AUGUST 2017 # 44

the Ophthalmologist

Keeping up with Precision Medicine

How one team are driving a targeted onslaught against ocular cancers

22 – 30

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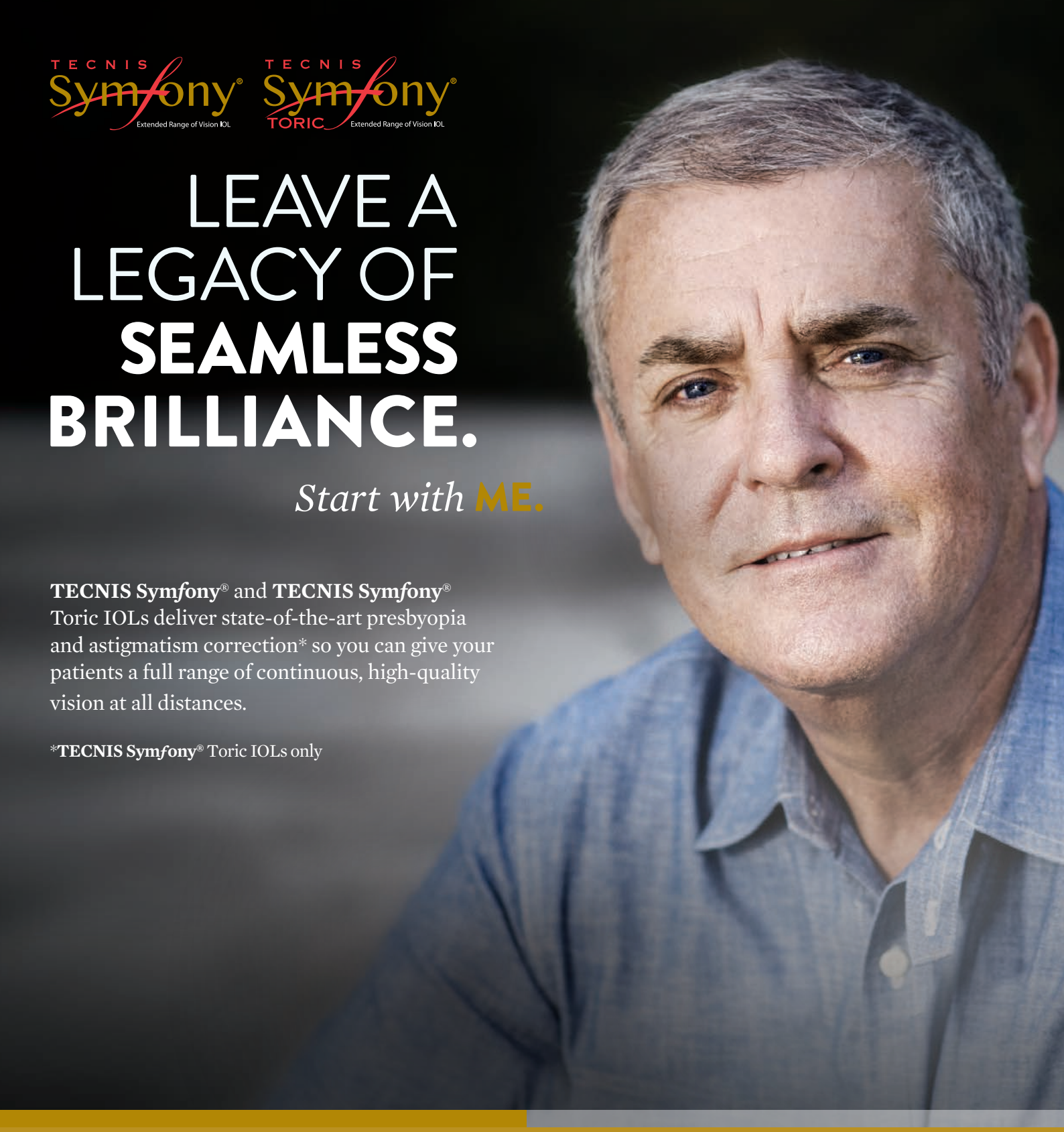

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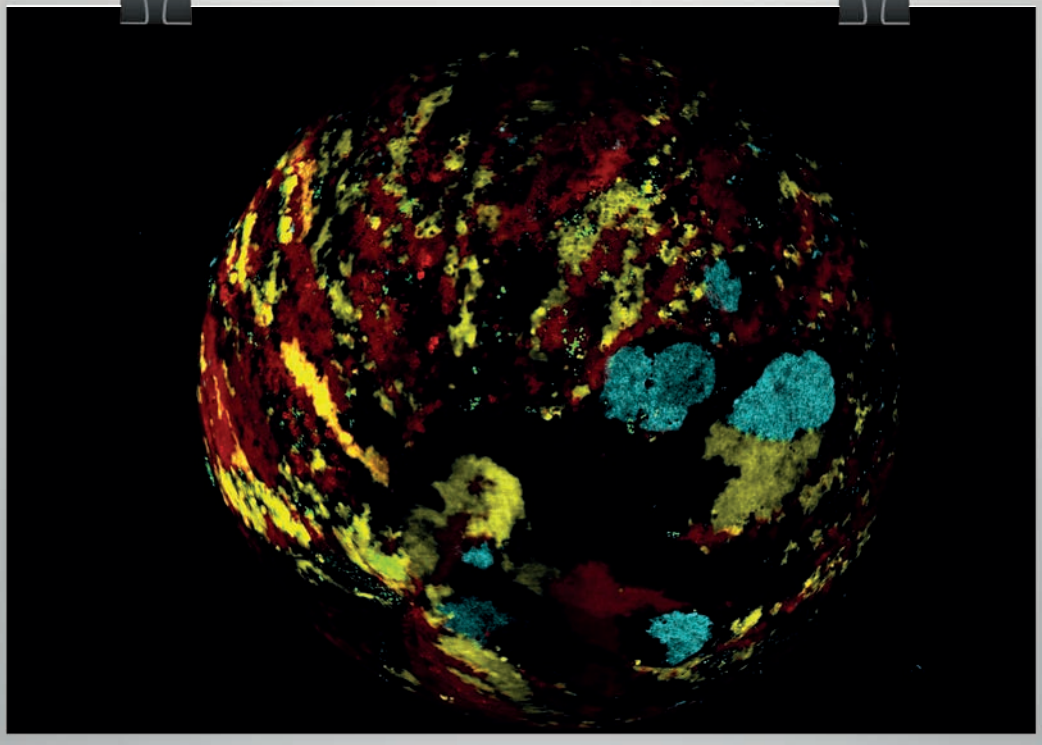
Image of the Month



Chaotic Confetti Cornea

This light-sheet microscopy image depicts a K14CreER^{T2}-Confetti mouse cornea that received a severe epithelial debridement wound, spanning limbus-limbus to mimic limbal stem cell deficiency. In this instance, instead of a neat linear array of multi-colored spokes which typically develop in a normal cornea, a chaotic patchwork evolved eight weeks after injury. The image of the normal confetti cornea can be viewed at: top.txp.to/issues/0916/207.

Image courtesy of Nick Di Girolamo and Mijeong Park, University of New South Wales, Sydney, Australia.

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

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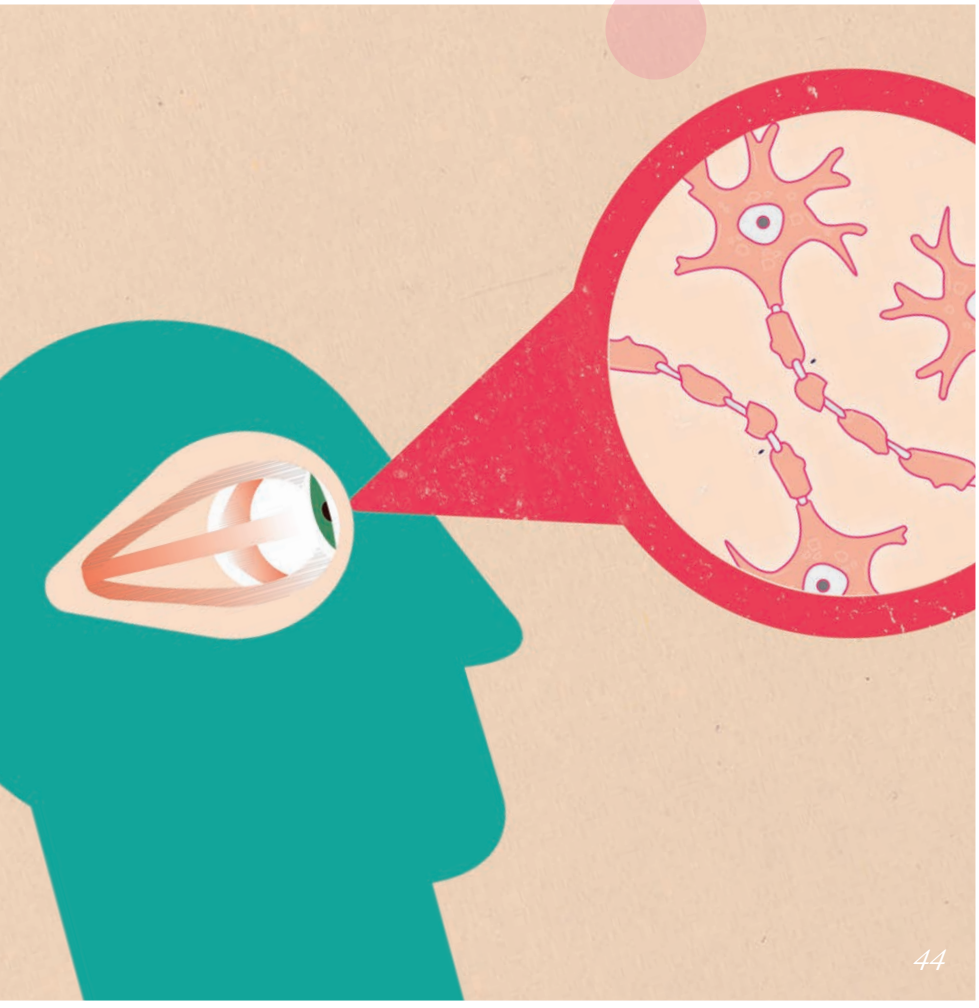

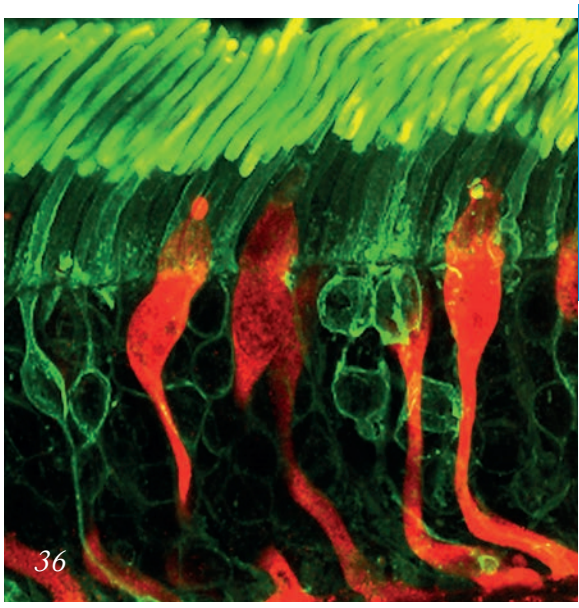

In My View

On The Cover

Artistic representation of precision medicine: targeting therapies to specific mutations.

Upfront

Features

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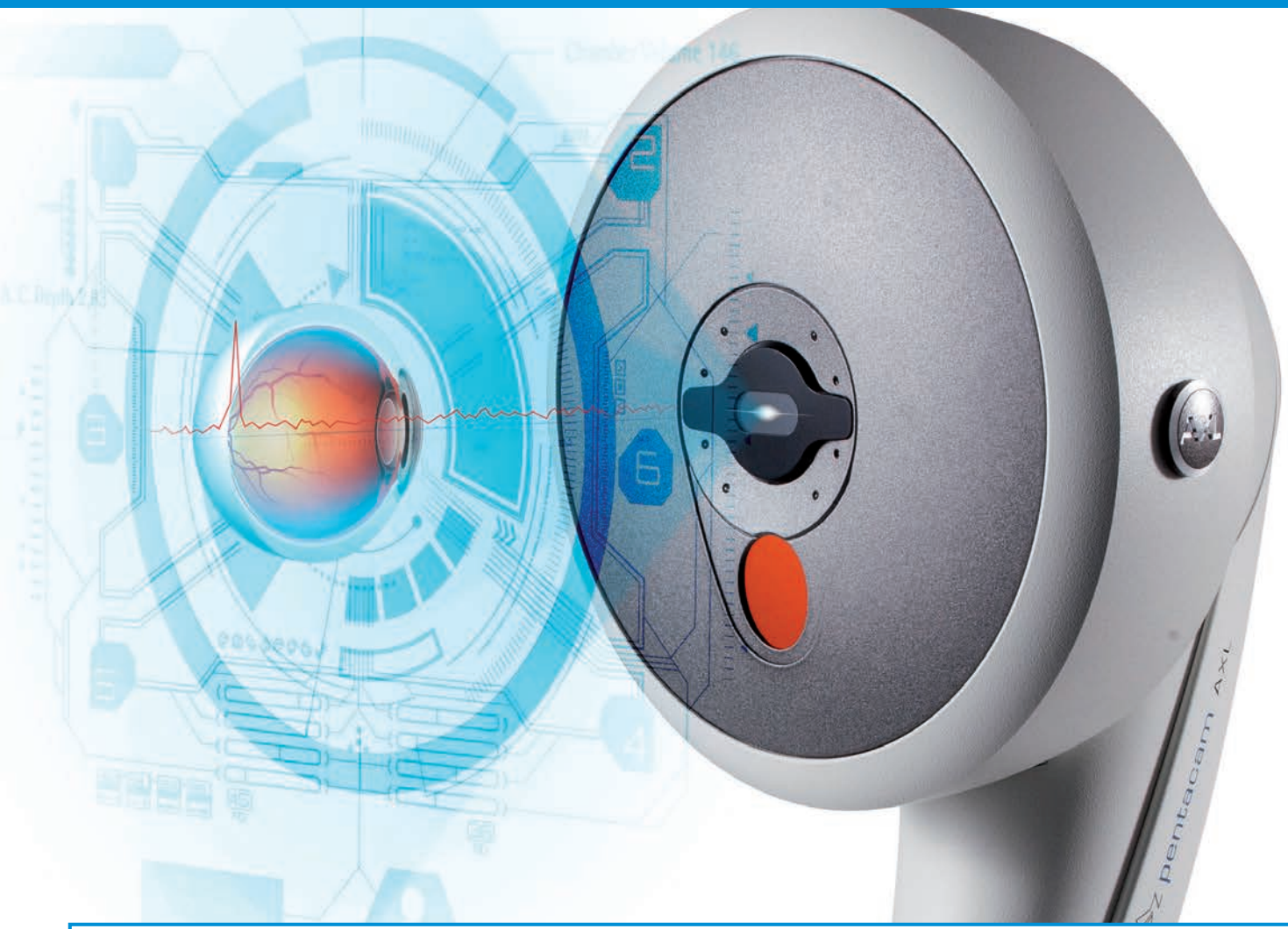

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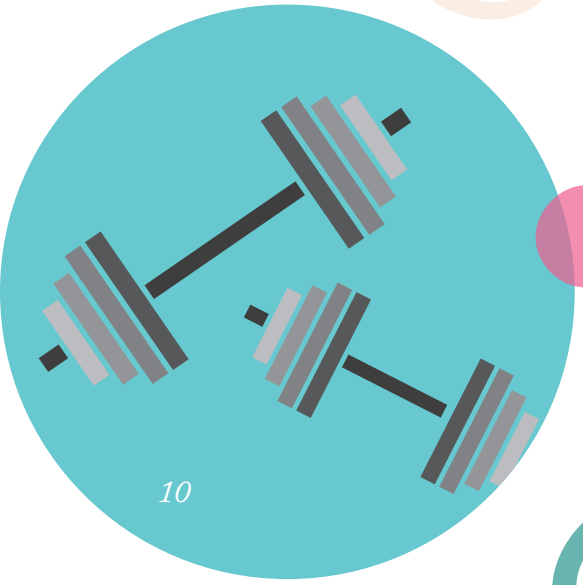
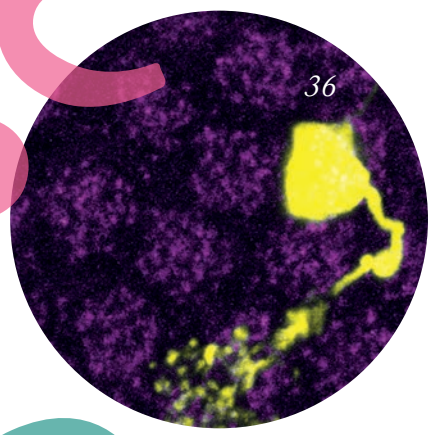
 *Interim 75-eye 24-Month Case Series, data unpublished (Mark J. Gallardo, MD). Data on file. Ellex Medical.





NextGen

Profession

Sitting Down With

the Ophthalmologist

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Access All Areas

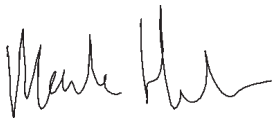
Why, in terms of congresses, bigger isn't always better

I love the big ophthalmology meetings. For me, it's a case of an ever-expanding circle of friends composed of ophthalmologists, scientists, congress staff, fellow journalists, PR and industry types (some of whom are generous with their significant expense accounts...). It's fantastic to see familiar faces and resume conversations against a backdrop of the latest and greatest in ophthalmology. But here's the thing: I think I prefer – and learn more from – the smaller meetings. And I'm not talking about the frustrations people feel when there are two must-see parallel sessions.

I find that the smaller the meeting, the easier it is to access the speakers. Few people reading this editorial will have a "PRESS" ribbon under their ARVO Congress badge, or MEDIA written at the bottom of their AAO pass. (Both of which literally open doors for me.) But even then, I often find it hard to catch the superstar speaker after she or he has presented their latest work on the podium at the bigger conferences. The speaker often gets crowded and has to rush off to another pressing commitment. However, when I found myself at the CXL Experts Meeting in Zurich last year, it was no problem getting hold of the likes of Theo Seiler after he'd presented some impressive data – he was sitting next to me at the back of the room before and after his presentation! I kept bumping into him during coffee and lunch – and he may have been sick of the sight of me by the end of the meeting. In fact, there was a whole host of excellent speakers – top names in the field – and I was able to chat to all of them at some point without issue.

Clearly, these people are busy and in high demand, so that sort of access – and the amount of time you can spend – is rare. And it's something I have to give Robert Osher great credit for. My first visit to his meeting – Cataract Surgery: Telling It Like It Is – was back in January this year. It's by no means small, but the faculty are only there on the condition that they're available to the delegates throughout the (very long) day. I could speak to surgeons like it was a conference a tenth of the size. And that's important. I always have questions and receiving answers makes me better at my job. I'm pretty certain that it's also the same for you. So consider the smaller meetings: if you manage to corner an expert, you might learn more than you could ever imagine...

