early surgeons.*

Every young surgeon graduates from training with a unique skill set that was cultivated over years of education. However, it is important to remain mindful of your limitations and biases, while always trying to improve.

We have had the opportunity to learn from skilled mentors as well as from our own experiences, and we hope our pearls of wisdom will help you in your early career. Although our article is focused on vitreoretinal surgery, many of these lessons can be applied broadly to other surgeons. You will find yourself torn in different directions in the operating room and some pieces of advice may seem at odds with others; learning the right balance of competing instincts is the key to becoming a good surgeon.



1. *Learn from other people's mistakes instead of making your own*
   The vitreous base is not the only thing that benefits from a little support – mentorship and support will be critical elements to your success. Sleepless nights and anxiety are common features of the very common but often under-diagnosed Early Surgeon Syndrome (ESS). It may seem cliché, but being a physician means being a lifelong student. Surgery can be overwhelming, even for seasoned veterans, so do not be afraid to ask questions. Your prior mentors will always be happy to hear from you and lend their insights – you will always be one of their fellows in their mind, your association with them does not end at graduation. Many young surgeons are afraid that asking for help will make them look weak to their new colleagues, and though some more established surgeons may not be very sympathetic, most of your co-workers are invested in your success. Surgeons have two phases in life – mentee and mentor. Most established doctors are happy to take a new physician under their wing and help guide them. Take time to identify some mentors at your new practice and figure out who will be a trusted and safe "no judgment" resource. It is important to have someone you can go to for all the "dumb" questions you might be afraid to ask others. It is critical to have people you can trust in a pinch – including those you can call from the operating room.
2. *Treat the patient, not the picture*
   It takes skill to know when to operate

on a patient, but it takes even more skill to know when it's best to hold off on surgery. Too many surgeons feel compelled to operate on a patient with a dramatic optical coherence tomography scan. Do not let yourself fall into the trap. Listen to the patient to figure out what, if anything, is bothering them as well as their visual priorities and goals. You will seldom impress an asymptomatic patient with an improved OCT scan, but you have everything to lose in the case of a rare complication.

3. *Undersell and over deliver*
Emphasize and make sure patients understand the goals and expectations of surgery before you go to the operating room. It is critical to also document these conversations in your charting for medico-legal purposes. Many patients consider all eye surgeries to be the same, so they might expect 20/20 vision after a chronic macula-off retinal detachment repair because their next-door neighbor could see really well after routine cataract surgery. For many conditions – even the routine macular hole or epiretinal membrane – patients need to understand that they may see better, but the chance that they will see perfectly is remote. If you feel like you are making "a pitch" to get a patient into the operating room, it's time to re-evaluate if it is the right surgical case or the right surgical patient. At the end of your consultation, the patient should be asking you to operate, not the other way around.

4. *Be willing to take it slow and to take a step back*
Do not be afraid to stage procedures instead of tackling too many issues at once. Let the patients know their problem might require more than one surgery. Young surgeons often feel like returning to the operating room is an intrinsic failure; however, it is sometimes safer and smarter to take a step-wise approach. Judging a surgeon by operative time is like grading a book report by word count. Speed comes with improved efficiency. Efficiency will come with time and patience. Avoid feeling rushed if you are taking longer than expected and avoid trying to finish by a certain time on the clock. It can be easy to start to feel the growing tension in the room as the operative staff starts to worry about getting home on time. Remember your only responsibility is to the patient – get the job done and get it done right.
Similarly, do not be afraid to send patients for second opinions or ask your colleagues to take on a particularly challenging case. Patients often appreciate the opportunity to get a second opinion and it can engender more confidence in you because it shows you have nothing to hide. You'll have more surgeries than you can count in 10 years, losing a case in the interest of being smart now will not make a difference in the long term. Most senior colleagues appreciate an associate that is conservative in their approach.

5. *Respect the lens, but do not be a slave to it*
In a competition between the retina and just about any other part of the eye, the retina wins. Your goal is to fix the retina – the most prime piece of ocular real estate (in our somewhat biased opinion). Young surgeons are often afraid to remove the lens intraoperatively or to perform maneuvers that might increase cataract formation (such as crossing a little beyond the mid-point to access a difficult to reach area or putting in long-acting gas). You are going to be kicking yourself far more over a recurrent detachment than an early cataract or aphakic patient.