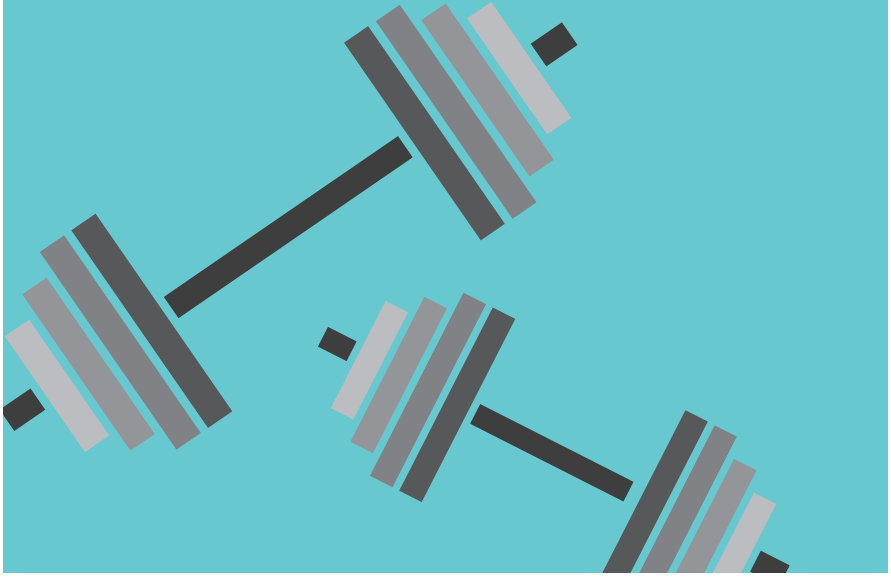
Mark Hillen
Editor



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



Pumping up the Pressure

Can lifting weights raise IOP?

Those who regularly "pump iron" down the gym will be familiar with the physical feelings that come with intense resistance exercise. But what impact may strength exercises have on the body, and IOP in particular? A team from the University of Granada, Spain, found that IOP significantly increased when resistance training exercises were performed (1).

Jesús Vera, lead author of the study, explains what led them to design the project: "We have a really active collaboration with the Faculty of Sport Sciences at the University of Granada, and we have each shown the importance of considering physiological changes induced by anaerobic exercise. This led us to consider changes in IOP."

Enrolling 17 male military officers from the Spanish Army, the team got them to perform jump squats and bench presses with progressively heavier loads, and measured IOP before and after each load using a rebound tonometer. IOP increase was found to be linearly associated with increasing load, and the bench press was found to induce a greater increase than jump squats at the same relative load. Though they were expecting to see an increase in IOP, Vera says that they "did not expect the almost perfect linear association between the magnitude of resistance and the change in IOP." The team also found that five minutes of rest was sufficient time for IOP to return to baseline values.

So what impact do the findings mean for glaucoma management? Vera urges caution: "Recent studies have shown that exercise is beneficial in the management of glaucoma, but our findings were obtained with healthy participants, and therefore the effect on patients with glaucoma still needs to be studied. We also want to highlight that the type and intensity of exercise is of vital importance depending on the main goal of this exercise prescription."

The team are now focusing on how fitness level impacts IOP increase during different exercise protocols, as well as testing the long-term effects of different physical training programs on baseline IOP levels and IOP responses to exercise. For now, Vera offers some advice: "From this study, and some others that we have recently conducted, we can state that exercise is highly beneficial, but that progressive involvement is desirable; individuals in poorer physical condition manifest higher IOP peaks with exercise and should avoid highly demanding physical activities." *RS*

Reference

1. *J Vera et al., "The acute effect of strength exercises at different intensities on intraocular pressure", Graefes Arch Clin Exp, Epub ahead of print (2017). PMID: 28702697.*

Conjunctival Cavalry

Team finds a commensal bacterium in the eye that helps protect the ocular surface from pathogens

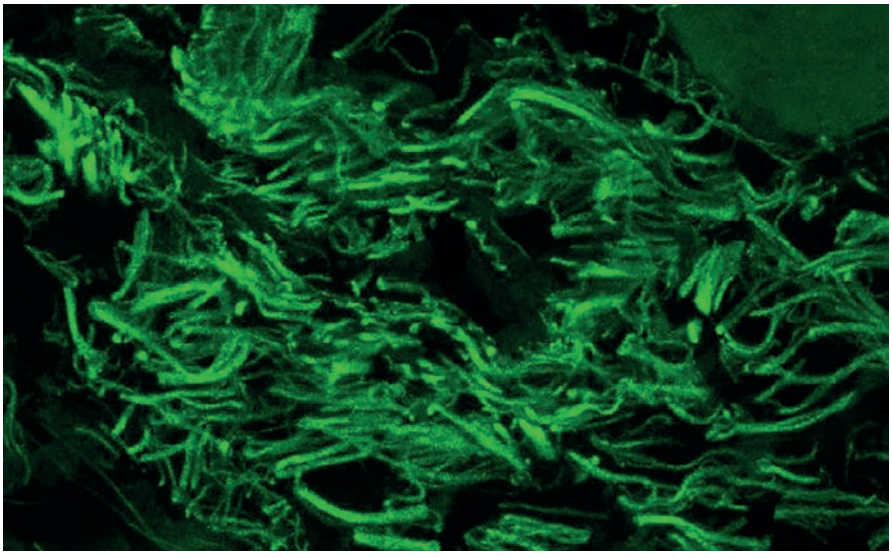


Figure 1. *C. mastitidis* on the surface of the eye. Frozen sections of whole eyes (with eyelids) were stained with fluorescent probes against Corynebacterium spp. Image credit: Rachel Caspi and Anthony St. Leger.

The question of whether or not the ocular surface harbors resident microbiota has been under debate for a long time; microbial organisms can be found on the surface of the eye, but they could have arrived there from the surrounding environment. Now there's an answer to this long standing deliberation; a resident ocular biome does exist – and it helps defend the ocular surface from pathogens by tuning local immunity.

"Originally, we were collaboratively studying Muckle-Wells disease, a condition which results in generalized inflammatory syndrome and is accompanied by conjunctivitis, in mice," says Rachel Caspi, of the National Eye Institute and lead author on the corresponding paper (1). Interested in the conjunctivitis aspect, the team hypothesized that these individuals (and the mice carrying the mutation) may be responding abnormally to normal stimuli from the environment. Caspi says, "We'd also observed that immunologically deficient mice at our facility developed conjunctivitis as they aged. Microorganisms were one possibility so we started to examine healthy and mutant mice, and the rest is history…"

The team identified that *Corynebacterium mastiditis* – a known skin commensal – formed stable colonies on the conjunctiva of wild-type mice bred at their institute, as well as mice provided by a collaborator at Washington University (Figure 1); *C. mastiditis* was not found on the ocular surface of commercially sourced mice. Caspi comments, "We expected to find stimuli from the microbial world on the ocular surface, but didn't expect them to be 'permanent' residents on the eye."

But how did they demonstrate the bacteria were resident and not simply being reinoculated into the eye from the air, mouth, nose or skin? "It is very difficult to show this, but we were lucky that the mice purchased from commercial vendors lacked this bacterium, and that it could not be transferred through co-housing with mice harboring the bacteria," explains Caspi. True commensalism was demonstrated through detecting *C. mastiditis* on vendor mice conjunctiva for as long as five weeks after inoculation. "This gives us a measure of confidence that *C. mastiditis* cultured from the eyes of vendor mice had taken up residence and wasn't the result of continuous reinoculation."

Interestingly, the team found that the conjunctival commensal helped protect the eye from infection: it induced secretion of interleukin-17 from γδ T cells, which consequently drove neutrophil recruitment and secretion of antimicrobial agents into the tears. They also discovered that mice treated with gentamicin and vendor mice lacking *C. mastidits* showed increased susceptibility to fungal (*Candida albicans*) and bacterial (*Pseudomonas aeruginosa*) infections, respectively.

The team believe their findings have implications for the use of antibiotics to treat conjunctivitis, which Caspi thinks may bring more harm than good. This suggests that current antibiotics should be used for the shortest period possible. Looking to the future, Caspi says, "Probiotics based on bacterial extracts could be developed for the eye to stimulate natural immunity on the ocular surface and promote the body's own defenses, reducing the need for antibiotics." *RS*

Reference

1. *AJ St Leger et al., "An ocular commensal protects against corneal infection by driving an interleukin-17 response from mucosal γδ T cells", Immunity, 47, 148–158 (2017). PMID: 28709803.*

Sweet Revelation

Team find that a sugar-modifying enzyme drives pathogenesis in HSV keratitis

Once someone is infected with herpes simplex virus (HSV), they have it for life. But whilst persistent oral infection means recurrent bothersome and painful cold sores, persistent infection of corneal epithelium can cause keratitis – and the symptoms can persevere even when the episode of viral infection has cleared. How and why HSV-1-induced inflammation continues to plague the cornea once infection subsides has so far been somewhat of a mystery… until now.

Enter a team from the University of Illinois at Chicago, USA, who have shown that heparanase, an extracellular enzyme that breaks down the glycosaminoglycan heparan sulfate (HS), drives the pathogenesis of HSV-1 corneal infection (1) (Figure 1). Their key findings?

i. In mice with corneal HSV-1 infection, overexpression of heparanase worsened herpetic disease, delayed wound healing, and disrupted cytokine production.
ii. Heparanase translocated to the nucleus upon infection, driving expression of pro-inflammatory factors and activation of NF-kB.
iii. Inhibition of enzyme activity decreased viral spread.

Investigators Alex Agelidis and Deepak Shukla tell us more…

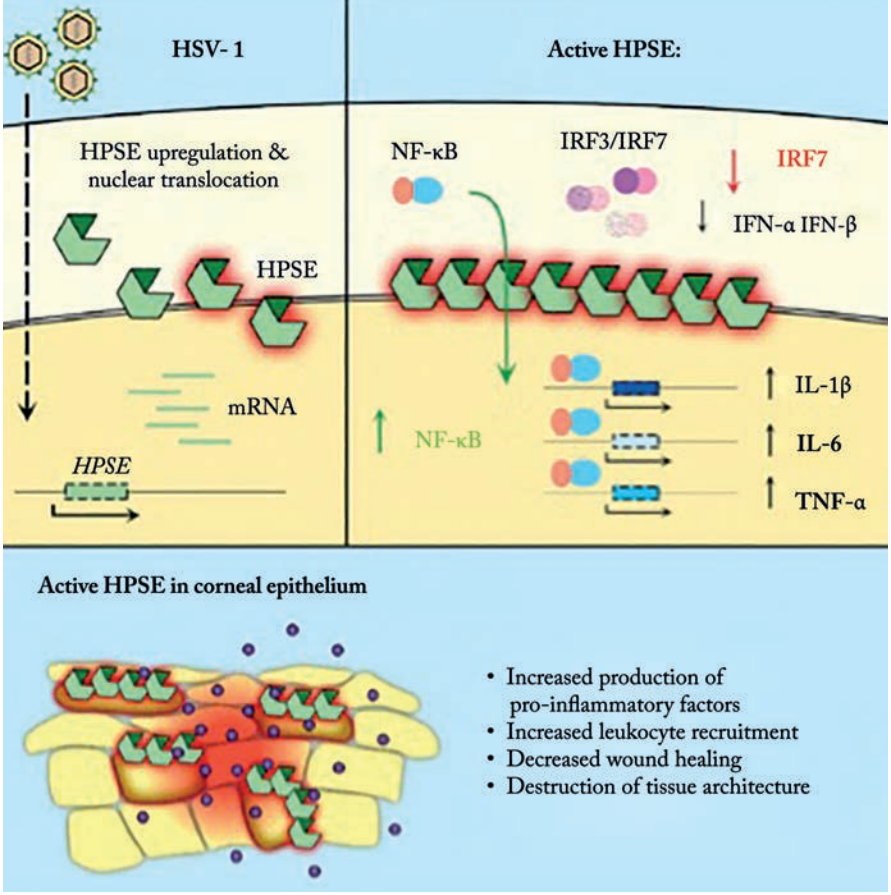


Figure 1. Summary of findings from the corresponding study. Adapted from (1).

What lead to your research?

For many years we have focused on HSV infection, particularly in the eye because herpetic stromal keratitis is a major unresolved medical mystery. It has been known for some time that HS – a glycosaminoglycan important for corneal tissue organization – serves as a major initial attachment site for ocular HSV-1 and many other viral and bacterial pathogens. As heparanase is the only mammalian enzyme capable of breaking down HS, we investigated whether it could be involved in HSV infection of the eye. We previously showed that HSV-1 infection increased heparanase expression in corneal cells, and that the enzyme was required for effective viral release from these cells (2). We also found that overexpressing active heparanase in the cornea dramatically exacerbated keratitis symptoms in mice. This formed the basis for our recent paper which describes multiple mechanisms by which the active enzyme drives some hallmark features of epithelial and stromal keratitis (1).

Did you find what you expected?

We were amazed that heparanase played such important roles in driving inflammation and other symptoms (e.g. neovascularization) in the eye, and were particularly surprised by its involvement in transcriptional regulation of pro-inflammatory factors that are already known to control chronic eye conditions including keratitis. As heparanase is normally found in the extracellular matrix (ECM), very little is known about its role in cell nuclei.

Does HSV-1 affect just HS?

Although there have been reports that other ECM components are involved in the process of viral entry and may be modulated during infection, their interactions with HSV-1 are unclear. We have focused mainly on heparanase because HS and its associated proteoglycans are major attachment receptors for several pathogens. Since our original discovery in 2015, several other groups have replicated similar findings with other viruses, and we are excited that heparanase appears to have a universal role in infection.

What impact do you foresee from your work?

With our findings, we have advanced the concept of a host-encoded virulence factor – a cellular protein that normally maintains homeostasis but can send

several cellular pathways spiraling out of control when upregulated and activated by a virus. Our work points to important roles for heparanase in corneal inflammation and hopefully will draw additional attention to innate or resident molecules driving inflammation and ocular disease. As we've shown that inhibiting heparanase reduces corneal symptoms, we hope that a new line of therapy could soon emerge for better management of HSV keratitis. A therapy such as this could have unique dual benefits, stopping viral release and spread as well as reducing inflammation and neovascularization.

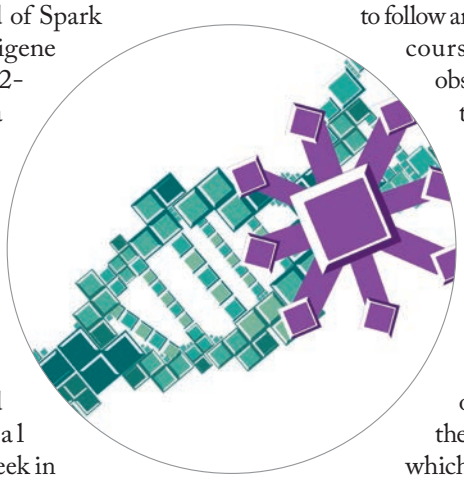
References

1. *AM Agelidis et al., "Viral activation of heparanase drives pathogenesis of herpes simplex virus-1", Cell Rep, 20, 439–450 (2017). PMID: 28700944.*
2. *SR Hadigal et al., "Heparanase is a host enzyme required for herpes simplex virus-1 release from cells", Nat Commun, 6, 6985 (2015). PMID: 25912399.*

Releasing the Gene Genie

The gene therapy era in ophthalmology edges nearer and is making RP... treatable

The last four months have seen a number of landmarks in retinal gene therapy for retinitis pigmentosa (RP). In April, Robert MacLaren performed the first ever human subretinal injection of AAV-XLRPGR gene therapy. But last month, the first phase III clinical trial data were published of Spark Therapeutics' voretigene neparvovec (AAV2-hRPE65v2), as a potential one-time gene therapy candidate for the treatment of patients with vision loss (20/60 or worse) due to confirmed biallelic *RPE65*-mediated inherited retinal disease (1). In one week in November 2013, 31 individuals were enrolled with 21 being randomized to receive bilateral subretinal voretigene neparvovec injections, and 10 to receive control injections – although one patient from each group withdrew before the injections occurred.



Just like with retinal prostheses, one of the big questions that has to be answered when people perform clinical trials of gene therapies for retinal degenerative diseases like RP is: how do you measure improvement in (or deterioration of) visual outcomes? The Snellen chart isn't particularly informative here. Instead, the investigators chose the change in multi-luminance mobility testing (MLMT) as the trial's primary endpoint. MLMT is a visual assessment that integrates aspects of visual acuity testing, visual field testing and light sensitivity into a quantifiable measure (2). How? With an assault course – or rather, trial participants were instructed to follow arrows on the MLMT course, while avoiding obstacles in or adjacent to the path, traversing raised steps, and identifying a door at the end of the course. Several light levels (ranging from 1–400 lux) were evaluated in order to determine the lowest light level at which participants could successfully navigate the course.

So how did the participants fare? After one year, mean bilateral MLMT score changes were 1.8 (SD 1.1) in the intervention group, and 0.2 (SD 1.0) in the control group (a 1.6 unit difference, 95% CI 0.72–2.41, p=0.0013). As a practical measure, 13 of the 20 participants who received the gene therapy managed to complete the MLMT course at the lowest luminance level tested (1 lux), whereas not one of the control group managed to achieve this. Significant improvements, relative to control, were seen in full-field light sensitivity threshold testing (p=0.0004), and visual field area with Goldmann III4a stimulus testing (p=0.0059) too, although the change in visual acuity averaged over both eyes was not (p=0.17). Hearteningly, no therapy-related serious adverse events were observed, and perhaps thanks to the perioperative immunomodulatory regimen employed, "no deleterious immune responses occurred."

The study authors succinctly (and modestly) summarized their work with, "Voretigene neparvovec gene replacement improved functional vision in RPE65-mediated inherited retinal dystrophy previously medically untreatable." The era of gene therapy for retinal disease outside of the clinical trial setting looks like it's got a whole lot closer. *MH*

References

1. *S Russell et al., "Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial", Lancet, Epub ahead of print (2017). PMID: 28712537.*
2. *DC Chung et al., "Novel mobility test to assess functional vision in patients with inherited retinal dystrophies", Clin Exp Ophthalmol. Epub ahead of print (2017). PMID: 28697537.*

Degeneration Through Time and Space

The past, present and future prevalence of AMD in Europe

Age-related macular degeneration (AMD) is one of the most prevalent age-related eye diseases of our time. But as populations age – and treatments improve – how has disease prevalence changed across Europe over the past two decades?