6. *Be a surgeon outside the operating room*
Pre- and post-game planning are critical elements to ensuring a smooth surgical experience, especially early in your career. Take time to think out each step of your surgery, even the mundane ones; consider where to position your Mayo stand, where to sit, and how to hand off instruments. Take the time to talk to your operating room staff to let them know what you plan on doing before the case, what to have opened (and what to have in the room ready), and how you like to run your ship. In the operating room, it's common to feel like you're in a rush to get the case started – but it is important to invest a few minutes to make sure things are set up like you want. Make sure the microscope is on the right settings, the foot pedals are in the right place, the bed is at the correct height, and the patient is draped like you want. Small issues in your setup can cost you far more time later during the case or prove to be a persistent headache while operating. It is important to plan for as many intraoperative possibilities before you head into the operating room – have a plan in place for every contingency, so you can have the appropriate equipment (and

mindset) in the room to smoothly fix the problem as soon as it arises – what if the lens falls during the case? What if you cannot get the hyaloid off easily? What if you lose your ILM flap before completing the peel? Early in your career, when your cases take longer, you should expect the view to worsen towards the end of the case – so anticipate in advance what to do. You will find the amount of cornea you scrape is an indirect measure of your surgical speed – remember, Viscoat is your friend. Most people want to relax after finishing a day in the operating room, but instead invest the time to think critically about your cases for the day – this works even better if you can record your surgeries and watch them. Think about places where you could have been more efficient, as well as what struggles you encountered and how you overcame them, as it will help you plan your future surgeries.

7. *Take the easy win*
Invariably, in any surgery, there comes the critical juncture of when to decide you are done. This can be a struggle for young surgeons. There is a balance between doing a limited core vitrectomy and a few dozen spots of endolaser for a diabetic vitreous hemorrhage and meticulously shaving the vitreous base for an epiretinal membrane. The longer you are in the eye, the greater the likelihood that something could go wrong; however, there is an important trade-off to consider, though some are fond of saying "the enemy of good is perfect" it can be equally true that "the enemy of good is 'good enough'." Finding the balance is one of the hardest parts of the "art" of surgery, but ultimately you have to learn what a "win" will be for each case. Once you hit the win threshold, you know you can comfortably end the surgery. You'll find yourself staring at a macula, vitreous base, or a row of laser and wondering if it looks good enough. If you are there to peel an epiretinal membrane, you shouldn't obsess over a stubborn piece of ILM that will not come off from the macula. You should go as far as you need to ensure a good result for the patient, without cutting corners. Resist the impulse to make it look perfect for the sake of looking perfect – the patient is not going to see how their retina looks, they only care how they see.

8. *Do not become complacent*
Avoid being too adventurous in the first few months of your career – stick to what works best in your hands. Over time, however, you'll want to venture out and try new techniques. It is important to strive for continued improvement and growth – the best surgeons are not doing the same thing they were 20 years ago. Take advantage of high-quality surgical videos available online and even reach out to authors for advice – most of them love passing on additional thoughts and helping you employ their techniques. Check in frequently with your former co-fellows and contemporaries to see how their surgical approaches are evolving. In a few years, you should be giving tips to your old fellowship mentors on how you have expanded on their methods.

9. *Your best chance to fix a problem is the first time*
The probability of success falls exponentially with each successive surgery. You do not want to be one of those surgeons whose patients know the OR staff's names by memory. Some patients simply have bad protoplasm and are destined to require repeat surgery; however, when the need for an extra step may be equivocal, lean towards over-treatment if it increases your probability of success (see Tip #7). Which brings us to…

10. *Scleral buckles still have a place in detachment repair*
Do not let anyone tell you otherwise. It seems increasingly popular to view the scleral buckle as a remnant of a bygone era, now obsolete due to advances in vitrectomy surgery. Although for many detachments a buckle is no longer necessary, it still holds value in the right context. While refractive shift, ptosis, and diplopia are legitimate concerns when to comes to scleral buckling, there will be many cases where you are more likely to wish there was one there than regret putting one on. You will often hear colleagues say they think they can "get away" or "get by" with just a vitrectomy. Focus instead on how to "get it right."

Bobeck S Modjtahedi is a vitreoretinal surgeon at the Southern California Permanente Medical Group (SCPMG) in Baldwin Park, CA, USA. He was voted #6 on The Ophthalmologist 'Rising Stars' Power List 2017. He can be reached by email at BobModj@gmail.com. Eduardo Uchiyama is a uveitis specialist and vitreoretinal surgeon at Retina Group of Florida in Ft Lauderdale, FL. He is also an Affiliate Assistant Professor of Clinical Biomedical Sciences at the Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL, USA. He can be reached by email at uchiyamamd@gmail.com.

Mr. Fix-It

Sitting Down With... Keith Barton, Consultant Ophthalmologist, Moorfields Eye Hospital, London, UK

What has been your most successful collaboration?

Without a doubt, working with Don Budenz; we've had enormously successful collaborations dating back more than 20 years. I owe the majority of my H-index to Don's relentless hard work in research. We started working together in 1996 with the first use of amniotic membrane transplantation in glaucoma surgery, initially in rabbits and subsequently in a human randomized controlled trial. After that, we collaborated – or rather, Don did all the work and I helped! – in the ABC study (which we co-chaired), the Tema Eye Survey and the Tema Eye Survey II. In between, we were both investigators in the TVT and PTVT studies. Parenthetically (and outside of Ophthalmology), Don's wife, Sue, rescued my 19-year-old son from a crack house in Chapel Hill!

Wait, what?

Yes. Four years ago, Don hooked my would-be medical student son up with a summer job in an HIV immunology lab in North Carolina, where he spent a few months "growing brain cells on cover slips," as he told his mother. Said son found himself accommodation using the highly reputable "Craigslist," but started grumbling about his party-animal housemates. The night of our first Asian Ophthalmology Futures Forum in Tokyo, at midnight (after a lot of wine), I received a call from him: he wanted to get out immediately. His housemates were always high on various substances, they partied all night every night, they never locked the doors, and so on… Sue, with 30 minutes notice, organized an actual SWAT team, who swooped in and transferred him (with all his stuff) to Chateau Budenz, where he remained!

Back to collaborations: a fruitful one of a different nature has been with Kuldev Singh and the Ophthalmology Futures Forums, which we first launched in 2012. Six European and three Asian Forums later, and it is exciting to see how they've grown and how they will continue to grow. This year we will host our first Retina Forum on September 19 (the evening before EURETINA).

What are the highlights of your career?

There have been many. Being asked to manage glaucoma in patients attending Moorfields' burgeoning uveitis clinics first springs to mind; I had an instant referral base of largely young patients – the majority of whom required surgery. One of the biggest moments was convincing Pharmacia in 1999 to bring the Baerveldt Glaucoma Implant to the UK. For context, my Moorfields clinic had become a bit of a "bleb-repair shop", with endless streams of patients returning for more and more trabeculectomy bleb fiddlings, revisions, repairs... Having access to the implant meant that we glaucoma surgeons finally had access to something that could control patients' IOP with a high level of efficacy in complex surgical cases.

Being part of the TVT, ABC and PTVT studies was also privilege, as I was able to help contribute to the generation of a firm evidence base for the role of aqueous shunts in glaucoma surgery. Then there's my involvement in the MIGS boom; watching glaucoma surgery – a field in which I have toiled for years – suddenly become hot and sexy, with a feeding frenzy of commercial interest, has been incredible. It's been quite a ride these past few years!

Who do you consider your mentors?

My first in medicine was Desmond Archer, retired Chair of Ophthalmology at the Queen's University of Belfast, a charismatic figure who by the early-to-mid 1980s had built one of the most impressive ophthalmology departments in the UK and who inspired me to take up ophthalmology. Then there was James McGill in Southampton, who told me in no uncertain terms in 1989 to apply to Moorfields. After James, there was Sue Lightman, who told me early on that I should be at a tertiary referral center and helped kick-start my career in uveitic glaucoma. John Dart taught me that surgeons can actually be very logical, scientific and, contrary to popular belief, sometimes even think a lot. Crucially, he taught me not to be scared of complex cases. Finally, Roger Hitchings, who gave me a consultant job, encouraged my entry into complex surgical glaucoma, inspired and encouraged my international career and, probably the greatest compliment, graciously permitted me to look after his private patients on his retirement.

"John Dart taught me that surgeons can actually be very logical, scientific and, contrary to popular belief, sometimes even think a lot."

What drives you?