Using the European Eye Epidemiology (E3) consortium, a large multi-center team performed a meta-analysis of prevalence data in Europe between 1990 and 2013 (1); over 42,080 individuals over the age of 40 were analyzed from 10 countries in Europe (Estonia, France, Germany, Greece, Italy, Northern Ireland, Norway, Netherlands, Spain, Portugal, and the UK).

Determining prevalence of early and late AMD, the team also analyzed visual impairment, choroidal neovascularization (CNV), and changes in prevalence before and after 2006. We summarize the key findings in the infographic (right). Interestingly, though they found that the prevalence of early AMD remained stable and late AMD decreased before and after 2006, the team predicted that the number of people with AMD will increase by 2040 because of aging populations, indicating "a continuous need to develop comprehensive modalities for prevention and treatment of AMD." *RS*

Reference

1. *JM Colijn et al., "Prevalence of age-related macular degeneration in Europe", Ophthalmology, Epub ahead of print, (2017). PMID: 28712657.*

42,080 individuals (mean age 65–69 years)

Prevalence of early AMD		Prevalence of late AMD
3.5%	55–59 years	0.1%
13.2%	≥70 years	3.0%
17.6%	≥85 years	9.8%

The prevalence of early AMD before and after 2006 was similar

After 2006, the prevalence of late AMD decreased

Prevalence of late AMD was higher in women aged **≥85 years**

Prevalence of CNV was higher in **Northern Europe**

After 2006, the numbers of eyes with CNV that were visually impaired decreased **≤P=0.026**

Looking to the future *Number of people with AMD*

AMD Stage	*2013*	*2040*
Early	15.0 million	21.5 million
Late	2.7 million	4.8 million

This Month in Business

Acquisitions, funding rounds, approvals and IP this month

- Alcon posted its Q2 2017 financial report. During this period, net sales were $1.5 billion (vision care and surgical sales rose by 2 and 3 percent, respectively), and the company made an operating loss of $19 million during that time. Parent company, Novartis, reported a net income over the same period of $2 billion (a rise of $0.2 billion over Q2 2016's value), with net sales of $12.2 billion, and an operating income of $2.3 billion.
- Allegro Ophthalmics announced the completion of a private round of equity financing of $10.7 million to help progress the clinical evaluation of its lead compound Luminate (ALG-1001) through Phase II and III trials of the drug in patients with diabetic macular edema or vitreomacular traction.
- Iantech has received investments from two investment funds, Visionary Venture Fund and the Global Health Investment Fund, for the further research, development, and commercialization of their nitinol microfilament-based lens fragmentation technology, miLOOP.
- Hot on the heels of its recent acquisition of Malosa Medical, Beaver-Visitec International announced it has acquired the Dutch ophthalmic technology company Vitreq.
- Spark Therapeutics has received two pieces of good news from the FDA regarding Luxturna (voretigene neparvovec – see page 13). The FDA offices of Orphan Products Development and Pediatric Therapeutics have designated it as a drug for a rare pediatric disease, and the company's application for a biologics license for the product was also recently accepted.
- Alimera Sciences have been given approval by the UK's Medicines and Healthcare Products Regulatory Agency to reduce the size of their post-marketing study of Iluvien. Originally intended to follow 800 patients over 5 years, the company states that their study "has shown consistent positive safety data, leading the company to seek a smaller sample size." To date, 550 patients have been enrolled.
- The FDA rejects Ocular Therapeutix' Dextenza for the second time, citing unresolved problems with manufacturing and quality control testing,
- Despite Verily, Samsung and Sony all filing patent applications that pertain to video cameras and intraocular lenses, it's Strathspey Crown LLC that have received the first US patent issued for this combination of technologies, the company announced.

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

A New Hope

Why certain myopic children should have refractive surgery

By Deepinder K. Dhaliwal, Professor of Ophthalmology at the University of Pittsburgh School of Medicine, PA, USA

Amblyopia therapy might work well for the majority of patients, but there are cases where all conventional options have been tried – and little hope of achieving visual improvements exists. It is in these children that I think there is a role for refractive surgery, and there is some evidence supporting this approach.

Compiled results of PRK and LASIK in patients aged 2–19 years with anisometropic amblyopia are favorable overall in over 200 eyes, with typical gains in best-corrected visual acuity (BCVA) and ~50 percent improvement in binocular fusion and stereopsis observed, with minimal complications (1–7). Favorable visual results have also been achieved in children with bilateral high ametropia, with observed improvements in developmental functions such as communication and socialization (8, 9).

From our pediatric LASIK study, I have seen the benefits of performing refractive surgery in these children firsthand (10). A clear advantage is full-time correction – these patients no longer need contact lenses or spectacles. There are also subjective benefits; we heard from parents that children had increased self-esteem and were happy to no longer need unbalanced myopic spectacles with one very thick lens. One child even said that they could, for the first time, see the stars.

Of course, there are considerations when performing refractive surgery in children. Because anesthetic gases can interfere with excimer laser function (10), patients need to be induced in a separate room or using a laryngeal mask airway to stop gas escaping. There is also the issue of fixation – children under general anesthesia cannot fixate and forceps are needed to keep the iris plane perpendicular to the laser beam. And of course there are risks. High myopia LASIK can lead to ectasia and there are theoretical flap-related issues (although none were seen in our study); with PRK there is worry about haze and regression, and the use of MMC in children can be risky. Children also need steroid drops after PRK surgery, and there can be issues with compliance.

> *"One child even said that they could, for the first time, see the stars."*

Another option for these children are phakic IOLs, which have multiple advantages including reversibility, exchangeability, high visual quality, lack of regression and no risk of ectasia or haze. Posterior chamber phakic IOLs have shown significant improvements in VA and binocular function over five years with no reported complications, but whilst anterior chamber iris-fixated IOLs have shown

promising visual results, complications (including accelerated endothelial cell loss, IOL dislocation and pigment dispersion) have been reported (9, 11–16). Some groups have also discussed pediatric refractive lensectomy (±IOL), but this has shown mixed results in two studies (33 eyes), and has inherent problems of increased risk of retinal detachment and loss of accommodation (17, 18).

To conclude, it is my view that pediatric refractive surgery should be considered in the myopic amblyopic child if conventional therapy has failed and there is no other option, on the provision that proper guidelines are followed, there is great effort to continue amblyopia therapy post-operatively, and ocular health is maintained in the long-term. It is also my view that pediatric refractive surgery is not indicated if the post-operative risks outweigh the benefits, if long-term follow up has not been studied adequately and preliminary data is raising concerns, or if the overall health of the eye might be compromised for short-term benefit. The idea of pediatric refractive surgery might be controversial to some, but we need to offer these children in whom conventional therapies are failing some hope of improvement.

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Adapting for the Future

How adaptive optics imaging can help your patients and the future of gene therapy for retinal diseases

By Judy E. Kim, Professor of Ophthalmology, Department of Ophthalmology & Visual Sciences, Medical College of Wisconsin, Milwaukee, WI, USA

Just as we might want to look closer at one star from the night sky, sometimes we want to see individual cells of the retina – and adaptive optics (AO) imaging technology lets us do this. Many of you reading this will be familiar with the concept of AO; it is a technology that improves the performance of optical systems by reducing the effects of wavefront distortions (that mostly come from the lens and the cornea), allowing resolution fine enough to visualize single photoreceptor, retinal blood vessels, or retinal surface. AO has three important components: a wavefront sensor, a controller and a wavefront corrector, which is usually a deformable mirror that corrects the distortion. The technology can be coupled to available imaging systems, such as fundus cameras or scanning laser ophthalmoscopes (SLO); for example, we are using an AO-confocal SLO system that was built at our institute. But how can AO help patients?

We have been using the technology to study the retina in normal and in disease states. Until recently, only cones could be imaged with AO systems, but scientists at the imaging laboratory of our institute were able to modify the system to show that rods can also be imaged (1). One interesting feature we have seen is that rod and cone reflectance varies over time; the brightness of rods and cones changes throughout the day, almost like they are twinkling (2).

As both rods and cones show similar patterns and durations of "twinkling," it could be related to circadian rhythm or a metabolic cycle, and we are planning to study this further to elucidate how these changes may indicate photoreceptor function. In retinal diseases, such as cone-rod dystrophy, we have observed bright cones as well as areas of darkness. We have also been studying macular telangiectasia (MacTel), and we also see bright and dark cones. The areas of darkness may indicate absence of cells, while dark cones may indicate abnormal or cones that are not waveguiding. Therefore, the location and the number of dark cones, the extent of dark areas, and the variation of cone density from normal could all be useful biomarkers of disease activity and tracking progression in retinal conditions (3).

I have also found AO useful in examining surgical patients because it can show abnormalities that are not visible with optical coherence tomography (OCT). We have imaged a number of patients following successful surgical closure of macular hole (4). Even though OCT shows excellent anatomic restoration in these eyes, we found significant photoreceptor disruption on AO imaging. We also found that the cone mosaic continues to remodel for over one to two years – which may explain why there can be continued improvement and symptoms of metamorphopsia after surgery in these patients.

Retinal imaging with AO is not limited to the photoreceptors (5). We can go deeper into the eye and see retinal pigment epithelium (RPE) cells and study how disease affects the RPE layer; we can also image the retina superficially at the nerve fiber layer, optic nerve and lamina cribrosa. Due to exquisite resolution, we can image blood flow without the use of a fluorescein dye.

We have found that patients with significantly advanced retinal disease with decreased numbers of photoreceptors compared to normal retina can still have 20/20 visual acuity. Therefore, there may be a "disconnect" between the anatomy (e.g. cone health and number) and function (e.g. visual acuity) at times. Given that accurate assessment of the type and the extent of diseased photoreceptors might be pre-requisite to improving the visual outcome following gene therapy in humans, AO could play an important role in helping identify which patients might be the best candidates for gene therapies. It can be used to monitor non-invasively which patients are anatomically responding to treatment before such information can be obtained by any other method. Therefore, the high image resolution capability of AO to help select ideal candidates may make it an excellent research tool for those who are studying gene therapy.

"AO could play an important role in helping identify which patients might be the best candidates for gene therapies."

As wonderful as the AO images are, there are currently issues that prevent wide usage in the clinic. While there is a type of AO fundus camera currently in the market, it is not yet FDA approved. Therefore, in the United States, it is used in a research setting. The type of AO cameras that are being used in the research labs such as ours tend to have higher resolution and can shed more information. However, the imaging time and processing times tend to be quite long at this time. It is hoped that in the future, these deficiencies that prevent use in the clinic can be overcome, allowing the clinicians to be able to fully utilize capabilities of AO imaging.

In summary, functional tests do not tell us everything. AO is a non-invasive imaging technology that can help us detect photoreceptor loss early and may assist us in the future as a biomarker of disease onset and progression. It can help with the selection of ideal candidates for therapies and earlier detection of treatment effect. I believe it will play an important role in the future for assessing the therapeutic potential and outcomes in patients with retinal disorders.

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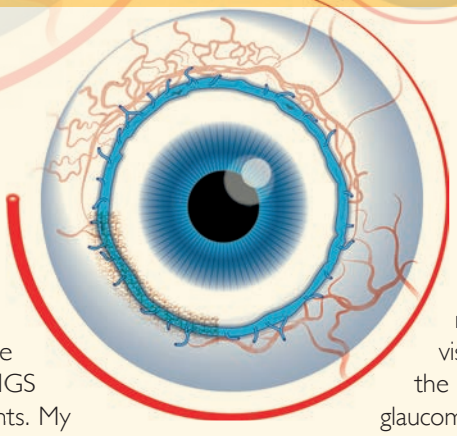
HEIDELBERG ENGINEERING

MIGS: *The ABC of ABiC*

When it comes to MIGS, ABiC's mild touch and manifest efficacy make it a compelling option for many patients

By Mark Gallardo, MD



What are MIGS procedures, and why are they increasing in popularity?

MIGS (micro or minimally invasive glaucoma surgeries) are a group of procedures that reduce IOP and/or medication burden (and associated compliance issues) with a safety profile that exceeds that of older, more aggressive glaucoma filtration procedures. They work by enhancing aqueous filtration through natural outflow systems, whether it's the conventional outflow system or via the suprachoroidal space. We've had experience with some MIGS procedures for close to a decade and found them to be highly effective, low-risk interventions, either when performed during or independently of cataract surgery.

Is it possible to define the ideal MIGS patient?

When performing procedures that manipulate the conventional outflow system, the distal system must remain intact, relatively patent, and amenable to rejuvenation – but we lack the tools necessary to clinically evaluate the functionality of the distal system pre-operatively and must therefore rely on visual cues in the proximal system, such as increased pigmentation of the trabecular meshwork (TM) in regions of increased outflow. However, when significant disease is present in TM, patients benefit from certain MIGS procedures, in particular, trabeculo-ablative interventions, such as a trabeculotomy or goniotomy. Similarly, patients with a sclerosed distal outflow system would benefit from bypassing it altogether with a suprachoroidal shunt.

The point is this: we can now match MIGS procedures to patients. My practice has changed considerably over the last five years following the adoption of MIGS. I once had to perform filters approximately 8–10 times a week, but since MIGS, I have seen a drastic drop: I now perform 1–2 filters a month, in patients where MIGS have failed to achieve target pressures or in those where pressures in the single digits are a must.

In what ways do MIGS procedures fall short of the ideal?

It's perceived that MIGS is not as effective as filtration procedures at reducing IOP. While we may obtain pressures in the single digits with MIGS, most patients with glaucoma (especially those with mild-to-moderate disease) don't require pressures that hover just above hypotony. We do typically obtain pressures in the mid and even low teens – even in patients with pre-operative pressures in the twenties who are already on 3 or 4 eyedrops. This is often sufficient. But if a surgeon opines that single digit pressures are needed to avoid progressive glaucomatous optic neuropathy and vision loss, as is typically the case with end-stage glaucoma, MIGS procedures likely won't offer the desired result.

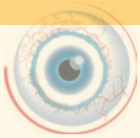
"My practice has changed considerably over the last five years following the adoption of MIGS."

Adopting MIGS procedures does involve a little bit of a learning curve – not only with the individual procedures, but also with performing intra-operative gonioscopy. All angle-based surgeries rely on our direct visualization of the nasal drainage angle, which requires direct gonioscopy. Most of us "cataract surgeons" had little experience using direct gonioscopy lenses during our training, much less manipulating structures of the outflow systems via an ab-interno approach. These small hurdles can be overcome with a little time, practice and patience, which is important given the rapid acceptance and adoption of MIGS devices.

Each MIGS device, when used in the appropriate patient can yield amazing results. The conventional outflow system has pathologic changes along each layer of the system, from the uveal portion of the TM all the way through the scleral plexus. Minimizing treatment to one layer of disease, while leaving other areas of disease untreated may lead to sub-optimal results. However, one procedure can addresses the entire drainage system through transluminal viscodilation – ab interno canaloplasty or ABiC.

How is ABiC an improvement over traditional canaloplasty?

Traditional canaloplasty is an elegant but laborious procedure that can take up to an hour to perform. It requires large conjunctival and scleral dissections, creation of a Descematic window and scleral lake, and placement of a tensioning suture. The extensive dissections also violate conjunctiva. By contrast, ABiC preserves the



conjunctiva and therefore does not preclude performance of any glaucoma procedures, should they be needed. The procedure is also rapid – perhaps less than five minutes – and requires virtually no recovery time.

Despite their differences, there is one very important similarity – efficacy. We once thought that the tensioning suture was paramount to the success of the procedure, but evaluation of three-year canaloplasty data proved otherwise – a subgroup of patients with successful viscodilation of the canal, who were unable to receive a tensioning suture experienced very similar reductions in IOP and medication burden to those who received a tensioning suture (2). With this data, we developed, adopted and evaluated ABiC. I compared the efficacy of ABiC and canaloplasty in a small case series of 12 patients – ABiC in one eye and canaloplasty in the other – and found that the results mirrored each other. We have since performed ABiC in several hundred patients and have anecdotally seen similar results.

One advantage of ABiC over canaloplasty is that ABiC can be performed more easily in patients in whom trabeculectomies and tube shunts have failed. No further conjunctival dissection is required, which can be challenging in patients that have had filters (or other procedures that damage conjunctiva), especially if a large 5 mm scleral flap is needed (as is with canaloplasty).

ABiC is less traumatic to the eye, preserves conjunctiva, decreases surgical and recovery times and recovery is similar to that of an uncomplicated, routine cataract extraction. In stand-alone procedures, patients are within one line of their best, corrected visual acuity on day one and return to their baseline pre-operative visual acuity within one week. It's a relatively comfortable procedure with little to no post-operative discomfort. Furthermore, many patients are able to reduce their medication burden after ABiC, which has the benefit of reducing cost to the patient, and exposure to the caustic chemical, benzalkonium chloride (BAK). This benefits not just the ocular surface but the TM; BAK induces apoptosis to endothelial cells of the cornea and cells lining trabecular columns, which can lead to fusion of adjacent damaged columns and an eventual reduction of the effective filtration area.

Despite all of the positives of ABiC, I still favor canaloplasty in patients with corneal endothelial disease, such as Fuch's endothelial dystrophy. I fear manipulation of devices within the anterior chamber in such patients could lead to further endothelial disease and possible corneal decompensation.

"ABiC is less traumatic to the eye, preserves conjunctiva, decreases surgical and recovery times..."

Compared with other MIGS procedures, what is ABiC's niche?

ABiC does not have to be coupled with cataract extraction. It can be done in phakic and pseudophakic patients or as an adjunct to cataract extraction. It is also not limited to mild-to-moderate disease and could be performed in patients with severe glaucoma (although outcomes may be more variable in such cases). It also treats 360° of the outflow system – and every layer from the uveal TM to the scleral plexus. Circumnavigation of the canal with a the iTrack is the only method that has the ability to lyse all herniations obstructing the collector channels, comprehensively treating the entire conventional outflow system. It is less traumatic and disruptive compared to most MIGS procedures – without ablating the TM or inner wall of Schlemm's canal, ABiC leaves the natural blood-aqueous barrier intact, avoiding the possibility of recurrent hyphema, as seen with some MIGS procedures. It is as effective as any other MIGS procedure; you don't lose efficacy by avoiding stent implantation or tissue ablation, and because all structures are left intact, performing other procedures is not precluded. Also, having done a multitude of procedures, I can say that ABiC is very safe with minimal risk.

How important is the iTrack device to ABiC?

The iTrack catheter's coating allows it to glide easily through the drainage canal. The fiber optic tip allows visualization of the device's location at all times. It's very easy to push a normal device into the suprachoroidal space; by contrast, you can follow iTrack's illuminated tip and direct it accordingly. The catheter is relatively long, so if you encounter a blockage within Schlemm's canal close to the intubation site, you simply circumnavigate in the opposite direction – you'll still get 360° of treatment. Further, the iTrack permits control of viscoelastic infusion. In a canal with many structures, you can infuse more viscoelastic to achieve better dilation; similarly, if you encounter an adhesion, you can bypass it by infusing additional viscoelastic to expand the canal sufficient for catheter advancement. No other device permits procedure parameters to be modulated in this fashion.

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Keeping up with PRECISION MEDICINE

How we're using a specialized next-generation sequencing panel to give ocular cancer patients access to new targeted therapies

Ruth Steer interviews Rajesh C. Rao

Ophthalmology leads the way when it comes to gene therapy and stem cells. But whilst we may be trailblazing in certain fields, in ocular oncology, we're trailing behind. For the most part, the treatment of ocular and orbital (abbreviated as "ocular") tumors have not yet benefitted from many of the emerging and established technologies in oncology and other disciplines to personalize medicine – and there has been no exploitation of cancer-causing genetic and epigenetic changes for diagnostics and treatment. For instance, some types of breast cancers can be treated by epidermal growth factor receptor (EGFR) inhibitors, and patients with certain lung cancers can receive anaplastic lymphoma kinase (ALK) inhibitors. These therapies are based on knowing the gene mutations in oncogenes and tumor suppressors, or copy number alterations (too many or too few copies of tumor promoting or protective genes) that drive the growth of the cancer. An emerging field that has deepened our understanding of how tumors form is epigenetics (See "Epigenetics Explained"). In our context, "epigenetics" refers to modifications to DNA or histones that aberrantly switch genes that promote or protect against cancer on or off, without changing the genetic sequence of DNA. No such epigenetic-based therapies currently exist for ocular cancers because epigenetic regulation of ocular cancers remains poorly understood. We're working to help change that. Here's our story so far...

EXPANDING THE HORIZON WITH EPIGENETICS

When we first started paying attention to epigenetics in 2008, the focus was on histone methylation – the addition of methyl groups to histone tails and how that affects gene expression. Though a "hot" area, no one had really examined it in the developing mammalian retina. So we decided to investigate, and published a paper showing how the histone and methyl marks change during retinal development in the mouse (1). We discovered some interesting trends: a lot of these histone marks were upregulated in the inner retina, and some of the enzymes involved were developmentally regulated. One of these, the histone methyl-transferase EZH2, was expressed only during the growth phase of the retina, and then switched off when the retina was formed. Interestingly EZH2 was emerging as a major target for cancer therapies because it appears to be enriched in cells that grow quickly, such as fetal cells as well as cancer cells.

From studying the developing human retinae, we found that EZH2 was highly expressed in fetal retinae, but not postnatally (2). Because embryonic proteins can be expressed in cancer cells (3), we studied retinoblastoma samples, and found that EZH2 was highly expressed in the tumor cells from this childhood cancer. We also found it to be a good biomarker; immunohistochemistry on these tumor samples for EZH2 was almost a black and white indication of where tumor cells are… and where they are not. Histopathologic detection of EZH2 expression allowed identification of single tumor cells that were invading into the optic nerve or adjacent tissues. Because the decision to use systemic chemotherapy is linked to whether retinoblastoma cells have spread to the optic nerve – and beyond – staining these specific markers could help provide better indications of whether further treatment beyond surgery is actually warranted.

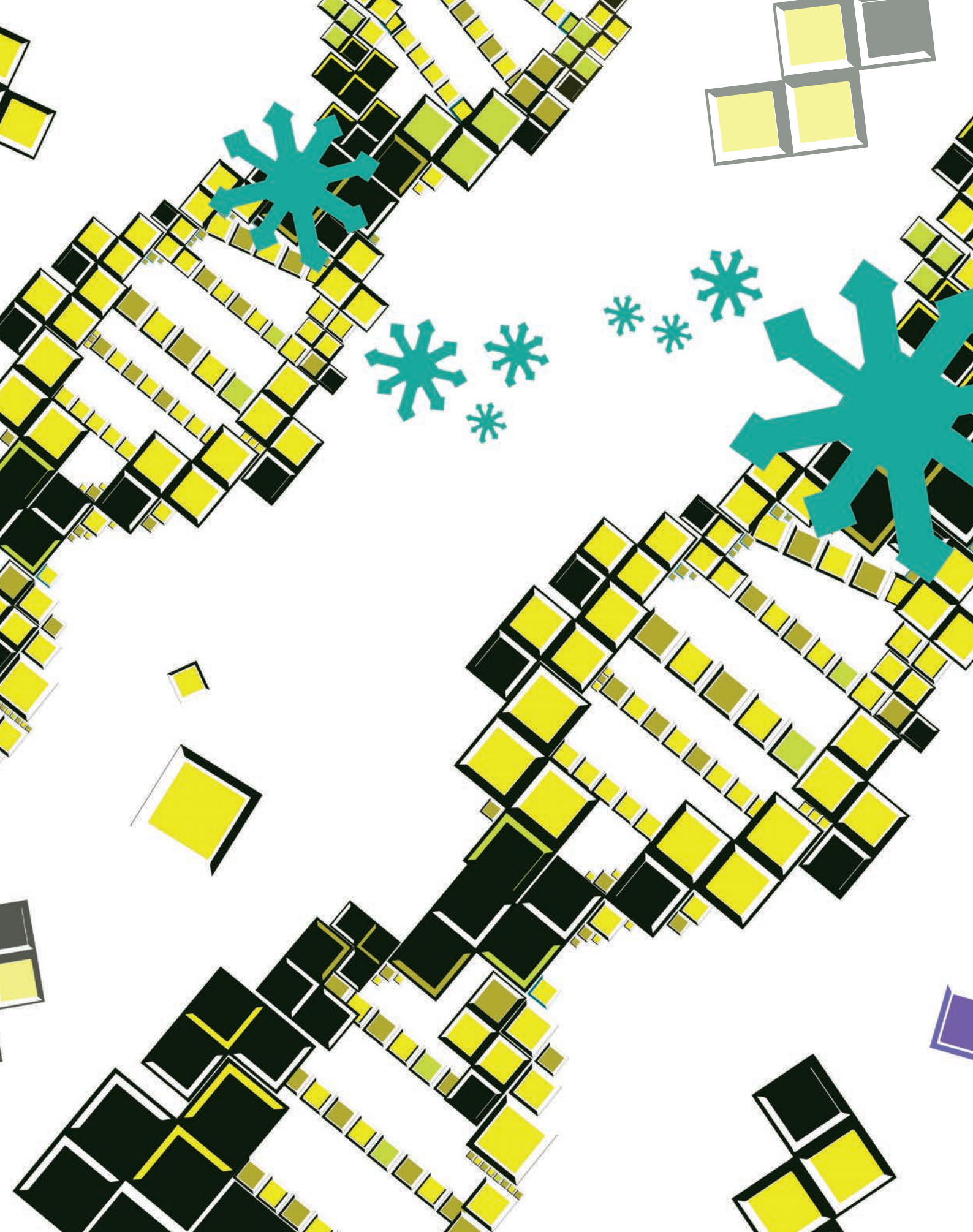
EZH2 was already under scrutiny by several companies, and small molecule inhibitors against it were in trials for other tumor types, such as lymphoma. We tested some of those inhibitors and found that they selectively killed the retinoblastoma cells, sparing the normal retinal cells. This was our entry point and, since then, we've published papers showing high levels of EZH2 in different tumors including vitreoretinal and orbital lymphomas, medulloepithelioma, and basal cell skin cancer, which can occur on the eyelid and the orbit, where it is difficult to treat (4–6). Right now, we are looking at some of the pathways downstream of EZH2, including DNA methylation.

A PRECISE APPROACH

An important part of our studies is to help patients with ocular cancers gain access to more targeted treatments. A close collaborator, Scott Tomlins, helped develop the panel for the National Cancer Institute (NCI) MATCH trial (See "The NCI MATCH Trial"). Together, we've been using the same technology to study eye and orbit tumors. But because ocular cancers are quite rare – there are only about five thousand cases per year in the United States (7) – acquiring tissue for study can be challenging. I use the analogy that studying cancer and human tissues is like studying freshwater; just like most freshwater is "locked up" in ice at the poles, most human tissues are embedded in wax and archived in hospitals and medical centers. But this fixation process and the wax can make downstream research applications more difficult, especially when trying to study the epigenetics. It's why we've had to take a unique approach.

> "WE HAVE HAD TO DIG DEEP INTO OUR ARCHIVES OR COLLABORATE WITH OTHER CENTERS; IN SOME CASES WE ARE ANALYZING SAMPLES THAT ARE 30 YEARS OLD!"

Using a scalpel, we "shave" off sections of samples to collect DNA, which we then put on a next-generation sequencing (NGS) panel (similar to NCI MATCH, see p27) to find mutations, gene alterations or copy number changes in those tumors. The panel is enriched for gene targets for which drugs have already been approved by the FDA (or in trial) for other cancer indications. So far, we've discovered many actionable alterations in genes, including *MYD88, ARID1A, EZH2, PTEN, TP53, HRAS* and *NRAS* (2, 4–6, 8). We've also found that eye lymphomas have a certain "flavor" and abundance



Epigenetics Explained

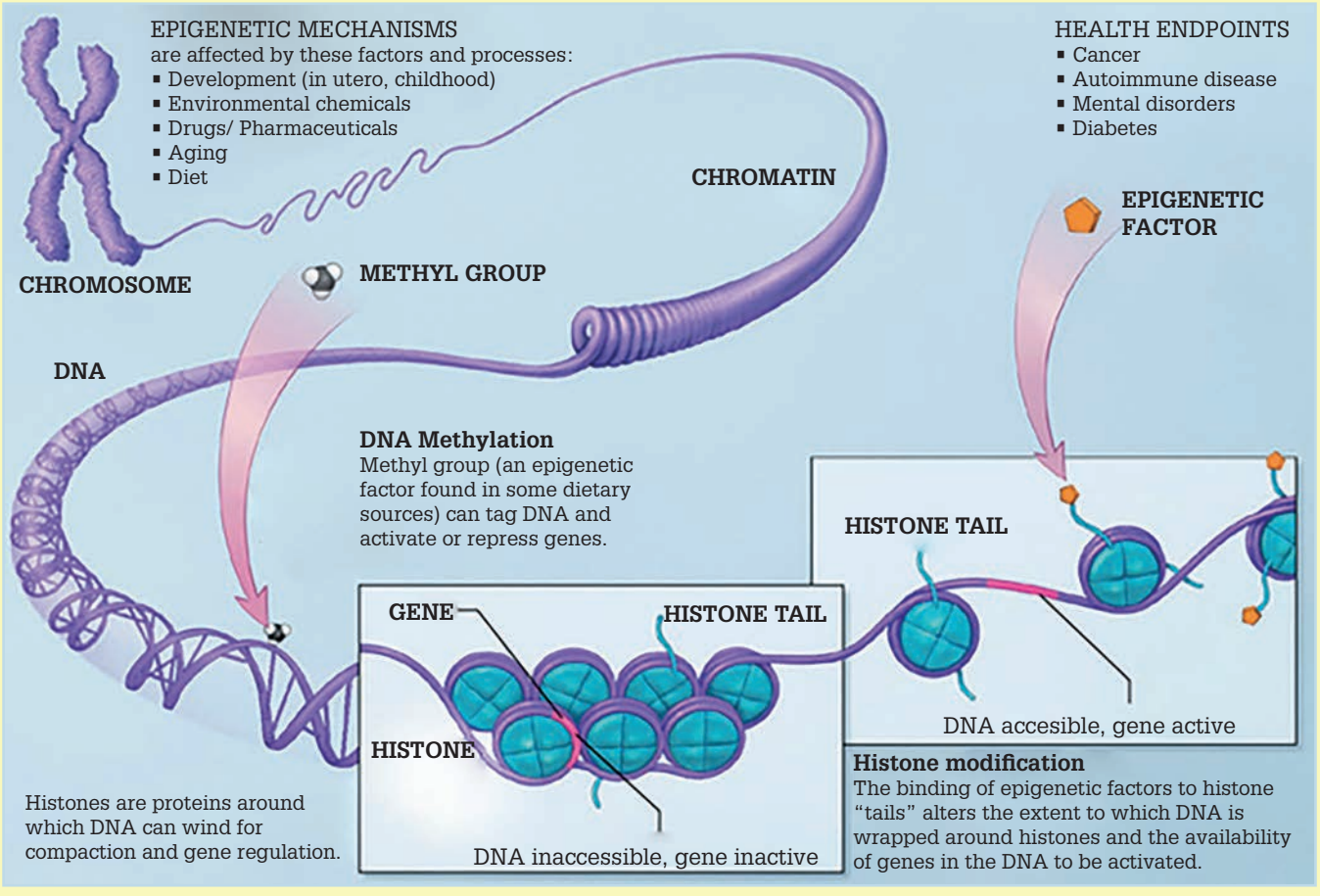


Image credit: The National Cancer Institute.

of mutations that are not present elsewhere; *MYD88* was commonly mutated in orbital marginal zone lymphomas, but uncommonly in marginal zone lymphomas elsewhere in the body (6). As there is already a drug in trial against the mutation we identified, we hope that our orbital lymphoma patients might be attractive candidates.

We're basically looking for the "low hanging fruit" – tumors that haven't yet been sequenced. And with orbit and eye tumors being so much rarer compared with other cancers, we have had to dig deep into our archives or collaborate with other centers to find tumor samples for study; in some cases we are analyzing samples that are 30 years old! But science and sequencing technologies have moved so fast that for relatively

> "OUR INITIAL GOAL IS FOR PATIENTS WITH EYE CANCER TO HAVE THE SAME OPTIONS AND TREATMENTS AS PATIENTS WHO HAVE OTHER CANCERS."

Image credit: The National Cancer Institute.

The NCI-MATCH Trial

The NCI-MATCH Trial (NCT02465060) is an ongoing precision medicine cancer treatment trial (11). In this study, biopsies from patients are analyzed using an NGS-based panel to identify actionable genomic alterations for precision medicine-based treatment strategies. Patients with advanced solid tumors, lymphomas, or myeloma who have progressed on standard treatment for their cancer, or patients with a rare cancer for which there is no standard treatment, are eligible for MATCH. Currently, there are 19 treatment arms open to patients, including genetic changes in *EGFR*, *ALK* and *mTOR* (11). In NCI-MATCH "basket trial," patients can be enrolled in a trial no matter what kind of cancer they have, provided they have the same mutation that the trial drug is targeting. The trial utilizes the Oncomine Comprehensive Panel (OCP) to detect genomic variants in patient samples (12). The OCP was developed from analysis of over 700,000 tumor samples, and combination of genomic alterations with available therapeutics and ongoing clinical trials.

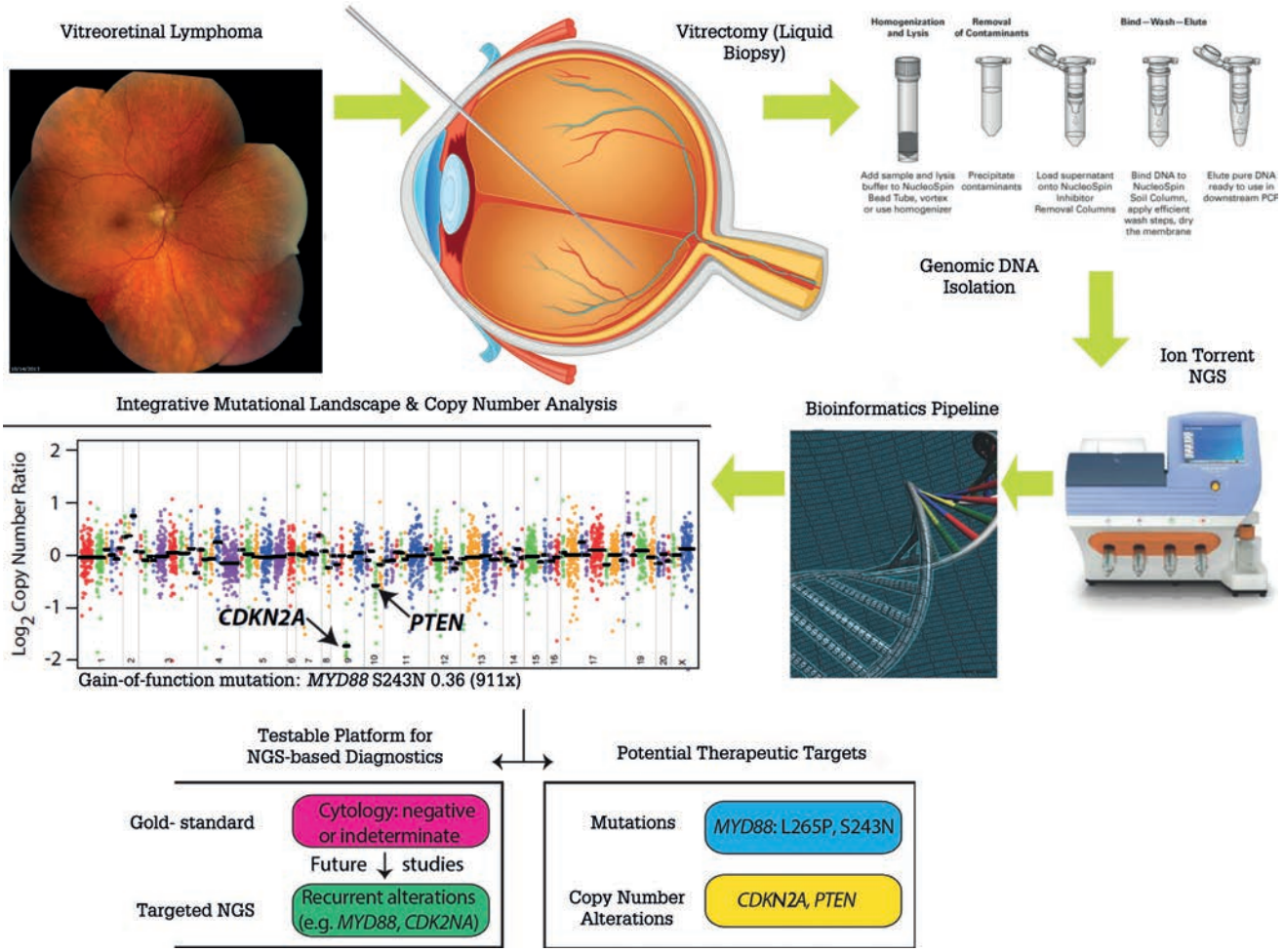


Figure 1. Workflow of determining driver and potentially actionable genomic alterations in vitreoretinal lymphoma. Adapted from (8).

little money we can use small amounts (as little as 5 ng of tumor DNA) of these archived samples – including those that we thought were "locked up in ice" – and still retrieve usable information. Our initial goal is for patients with eye cancer to have the same options and treatments as patients who have other cancers through basket trials (clinical trials that target cancers based only on whether they contain specific genetic alterations, rather than the part of the body they come from). We hope to exploit drugs in our armamentarium that may be more specific than chemotherapy because they target genetic alterations present in the tumor but not in normal tissue. In the future, we want to help other ophthalmologists and ocular oncologists who see patients diagnosed with eye cancer by using these precision medicine strategies to identify diagnostic or druggable targets in their patients' ocular cancers – and thus which clinical trials a patient may be eligible for. And if the drug receives approval, we'll have made an important link in bridging a drug from other types of cancer or diseases to the field of eye cancer, and help our patients access more targeted therapies.