Caffeine, patient's appreciative comments after controlling the pressure in seemingly impossible cases, training surgical fellows and teaching them not to shy away from complex cases, like John and Roger did for me. Caffeine again. And the pursuit of something that is at least as effective as the Baerveldt Glaucoma Implant, that is at least as predictable as femtosecond laser-assisted cataract surgery, that doesn't require Heath-Robinsonian systems of occluding sutures to prevent early hypotony, and that doesn't risk endothelial cell loss, later erosion or double vision.

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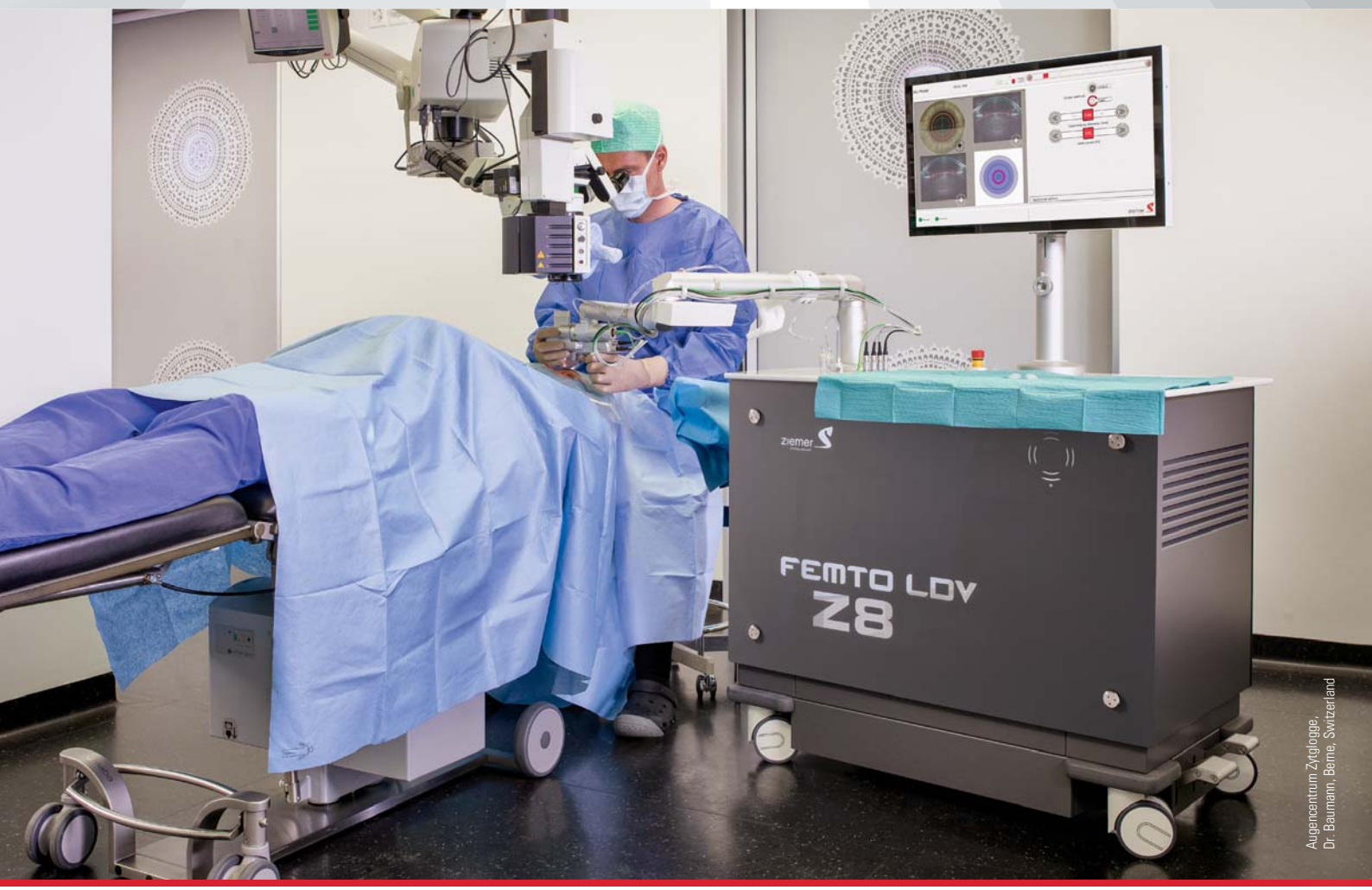

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