A CALL FOR COLLABORATION

We're also hoping to improve diagnosis. Vitreoretinal lymphoma is rare – there are only around 400 cases per year in the US (9). Because of its link to CNS (brain) lymphoma, it's a deadly disease, with only a quarter of patients surviving more than five years after diagnosis (10). It represents a

Why 'SEXY' NEEDS SUBSTANCE

By Rajesh C. Rao

We all like to hear things in soundbites but, in my view, we should also explain what we mean when we use terms such as epigenetics, stem cells and precision medicine.

I've been in the stem cell field since 1999, and in epigenetics since 2008, and I think the term epigenetics is becoming like 'stem cell' in that it means many different things to different people. Scientists and clinicians have been expressing their concerns about how the term epigenetics can get misused in the media (13) – and we need to be more cautious with it. Why? Epigenetics could essentially mean anything; some of the influences are outside genetics. My concern is that using epigenetics as a 'grab bag' term is not helpful for science, patients or clinicians.

Whenever I talk about epigenetics, I quickly provide context of how I intend to use the term, stating that I am using it to refer to chemical modifications that occur to DNA and histones, and how these changes link to gene expression. Doing so brings me to a relatively focused area, so I can talk about some of the mechanisms driving the changes.

Going back to the stem cell analogy, some clinics state they are using stem cells – but don't truly know if the "stem cells" they purport to use share defining characteristics of these cells such as self-renewal and tissue-specific differentiation (14). And in some cases, these clinics are putting patients in danger; take, for instance, the widely reported case of three female patients in Florida who suffered blindness as a result of an untested "stem cell therapy" (15).

Precision medicine is another grab-bag term. But haven't we always been doing precision medicine? I am a retina specialist, and when I see a patient with macular degeneration or diabetic retinopathy, I routinely take into account their medical history such as whether they smoke and what medications they take, their A1C, and the findings from the retinal exam. One could (truthfully) say, "I'm practicing precision medicine!" – after all, the treatments are being tailored to the patient based on the unique characteristics of their disease. So again, rather than using 'precision medicine' as a grab bag term, I try to contextualize my usage: "By precision medicine, I mean that the patient has particular germline or somatic genetic changes (mutations or copy number alterations) or epigenetic changes (over expression or under expression of specific genes) – and based on those genetic or epigenetic alterations, I can now link the patient's disease to a more tailored diagnosis, treatment, or experimental intervention being tested in a clinical trial."

The bottom line? The moment we start using specialized terms, such as epigenetics, stem cells and precision medicine, we should also define them and include the context of how we are using them to describe our patients or their treatments.

crucial unmet need, not only because there is no standardized treatment – but also because it is very difficult to diagnose. In small volume vitreous samples taken from four patients with confirmed or suspected vitreoretinal lymphoma, we identified alterations in *MYD88, CDKN2A* and *PTEN*, showing that it is feasible to perform targeted NGS on intraocular liquid biopsies (as small as 500 µl or 5 ng of DNA) and identify the presence of tumor-causing mutations or copy number alterations (8) (Figure 1 - see p28).

This approach could potentially enhance vitreoretinal lymphoma diagnosis and influence patient care. For instance, prior vitreous biopsies from one of the study cases had all been read as cytologically negative, with neither eye showing the presence of cancer cells. Two years after initial consultation, the patient presented with vision loss and right hemianopia; he had a brain lymphoma mass that was pressing on his visual centers. When we analyzed his original vitreous samples which had been stored in the freezer when collected two years prior to the brain lymphoma, we found tumor DNA confirming what later showed up in the brain: diffuse large B-cell lymphoma. Vitreoretinal lymphoma can be difficult to diagnose through standard cytology approaches, but because our test is so sensitive, as little as 5 or 6 ng of DNA is needed – which can come from just a few tumor cells in the eye. In the near future, we'd like to develop a diagnostic test that can be used by anybody. We already have the basis for the test, but because our research was only based on four samples – about one percent of all cases in the US – we want to collaborate with others; we need more samples to show that diagnosis using this precision medicine approach could be accurate and beneficial.

MAKING STRIDES FORWARDS

The key take home message is this: the technology we need is there, but to make more progress in the field, different teams need to talk. Just as ophthalmology has led the way in stem cells and gene therapy, we can learn from other fields that are leading in precision medicine, and then apply it to ocular oncology. We can use today's technologies to make powerful advances, to improve both diagnosis and treatment for our patients. Because ocular tumors are so rare, collaboration is really the key – it helps us bring the power of NGS, "big data" bioinformatics, precision medicine and epigenetic technologies to bear on this intractable problem.

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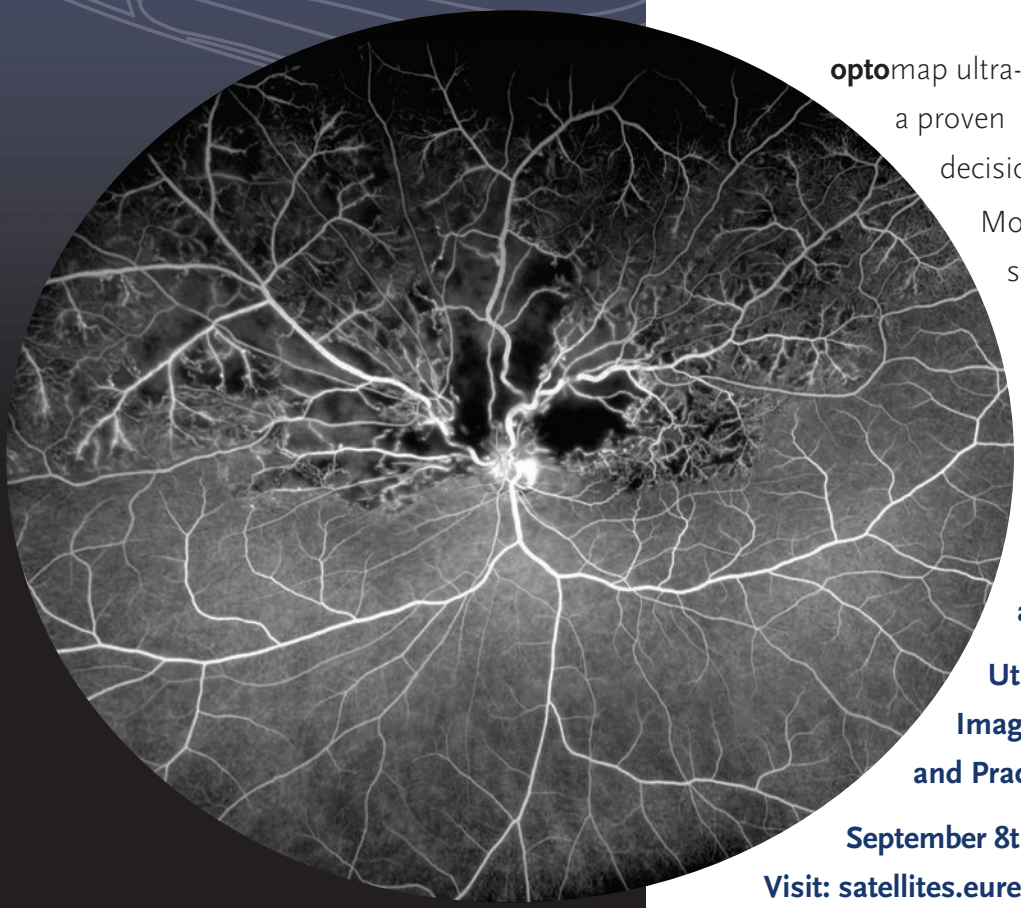

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When MIGS Goes Awry

Using your laser to optimize outcomes and treat complications

By Dan Lindfield

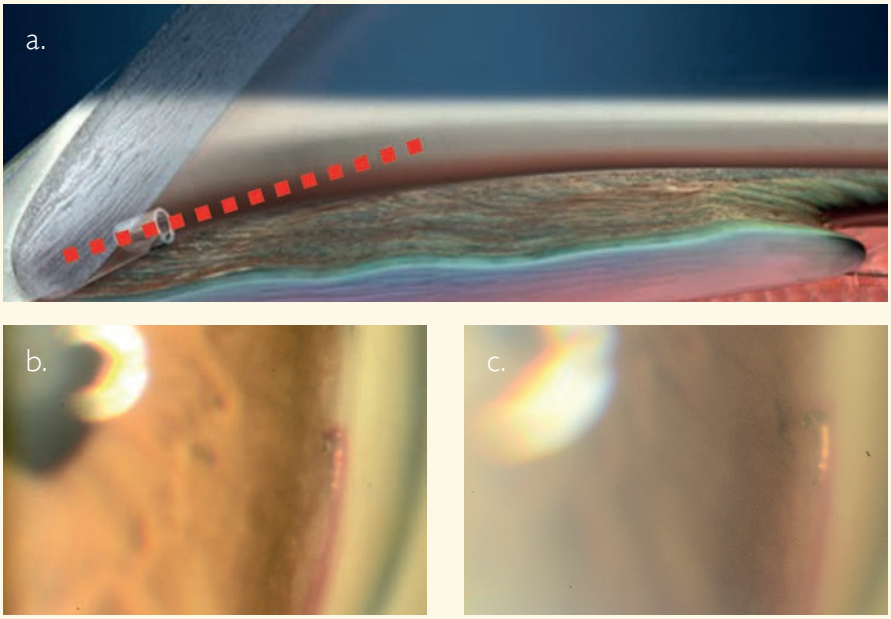

Figure 1. iStent: an illustration of a perfect insertion (a). However, if the angle of the stent's lumen points down toward the iris (b), rather than being perpendicular or upwards toward cornea, this can be a problem. If the lumen points below this plane (red dotted line in (a)) or if the angle is cramped, then there's an increased risk of the iris "surfing" into stent lumen when the flow of aqueous is higher. YAG laser energy can be used to unblock the iStent and ablate some of the iris to stop it from becoming blocked again (c).

The last five years has seen the rise of MIGS – in terms of the "micro invasive" approach, and the devices that go with them. The information that's currently out there (and there's little beyond manufacturer-sponsored studies at the moment) suggests that, relative to interventions like trabeculectomy or tube shunts and valves, it's a relatively safe approach to moderately lower IOP. MIGS, however, is not a panacea. There are other options, such as selective laser trabeculotomy (SLT), to control a patient's IOP that are often worth pursuing first, and it's definitely worth bearing in mind that the MIGS umbrella encompasses many unique devices, with unique implantation techniques, unique learning curves – and also unique issues.

Every ophthalmology department has a laser – and it's more useful than you might think. I want to tell you about how I use YAG and Argon lasers to fix some of the issues that can arise with MIGS devices – and how this can be achieved in the clinic, rather than requiring a return to the operating theater for surgical stent revision.

Optimizing outcomes

There can be a big difference between what you can visualize with pre-operative gonioscopy at the slit lamp and what you can see through a gonio lens during surgery. First, patients can be more mobile on the operating table due to anxiety. Second, and most importantly, it's about optics and lighting. It's easy to get an adequate gonio view at the slit lamp and clearly define the corneal light wedge and Schlemm's canal. Intraoperative microscopy is always coaxial, meaning you can't illuminate obliquely, which makes it harder to identify exactly where you want to place the stent. Normally or heavily pigmented angle structures might be adequately visible under these conditions – but this isn't the case with very pale angle structures. When I come across this during slit lamp gonioscopy, I use an Argon laser to "mark" the meshwork in the nasal quadrant (in three areas usually) meaning I just have to insert my stent on the mark during surgery. Anecdotally, because the region has also been photocoagulated by the laser, it also reduces the hemorrhage that sometimes occurs as the sharp tip of iStent enters the angle.

Treatment complications

Anything with a lumen in the eye can get blocked, and MIGS devices are no exception. Be it blood, fibrous or inflammatory membrane – or even iris tissue – it's important to note that, rather than performing revision surgery, you can use a few shots of a YAG laser to clear the blockages. There are a number of risk factors for stent blockage – and a lot of it comes down to ocular anatomy. Let's take the iStent (Glaukos) as an example (Figure 1). If you're placing an iStent into an eye that's slightly shallow or the angle is not wide open, the iris is, by definition, quite close to the stent. If your patient's iris is a bit high, or for some reason, someone's dilated the pupil, the pupil can plug the lumen of the stent. The iStent lumen can rotate anteriorly or posteriorly whilst still perfectly seated in the canal. If you leave the stent pointing to the cornea it should never block. However, leaving the lumen pointing below the iris plane (or if your stent rotates) results in an increased risk of problems. These risks increase in shallow eyes and eyes with narrow angles – there's simply less margin for error. A recent review of the iStent literature (1) found that the rates of occurrence of malpositioning and occlusion that necessitated surgical intervention (YAG laser, tissue plasminogen activator [tPA], or stent revision) ranged

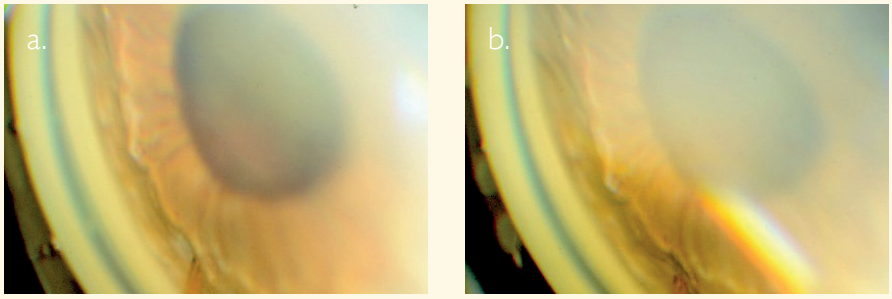

Figure 2. A poorly positioned Xen stent (a) where the flat tip has been blocked, and post-YAG laser treatment (b) – still flat to the iris, but the tip has been cleared, and an "iridoplasty crater" has been created to prevent further blockage.

from 4.5–11.3 percent – and was cited as the most common complication across the studies. But irrespective of whether the iStent has become malpositioned and blocked because of anatomy, poor surgical technique, postoperative movement or plain bad luck, it can be fixed with the YAG laser in just a few shots – in the clinic, rather than the operating theater. After all, prevention is better than cure.

Box 1. Treatment of blocked iStent

- Blood in lumen. Wait, try steroid drops, YAG laser to clear if no response at 2 weeks
- Inflammatory membrane. Wait, steroid drops, tPA injection in anterior chamber at 1 week, YAG laser to clear at 2 weeks
- Iris blockage. Don't wait. Try Pilocarpine - see 1 hours. Argon laser iridoplasty around the tip to contract. YAG laser to clear any remaining strands

It's a similar story with Xen (Allergan): it's a longer stent, and it can go much further into the anterior chamber. Problems can arise with Xen if it's inserted too posteriorly (below the trabecular meshwork, closer to the iris), or even if it's inserted at the correct angle landmark, but the stent extends too far into the anterior chamber – resulting in iris block in the mid-periphery. The emphasis has to be getting this right the first time by using an intraoperative gonio lens to place the Xen rather than the unguided/ "blind" Xen insertion approach some surgeons take. Having said that, if iris block or iris chafing occurs, this can result in persistent uveitis and inflammation, so it needs to be dealt with promptly (Figure 2).

Again, the laser can help. If there's hemorrhage, the best course of action is to use the YAG laser to clear the stent early – it's important to get aqueous flowing early though the Xen. If you wait for the hemorrhage to clear naturally then you risk a situation of no flow down the tube and conjunctival healing/scarring and early bleb failure. It's the same with inflammatory membranes – you really do need early flow to protect the bleb. In essence, the message is: use the laser, don't wait for the medication to work.

So once again, the approaches I take to fix these situations are:

i. Clear any blockage – I use my Optotek YAG laser to quickly clear the stent, and
ii. If the iris is being chafed or snagged, I use an Argon laser to contract the iris out of the way (behind the stent), so there's no longer any contact.

The use of the YAG laser to unblock stents isn't limited to iStent and Xen – the "intracanalicular scaffold" Hydrus (Ivantis) stent has an inlet and three fenestrations that can also be subject to blockage, and can be opened with the YAG laser too.

Glaucoma surgeons are familiar and comfortable with using lasers to lower IOP – and, as you can see, they can serve a double purpose with MIGS stents, and help avoid revision surgery in some cases of blockage or malpositioning. As increasing numbers of cataract surgeons are implanting MIGS devices as part of their offerings, I feel it's important they're aware of the utility of these lasers and what they can do.

Dan Lindfield is a consultant ophthalmic surgeon at Optegra, and glaucoma lead at Royal Surrey County Hospital, England, UK, and reports receiving honoraria and travel support from Allergan applicable to Xen.

Optotek Medical Milestones

- 1991 Optotek founded
- 1996 R&D and production of optoelectronic products
- 1997 First laser systems for dermatology produced
- 1999 First ophthalmic laser systems
- 1999 OEM YAG laser system and Q-Las photodisruptor launched
- 2004 HawkEye portable slit lamp launched
- 2007 Acquired by OptoPol technologies
- 2008 LacriMax, OptoYag, OptoSLT, OptoYAG&SLT launched
- 2009 OptoPol technologies acquired by Canon Inc.
- 2014 OEM YAG laser system and OEM combined laser system launched
- 2015 New LacriMax launched
- 2016 OptoSLT nano launched – the first DPSS laser for SLT

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First Glimpses of Foveal Function

Can a new understanding of the mechanisms underlying the functional specialization of the fovea change our approach to visual disorders?

By Raunak Sinha

Relative to the rest of the retina, the fovea exhibits striking anatomical and structural specializations that not only support spatial and chromatic sensitivity, but also enable maximal visual acuity. So although the fovea subtends only a tiny part of the visual field – about the size of a thumbnail at arm's length – it accounts for approximately half of the information sent to the visual cortex. Given this striking anatomical specialization, should we also expect to find differences between foveal and non-foveal neural cells at the physiological level?

Certainly, the temporal sensitivity – the ability to distinguish changes in visual inputs over time – of foveal circuits is known to be relatively low compared with that of peripheral retinal cells. In fact, foveal temporal sensitivity determines key features of the modern environment, such as celluloid film frame rates and computer monitor refresh rates. Aside from this, we know very little about neural signaling in the fovea; most of our knowledge stems from sparse, decades-old literature. The dearth of data is mainly due to the historical challenges associated with foveal research, not least the technical difficulty of recording intracellular electrical activity in foveal neurons. Moreover, animal models are scarce and expensive, as the fovea is found only in diurnal primates. Only a few labs in the world have worked in this field, and our understanding of neural function in this specialized retinal region remains limited.

At a Glance

- *Foveal signaling and neurophysiological function has long been poorly understood, partly because of long-standing technical challenges; patch clamp electrophysiology and transient gene expression techniques have now permitted the first detailed investigation of how the fovea functions at a cellular and circuit level*
- *Unexpected findings include the observation that perceptual differences in temporal sensitivity between foveal and peripheral vision originate in the first stage of visual processing i.e. phototransduction in the cone photoreceptors*
- *Another striking finding is that the responses of the dominant output neurons in the fovea are minimally modulated by synaptic inhibition, unlike most neural circuits*
- *The study has caused a re-evaluation of foveal function at the cellular and neuronal circuit level and may inform future therapeutic strategies for visual disorders.*

New approaches

To me, the sparse literature on foveal function seemed like an incredible opportunity to explore relatively uncharted territory in visual signaling. I had no background in retinal research – but that was something of an advantage, as I wasn't fully aware of the technical challenges that lay ahead! So I joined Fred Rieke's lab at the University of Washington (UW), and began generating patch-clamp recordings from neurons in the fovea. This technique

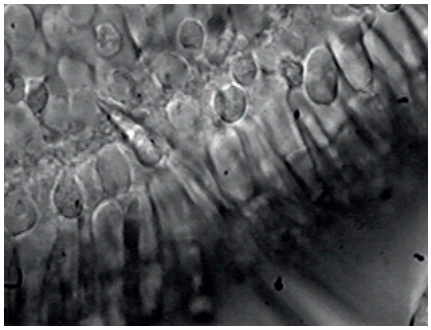


Figure 1. Patch clamp electrophysiology being performed on foveal neurons.

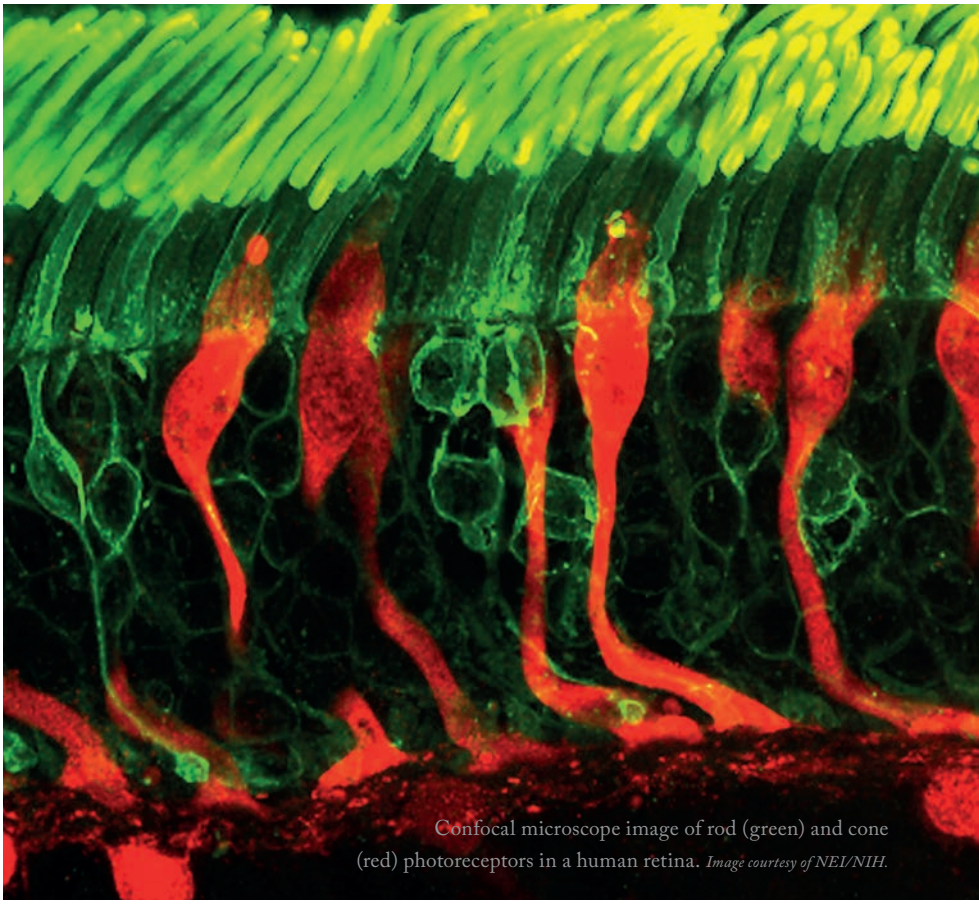
Credit: Rieke Lab: rieke-server.physiol.washington.edu

(Figure 1) allowed me to measure light-induced electrical responses from single output neurons called ganglion cells. I could measure both the output of the foveal neurons and also the inputs they received from upstream neurons, and compare these measurements with those recorded from their counterparts in the peripheral retina. To complement the electrophysiological results with detailed anatomical investigation, we used gene expression techniques, such as particle-mediated gene transfer – not previously used in primate fovea – in collaboration with Mrinalini Hoon from Rachel

"Our study offers the first glimpse into how the fovea works at a cellular and circuit level and has opened up a whole new research field."

Wong's laboratory at UW. This allowed transient expression of proteins in various ganglion cells in the fovea.

In essence, my aim was to understand the physiological basis of the differences between foveal and peripheral vision at the level of perception. It wasn't straightforward but it was exciting. Technical challenges included the development of in vitro approaches that minimized foveal damage while permitting reliable measurement of light-evoked responses in the foveal photoreceptors and in the dominant class of output neurons (midget ganglion cells). We were able to measure responses to a visual stimulus from midget ganglion cells within the range of contrast sensitivities previously reported in in vivo recordings. This enabled us to make direct comparisons of the physiological properties of foveal and peripheral retinal neurons. We reported the first intracellular recordings of light-evoked responses from photoreceptors and ganglion cells in the fovea and the first structure-function correlation in the fovea. Patch-clamp electrophysiological methods were crucial for directly measuring excitatory and inhibitory synaptic inputs to foveal ganglion cells and comparing those with ganglion cell outputs (action potentials). When we commenced this research, the published literature showed a complete lack of intracellular recordings from foveal neurons, so it really was uncharted territory – we didn't know what we would find.



Confocal microscope image of rod (green) and cone (red) photoreceptors in a human retina. *Image courtesy of NEI/NIH.*

New findings

In brief, our work provided the first glimpse into the cellular, synaptic and circuit mechanisms of foveal function, and it turns out to be very different from the operation of non-foveal retina (1).

Firstly, we found that foveal midget ganglion cells expressed fewer inhibitory postsynaptic receptors on their dendrites than their peripheral counterparts. This meant that responses of midget ganglion cells in the fovea are only minimally shaped by synaptic inhibition – very surprising, because integration of excitatory and inhibitory signals is a key feature of most neural circuits in the brain, including peripheral midget ganglion cells. Indeed, a major research theme has been the extent to which the computational specialization of non-foveal retinal circuits relies on signals from inhibitory retinal neurons (2). For us to show that the responses of foveal ganglion cells are not significantly modulated by either pre- or post-synaptic inhibition, therefore, was most unexpected. Effectively, these cells participate in a neural circuit that operates independently of synaptic inhibition, which is extremely unusual.

Secondly, and contrary to our expectations, we showed that the different temporal sensitivities of the fovea and peripheral retina did not arise from differences in synaptic inhibition. Rather, they originated in the cone photoreceptors. Foveal cones exhibit response profiles two-fold slower than those in peripheral retina, which is nearly identical to the difference in perceptual sensitivity observed between the foveal and peripheral vision. Thus, lower levels of synaptic inhibition do not seem to be behind the lower temporal sensitivity of the fovea. Instead, it seems that the "frame-rate" capacity of our visual system is set by the very first neurons in the visual pathway.

So, to recap, there were several surprises in this study. We revealed a key difference between foveal and peripheral midget ganglion cells in terms of synaptic

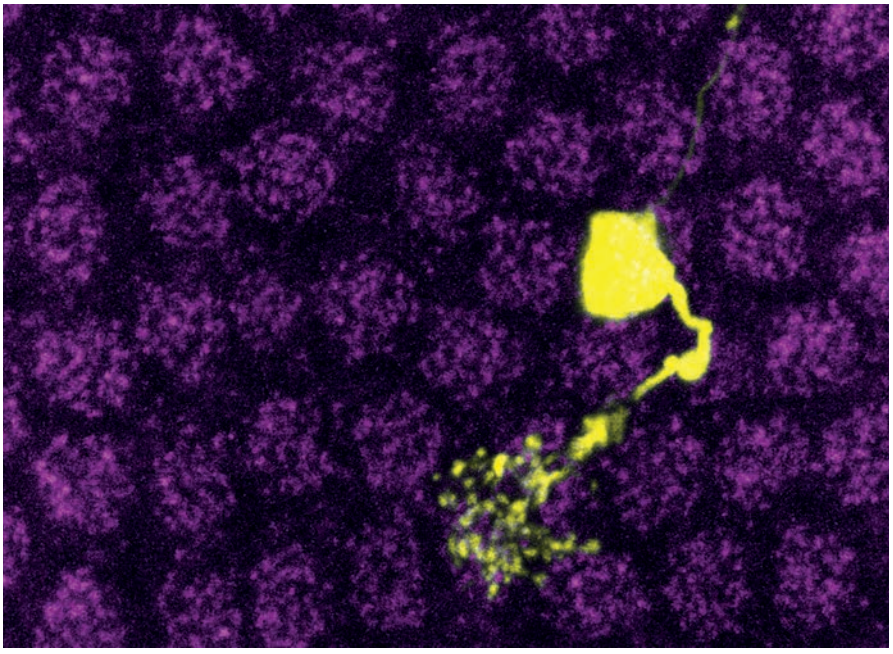


Image of a midget ganglion cell (yellow), the dominant retinal output neuron in the fovea, overlaid on an image of the cone photoreceptor array (magenta) in the fovea. *Image courtesy of Mrinalini Hoon*

inhibition; the minimal role of synaptic inhibition in the foveal midget ganglion cells was completely unforeseen, given the importance of balanced excitation and inhibition for the operation of most other neural circuits in the brain. Additionally, we found that differences in temporal sensitivity between the two retinal regions may originate in the cones within the phototransduction cascade. The differences provide a simple explanation for the observation that foveal vision is less sensitive to rapidly varying light inputs than peripheral vision, and has significantly changed our understanding of foveal function. Previous models of visual function assumed that differences between foveal and peripheral vision originated in the neural circuits that received input from cone photoreceptors. The heterogeneity of cone responses that we observed means that we must re-evaluate old models – and the conclusions drawn from them.

Our work clearly illustrates that the fovea is not only structurally specialized, but also employs different computational strategies compared to peripheral retina. This distinction is also important when considering how visual computations are partitioned between the retina and higher visual centers. In sum, our findings have revised our understanding of how the fovea operates at a cellular and circuit level.

New horizons

Our study offers the first glimpse into how the fovea works at a cellular and circuit level and has opened up a whole new research field. The novel application of gene transfer approaches that we've described may permit a wide range of transient genetic manipulations that will allow us to understand the properties of other cell types in the fovea. And that will enable us to fill the void in our knowledge of this crucial component of the human eye. Indeed, given the distinct functional properties of foveal neurons we have revealed, the lack of significant functional data on foveal circuits, and the implications for the division of computational labor between retina and cortex, our work should be of broad interest to scientists studying visual signal processing. I am certainly pursuing this unique opportunity to unravel the mechanistic basis of other aspects of foveal vision!

The data we present also have implications beyond the theoretical. For conditions involving central vision loss, current therapeutic strategies – including the design of visual prosthetics – are based on studies in peripheral retina, or in retinas from model systems that lack a fovea. The underlying assumption has been that the fovea is a scaled-down version of the peripheral retina, but our study shows that the computational architecture and visual processing mechanisms of the fovea are dramatically different from non-foveal retina. Our new understanding may assist strategies to alleviate important visual deficits, such as macular degeneration.

After a Physiology degree at the University of Calcutta, Raunak Sinha worked at the Tata Institute of Fundamental Research in Mumbai before undertaking his PhD at the International Max Planck Research School in Göttingen, in the Department of Membrane Biophysics at the Max-Planck Institute for Biophysical Chemistry headed by Nobel Laureate Erwin Neher. His doctoral thesis was awarded the Otto Hahn medal. Raunak works in Fred Rieke's laboratory at the Howard Hughes Institute, Seattle, WA, USA.

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Benchmarking Retinal Detachment

What does analysis of the last five years of the retinal detachment literature tell us about the priorities of the field and the major contributors to it?

By Mark Hillen

Retinal detachment has many causes, from trauma to pathological myopia to complications arising from cataract surgery. It affects between 0.6–1.8 people per 10,000 per year (1) – and about three in every thousand people will experience retinal detachment at one point in their life (2). Treatment options vary by the type and location of the detachment, but include cryopexy and laser photocoagulation, scleral buckling, pneumatic retinopexy and pars plana vitrectomy.

However, the field advances; from smaller gauge vitrectomy needles to smarter approaches to scleral buckling. To provide insight into the past and predictions for the future of the field, a series of metrics were applied to the last five years of published literature. We asked:

- What are the major topics for the field?
- Which publications have the greatest impact?
- How is the knowledge available online?
- Who are the most prolific authors?

PubMed was searched for "cone dystrophy", with results limited to the last five years in humans (for a clinical focus). The data were analyzed in Microsoft Excel 2013.

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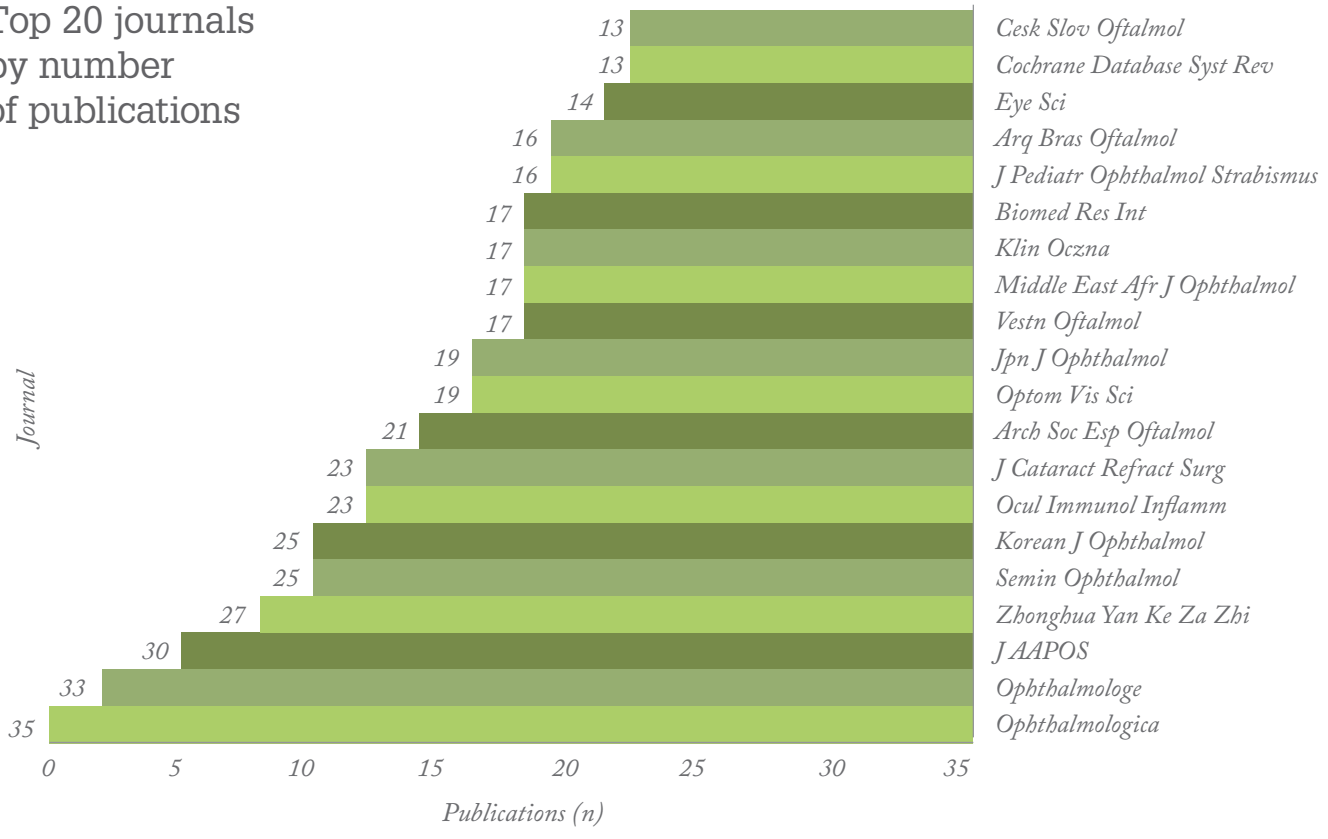
Top 20 journals by number of publications



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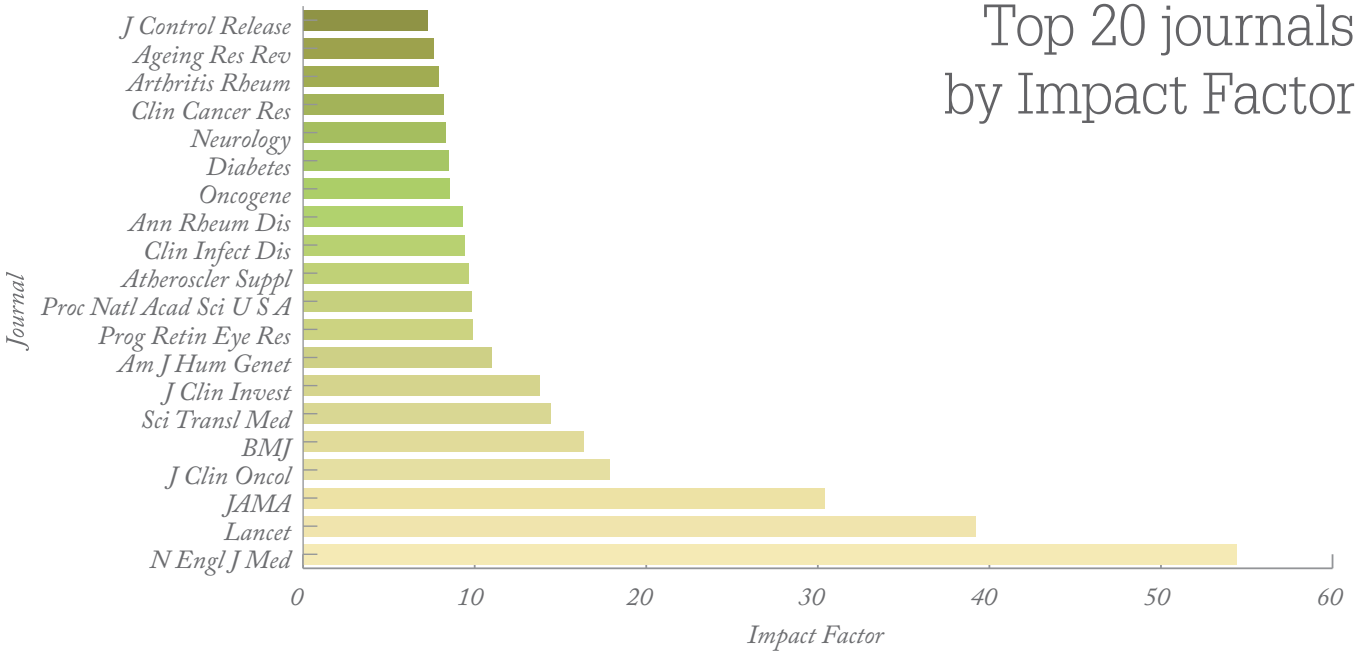

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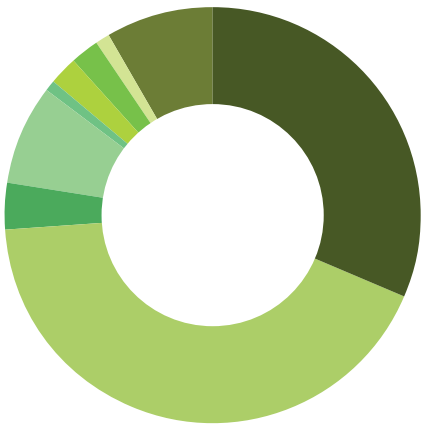

1% Other
1% Meta-Analysis
2.2% Multicenter Study
2.3% Observational Study
3.6% Clinical Trial
7.8% Comparative Study
8.2% Review
31.5% Case Report
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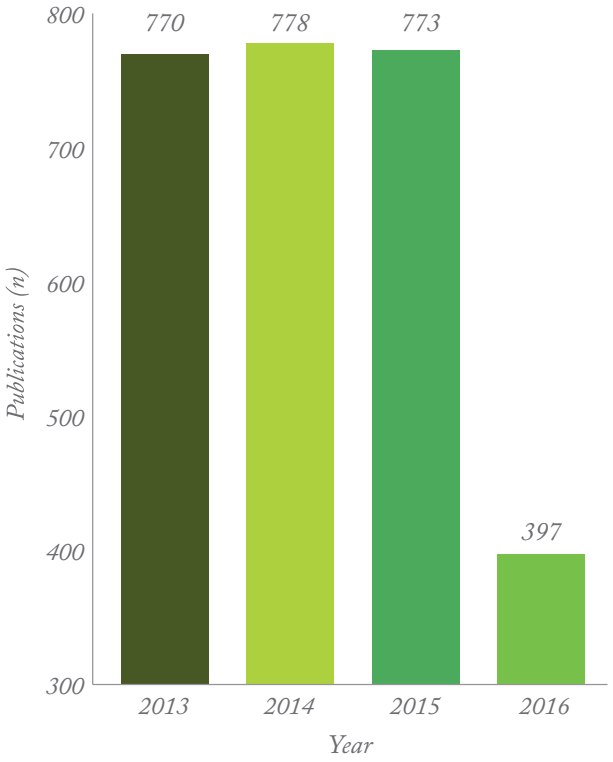

Important words

1	Detachment	2,803
2	Retinal	2,803
3	Acuity	1,418
4	Vitrectomy	990
5	Macular	943
6	Coherence	915
7	OCT	615
8	Rhegmatogenous	477
9	Subretinal	425
10	Intravitreal	407
11	Plana	404
12	Vitreoretinal	328
13	Vitreoretinopathy	249
14	Epiretinal	227
15	LogMAR	203
16	Bevacizumab	155
17	Tractional	118
18	Vitreomacular	115
19	Iris	82
20	23-gauge	76

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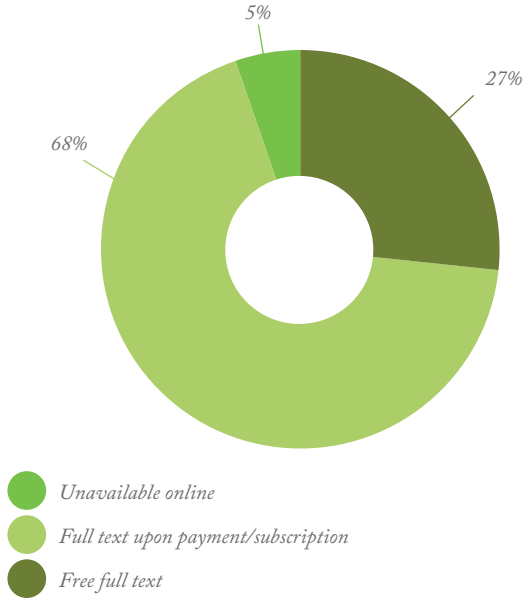
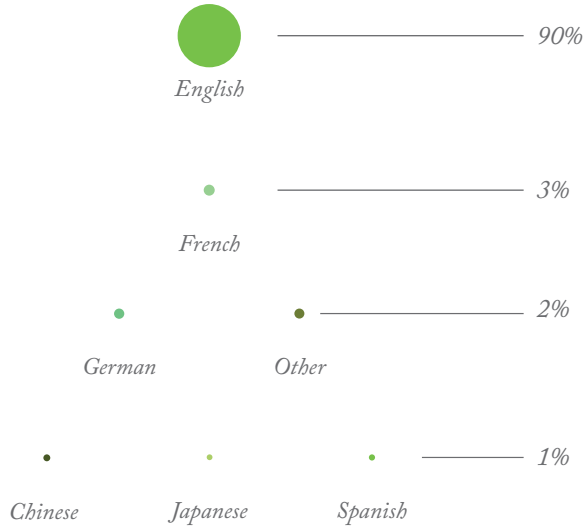


Language of publications



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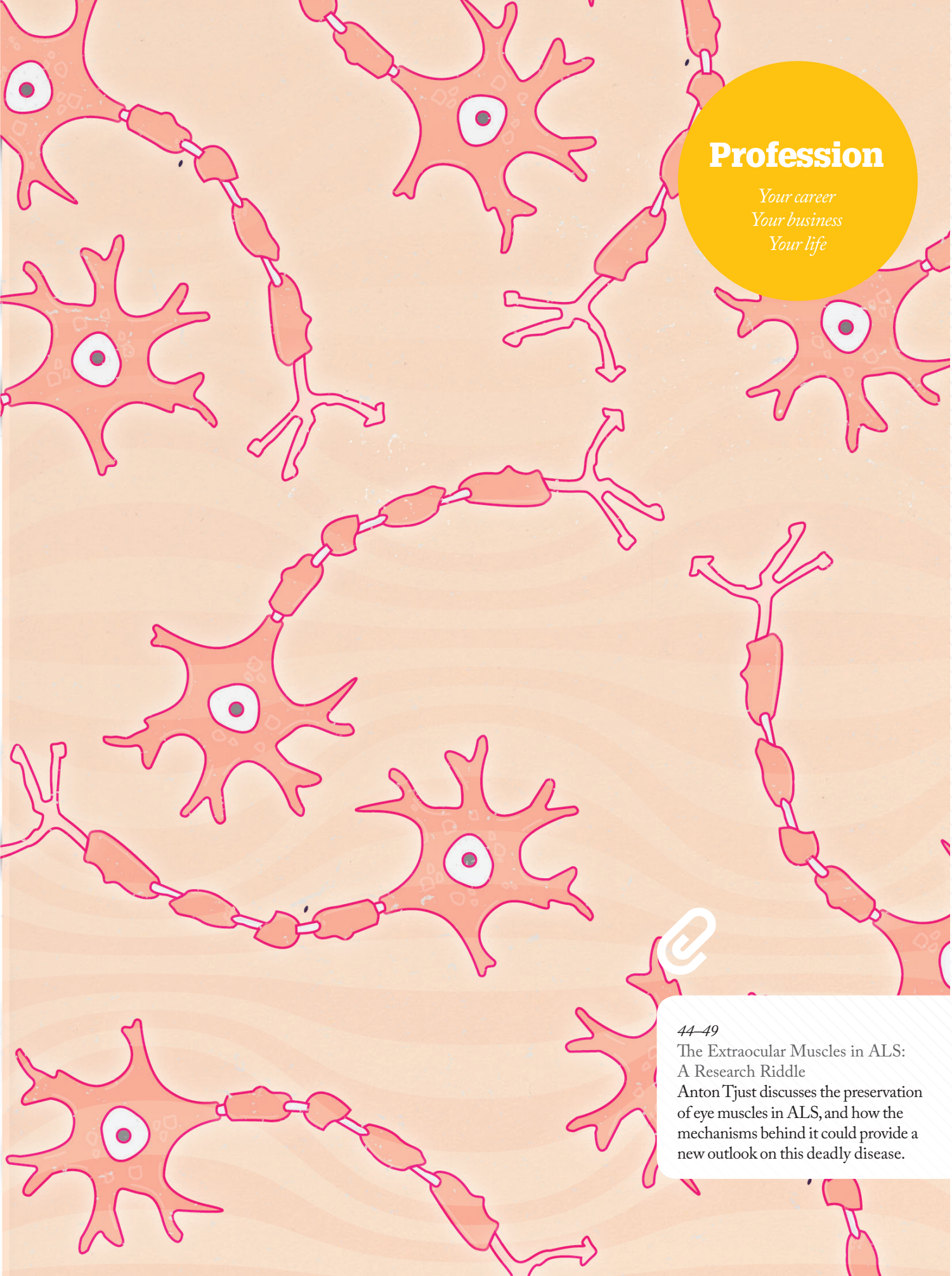

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The Extraocular Muscles in ALS: A Research Riddle

Could the preservation of the eye muscles in ALS provide a new outlook on a deadly disease?

By Anton Tjust

Amyotrophic lateral sclerosis (ALS) is a devastating condition. An incurable neurodegenerative disease, it is characterized by a progressive loss of upper and lower motor neurons, leading to complete paralysis and eventually death through respiratory failure, usually within three to five years of symptom onset. Currently, the only treatment available is riluzole, but this drug only extends the lifespan of ALS patients by an average of two to three months.

Clinically, the disease can present itself with intriguing variability. It may manifest at any age, but often occurs in people who are middle-aged or older. Subsequent survival is also variable, with some patients surviving under a year, and a small proportion living for decades. When the patient experiences the first symptoms, they are mostly restricted to a single extremity – for example, the right hand. The disease most commonly presents itself distally with a mixture of upper and lower motor symptoms, such as weakness and loss of dexterity. This is later followed by a progression into more proximal muscles, appearance of the same symptoms in the ipsilateral leg, and eventually, involvement of all voluntary muscles in the body. In about 25 percent of the cases, the disease manifests in the bulbar region, first affecting muscles of articulation and mastication. Another variable trait in ALS is the degree of cognitive involvement. Some patients retain all of their premorbid personality and functions, and some patients develop an outright frontotemporal lobe dementia.

ALS and the eye

Despite the various ways in which ALS can present itself, nearly all ALS patients have one thing in common: you don't encounter them in the ophthalmologist's office. With some notable exceptions (1), the extraocular muscles are seemingly preserved in most ALS patients, even until the terminal stage. Notably, eye movements and blinking are usually the last modes of communication available to terminal ALS patients (2). But why?

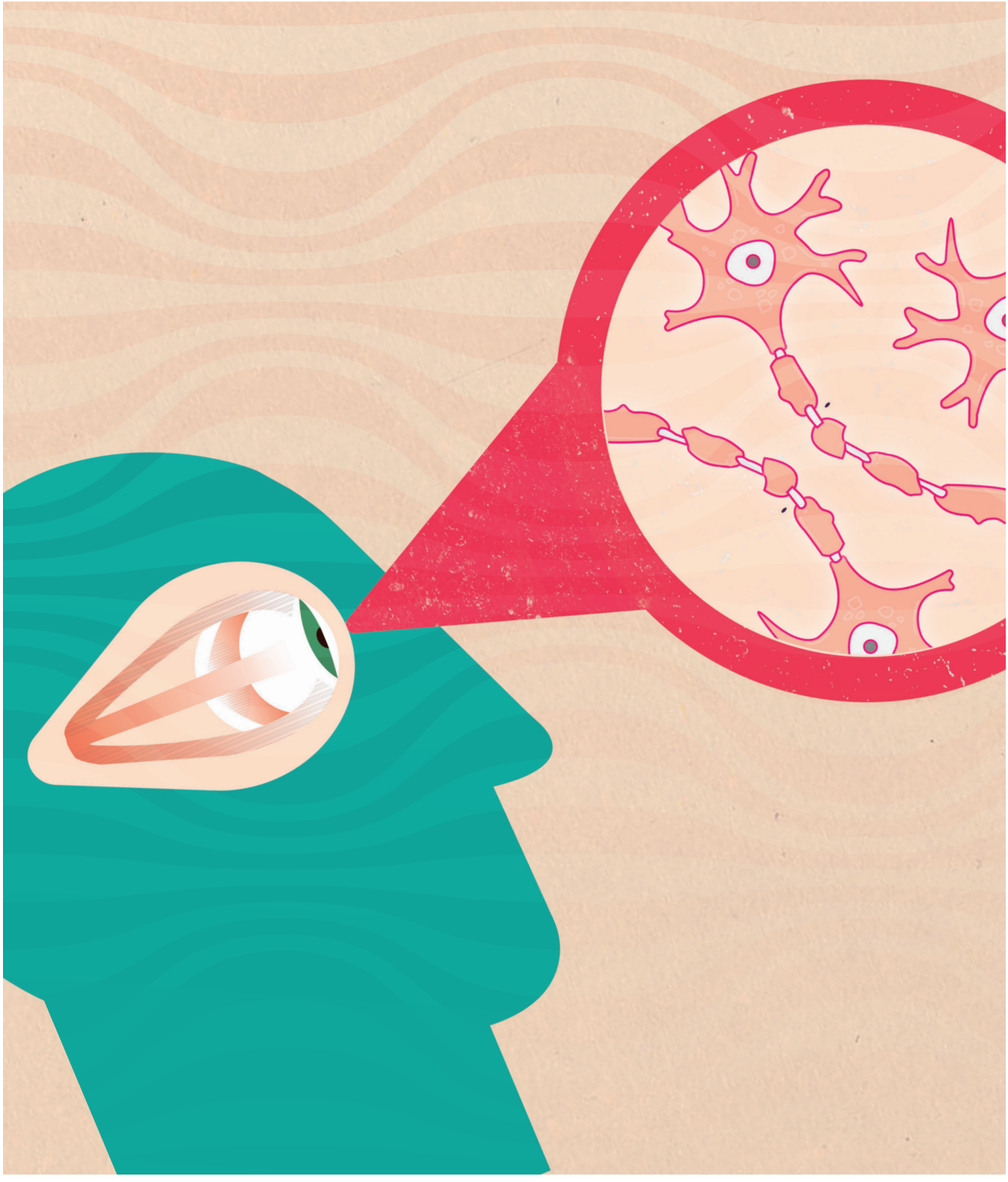
"Nearly all ALS patients have one thing in common: you don't encounter them in the ophthalmologist's office."

That simple question presents an area of study with huge potential; understanding the underlying mechanisms for eye motility sparing in ALS could provide new insights into how the progress of ALS could be slowed down in more vulnerable muscles.

From an evolutionary perspective, extraocular muscles and their motor neurons are ancient companions that pre-date the advent of terrestrial life on Earth. Extraocular muscles are present and innervated according to a principally similar system in lampreys, whose ancestors (Cambrian cyclostomes) diverted from what would evolve into jawed fish (gnathostomata) between 460 and 535 million years ago. This implies that extraocular muscles are at least that old. The muscles of the trunk, gills and fins of Cambrian fish have since evolved into muscles of terrestrial locomotion, anti-gravity balance, breathing and grasping, but the extraocular muscles still serve (though with greater performance) the same basic function of orienting the gaze, just as they did half a billion years ago.

Exploring the mysteries of eye motility

In my recent doctoral thesis, I explored the sparing of eye motility, using histological studies of the extraocular muscles of ALS patients and the most commonly used mouse model for ALS. Although ALS is a motor neuron disease and therefore frequently studied from the perspective of the central nervous system, skeletal muscles are also important players in its progression. During embryonic development and after the initial establishment of the neuromuscular junction – the specialized synapse that forms between muscle fibers and motor neuron axons – muscle fibers provide the innervating motor neuron with neurotrophic factors, such as glial cell-derived neurotrophic factor (GDNF). The neurotrophic factors are retrogradely transported along the axon back to the nerve cell body in the central nervous system, promoting neuronal survival signaling. The relationship between muscle fibers and motor neurons is critical during embryonic development, where 30–50 percent of all motor neurons projecting to muscles in the limbs and trunk are lost to apoptosis in favor of those motor neurons that are more successful in establishing contact with many muscle fibers. In contrast,



Asking the Right Questions

The relative resistance of extraocular muscles in the context of ALS, when viewed on its own, seems like a pathophysiological oddity. But if we take a broader view of the numerous degenerative diseases being studied across different areas of medical research, a very different picture emerges.

In different neurodegenerative diseases, monogenetic, dominantly inherited sub-forms of diseases have been identified, where a seemingly ubiquitous (or near-ubiquitous) gene product mysteriously exerts its pathogenic effect mainly on a specific type of cell. For example, whereas hexokinase 1, an enzyme responsible for the phosphorylation of glucose, is present in most tissues in the body, specific mutations in the gene that codes for it can lead either to a dominantly inherited retinitis pigmentosa or, in the case of another missense mutation, a recessive form of Charcot-Marie-Tooth disease. Mutations in the gene coding for superoxide dismutase 1 are responsible for approximately six percent of ALS cases. But despite the pancellular ubiquitous nature of this enzyme (with the highest concentrations actually found in the liver), the mutated form of the protein seems to primarily affect motor neurons in the CNS.

Again, in retinal disease, mutations in the gene coding for bestrophin-1 leads to vitelliform macular dystrophy, a progressive retinal disease that mostly spares the rods. Interestingly, bestrophin-1 seems to be important in chloride ion shuttling in different types of epithelia throughout the body (such as in the airways and colon), not just in the retina. Apparently, in the complex constellation of genes and proteins that sustain our cells, certain cellular processes have become more robust and tolerant to flaws in some cell types than in others.

It is reasonable to look at any disease based on how the patient presents him or herself and ask yourself: "What is wrong with organ X in patient Y?" However, as researchers and physicians, we are looking for solutions to problems. Sometimes we should look for answers from the other end of the tube and ask ourselves, "If this cellular problem is so ubiquitous in my patient, what are cells X and Y doing right that cell Z is doing wrong?"

muscle fibers in the extraocular muscles appear to provide maturing motor neurons with more generous amounts of neurotrophic factors, and therefore a much larger proportion of motor neurons escape apoptosis – a fact that also explains the exceptionally small motor unit sizes (the relationship between the number of muscle fibers controlled by a single neuron) present in the extraocular muscles.

Studies have shown that deterioration of the contact between muscle fibers and motor neurons, starting at the so-called neuromuscular junction, is an early manifestation of ALS that precedes the actual loss of motor neurons. Therefore, adaptions and maladaptions that take place at the level of the neuromuscular junction could play a large role in the progression of ALS. A good example of this is the observation that when GDNF is overexpressed in the muscles of ALS animal models, it leads to a prolonged survival of the animals, whereas overexpression in glial cells located much closer to the motor neurons in the spinal cord has no such effect. Further examples of this relationship between muscle fibers and motor neurons are conditional knockout mice where ablation of satellite cells, resident stem cells of muscle tissue, leads to impairment in the re-establishment of neuromuscular junction following nerve injury (3).

"We asked ourselves – what role might satellite cells play in the resilience of extraocular muscles?"

Satellite studies

Satellite cells are present in all muscles of the body, and are normally in a resting state. In response to training or injury, they can become activated, causing them to proliferate and generate new myonuclei for growing and regenerating muscle fibers. Satellite cells in extraocular muscles differ from other satellite cells in several regards. Compared with other satellite cells, they maintain a heightened expression of several developmental transcription factors and have been shown to proliferate and produce new myonuclei more efficiently than limb muscle satellite cells when engrafted into muscle tissue. It has also been proposed that they are more abundant, and in a more continuous state of activation, when compared with satellite cells in

limb muscles (4). Interestingly, in vitro studies involving satellite cells from limb muscle biopsies of ALS patients and satellite cells from the most commonly used mouse model for ALS have shown that their growth performance in vitro is impaired compared to satellite cells derived from unaffected patients. Could satellite cells in limb muscles become worn out in a protracted disease course?

In our research group, we asked ourselves – what role might satellite cells play in the resilience of extraocular muscles to ALS? Our results (both published and as of yet unpublished) (5, 6) suggest that the previously reported abundance and continuous activation of satellite cells in extraocular muscles might have been overstated, and that only a small portion of the extraocular muscle, close to the tendon, maintains an increased pool of satellite cells. We found that the majority of the muscle belly contains generally low numbers of satellite cells, and the majority of them are not in an active state. Further analysis of extraocular muscles from ALS patients revealed similar results. Analysis of limb muscles revealed more dynamic changes, with varying numbers of satellite cells in limb muscles of different ALS patients. Importantly, however, satellite cell numbers in ALS patients typically varied between normal and high levels compared with normal elderly sedentary individuals and did not appear to wear out or decrease in numbers during a protracted disease course (Figure 1). Rather, those muscle fibers in the most severely affected limbs that still retained contact with a motor neuron tended to increase in size together with an increase in the number of satellite cells and myonuclei associated with them. Therefore, it seems that satellite cells, while possibly affected at a level that can be demonstrated in culture conditions, are able to perform well enough in their native niche

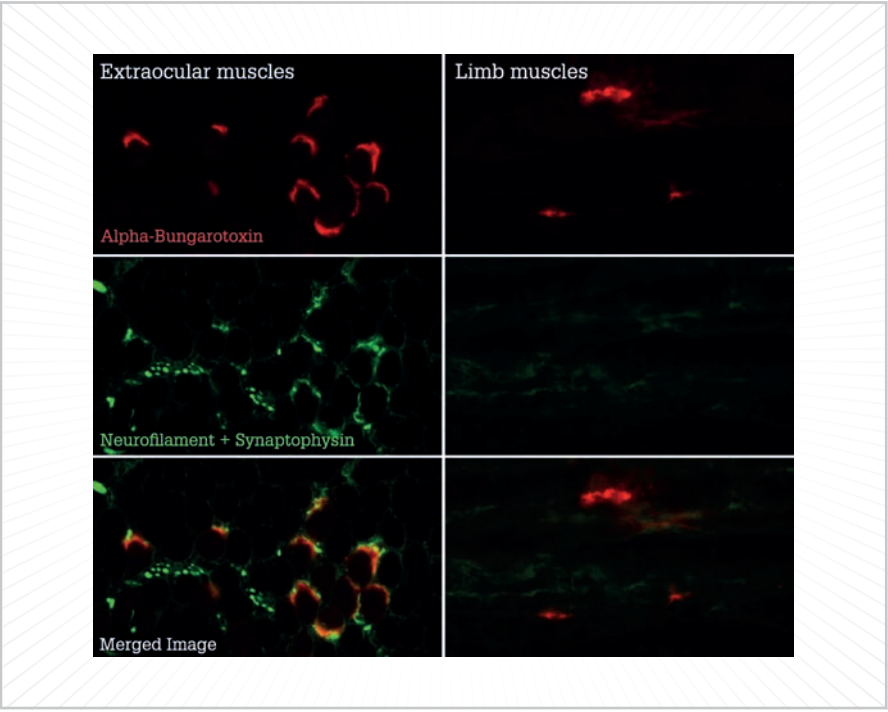


Figure 1. Fluorescence images of neuromuscular synapses, in one extraocular muscle (left column) and one limb muscle (right column) in an ALS mouse model. The contact between motor axon (green) and motor endplate (red) is retained in extraocular muscles (bottom left), whereas the contact is broken and disappears in limb muscles as the disease progresses (bottom right).

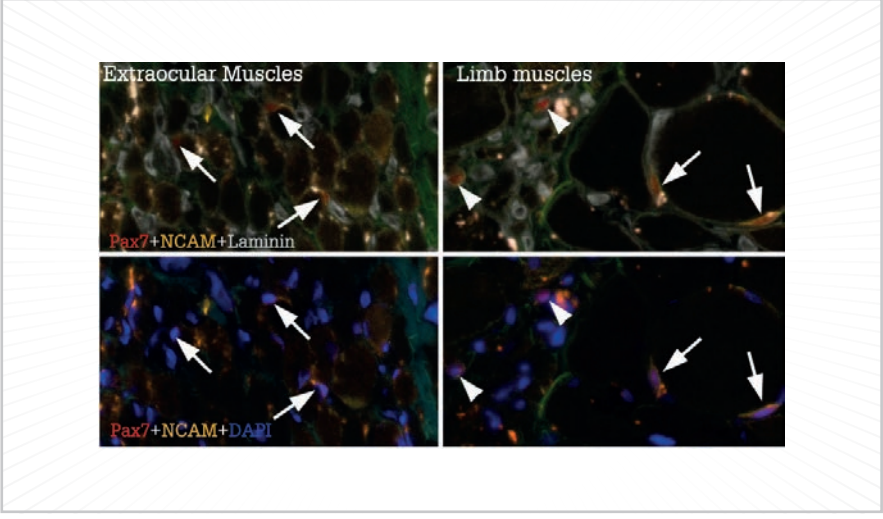
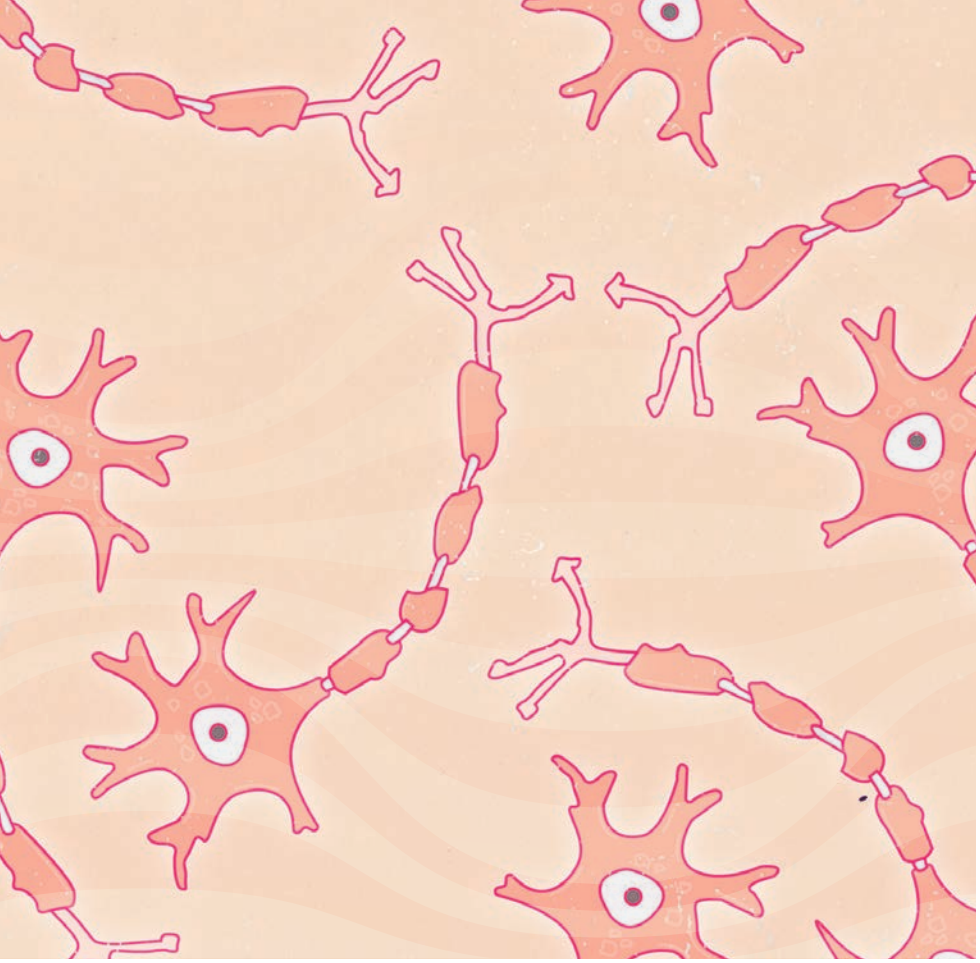


Figure 2. Fluorescence images of a cross-sectioned extraocular muscle (left column) and a cross-sectioned limb muscle (right column) from an ALS patient. Satellite cells (white arrows) and other myogenic stem cells (white arrowheads), are identified by their molecular markers Pax7 (red) and NCAM (yellow) and presented in relation to cellular membranes (grey – top row) and to cell nuclei (blue – bottom row). It seems that satellite cells are still present in both extraocular muscles and limb muscles at the very terminal stage of the disease.



"We believe that eye motility is maintained because of compensatory mechanisms elicited by specific fiber types."

within the muscle. By extension, the distinguishing traits of satellite cells in extraocular muscles does not appear to be a key element in the sparing of eye motility in ALS.

Making connections

In both the animal model (Figure 2) and in ALS patients, there is a maintained presence of terminal axons at the muscle fiber endplate, in contrast to limb muscles, where large portions of the muscle fibers lose axonal contact (7, 8). Loss of axonal contact is an early manifestation of ALS, which suggests that the protective mechanisms present in the extraocular muscles are influencing disease progression at a relatively early stage. However, my preliminary, unpublished data suggest that not all fiber types in the extraocular muscles are preserved. Slow-type muscle fibers, which in the extraocular muscles are innervated at several points along the length of the fiber rather than at a single point in the middle (as is usual for muscle fibers) appear to be affected by ALS, decreasing in size and proportion in terminal patients. We believe that eye motility is maintained not because of a general sparing of all fiber types in the extraocular muscles, but rather because

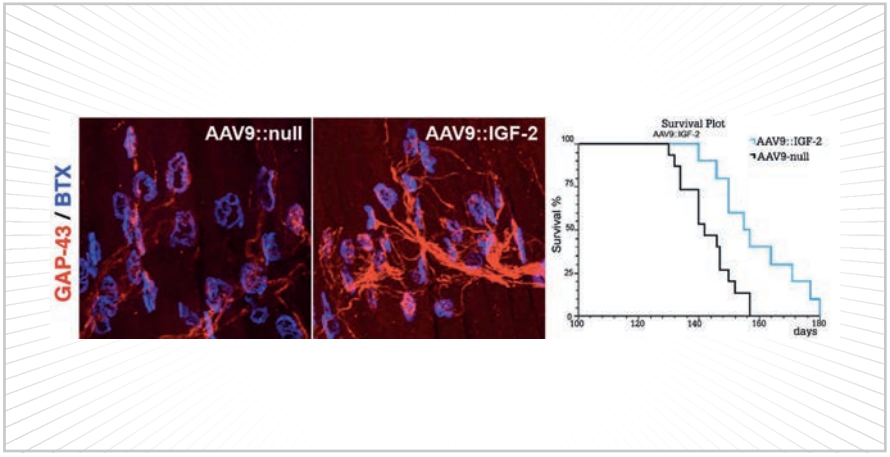


Figure 3. Comparison of motor axons (red) forming synapses with the motor endplate (blue) in limb muscles from two SOD1 ALS mice that were injected after symptom onset with either an empty AAV9-vector (left panel) or an IGF-2-expressing AAV9-vector (middle panel), showing how IGF-2, a growth hormone normally more highly expressed in oculomotor neurons than in spinal cord motor neurons, improves the sprouting capacity of the remaining motor neurons. Mice treated with this vector also exhibit a slower progression rate and survive longer than mice that were treated with the sham vector (right panel). Adapted from (10).

of compensatory mechanisms elicited by one or several other of the specific fiber types present in the extraocular muscles.

A powerful tool

Other investigators have tried to answer the question of differential vulnerability in ALS by comparing the transcriptomes of vulnerable motor neurons with spared motor neurons. One such study (9) has revealed that oculomotor neurons natively express higher levels of several growth factors. And the factor IGF-II seems to exert a neuroprotective effect on spinal cord motor neurons cultured in vitro, and when overexpressed through an injected viral vector (Figure 3), extends the lifespan of the most commonly used ALS mouse model by around 10 percent (10). Also, besides the presence of neurotrophic factors and other growth factors, the intense activity in oculomotor neurons has also lead to numerous evolutionary adaptations to sustain the constant activity and stresses of ion cycling that takes place with each depolarization cycle. Such adaptations include a different composition of GABA-receptors with more powerful inhibitory responses, as well as a lessened susceptibility to glutamate excitotoxicity, a mechanism that has been recognized as an important contributor to ALS pathophysiology since the early 1990s.

Future studies will hopefully answer the question of whether the sparing of eye motility in ALS is a result of the summation of many factors that happen to be beneficial in delaying the deleterious processes of ALS, or whether more specific traits present in the oculomotor neurons have the coincidental effect of delaying ALS. Nevertheless, studying selective sparing is a powerful tool for researchers in different fields, as it encourages us to learn from biological systems that already, through pre-existing tools, have a solution to the problems we face.

Anton Tjust is a Researching Physician at the Department of Pharmacology and Clinical Neuroscience, Umeå University, and an intern at the University Hospital of Umeå, Sweden.

The author reports no conflicts of interest relevant to the content of this article.

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Setting a Great Example

Sitting Down With... Mike Burdon, Consultant Ophthalmologist at Queen Elizabeth Hospital, Birmingham, and President of The UK Royal College of Ophthalmologists

What is the role of the college?

If we go back to the Royal College's charter, we have a very defined role which is essentially focused on setting standards, propagating good practice, educating the public, encouraging and facilitating research, and running exams to maintain standards. The challenge is applying that role in the setting of the current UK National Health Service (NHS)...

How would you define the modern ophthalmologist?

One of the biggest changes I have observed over the past 30 years is the shift in the NHS to a consultant-led service. We at the college are reviewing and reflecting on what a modern ophthalmologist is – and assessing what they need in their working lives so that we can support them. We recognize that there are challenges for trainee ophthalmologists – challenges that we probably didn't have to face when we were training. There is no doubt that the whole NHS is under pressure – and it is being felt by every single person working in an eye department today.

It is very difficult to predict where the future is going to take us. In my lifetime, we have gone from saying "We're very sorry, we can't do anything for wet age-related macular degeneration (AMD)" to an era where anti-VEGF drugs have brought about a huge change in how that condition is treated. We could end up with an AMD drug that is a one-off treatment, but we could equally find ourselves treating dry AMD in a similar way to how we treat wet AMD now – and either could have huge implications on the practice of ophthalmology.

Why medicine and why ophthalmology?

There are all sorts of answers. My dad was a general practitioner and that almost certainly subliminally encouraged me! When I was at school I really enjoyed physics and mathematics, but it dawned on me that I was never going to lead the field in these areas. It might be trite to say, "I've always wanted to help people," but it's true. You can't practice medicine for 30 years without at least wanting to try, and despite some of the pressures we are under, it is still a great joy to be able to help patients. This personal satisfaction certainly keeps me going in ophthalmology.

Why I chose ophthalmology in the first place is a question I ask trainees to reflect on. In my day, we had the opportunity to try a variety of subspecialties before choosing – I wanted to try ophthalmology, found I liked it and carried on. There is less opportunity nowadays, so I encourage trainees to consider the routine procedures of each subspecialty, and ask themselves the fundamental question: "Can you stand the thought of doing that for 30 years?" For ophthalmology, the routine procedure is cataract surgery, and although I have performed many thousands of procedures I still find great personal satisfaction in doing it and doing it well. So I can justify why I have chosen ophthalmology.

And your journey towards neuro-ophthalmology?

A combination of people influenced me towards considering neuro-ophthalmology as a career. After training in Oxford and Birmingham, I had the opportunity to spend a year in Brisbane where I started working in neuro-ophthalmology with John Harrison. I was also fortunate enough to be appointed at St. Thomas' and then the National Hospital (London) to train as a general ophthalmologist with an interest in neuro-ophthalmology. I still do general clinics, manage glaucoma and perform cataract surgery, but half of my life is neuro-ophthalmology. One nice thing to look back on is being involved in setting up a center at the Queen Elizabeth Hospital in Birmingham, which is now of a size to rival any other neuro-ophthalmology service in the world.

What makes a good mentor?

The people that I really look up to are those who set an example. Early on in my career I would point to Hung Cheng, a consultant ophthalmologist in Oxford, who set a quiet example of professionalism that I took with me. Similarly, in neuro-ophthalmology, Michael Sanders and Liz Graham, in particular, set standards of professionalism and knowledge, and how to be a doctor that people can learn from. I don't think anybody sat me down and said "Mike, you've got to do this," but instead influenced me by setting examples that I aspire to follow. I also want to mention John Harrison from Australia – he's a man of very few words but his intellect is significant and he taught me a lot, whether he knows it or not.

What has been particularly memorable in your career so far?

I've had some interesting moments. For example, I was invited to Tony Blair's most recent evening function when he was thanking hospital staff for looking after soldiers from the wars in the Middle East. Another time I was teaching in Christchurch, New Zealand, when the major earthquake happened – so I know what 7.1 on the Richter scale feels like! The other thing I would like to emphasize is the international work. One of the things that the college can be proud of is its increasing support of international ophthalmology, particularly in East Africa, and I'm very proud to have been a part of it. I don't want to sound smug or trite; there is a genuine sense of satisfaction from helping in Africa. You can see the clear need – and if you can make a difference, it's rewarding.

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