MARCH 2020 # 42

the Ophthalmologist™

Head in the Clouds

Is organ-to-cloud technology the answer to ophthalmology's glaucoma management problem?

Santen

A Clear Vision For Life™

WORKING TO EMPOWER A NEW ERA OF GLAUCOMA SURGICAL DEVICE INNOVATION

We're dedicated to advancing proactive glaucoma surgery by working toward more predictable and sustainable outcomes

PREDICTABILITY

- A minimally invasive device would help mitigate trauma and expedite recovery[1]
- Subconjunctival drainage is a proven method to achieve target IOP[2]

SUSTAINABILITY

- Device design could help maximize outflow while minimizing hypotony[3,4]
- Biocompatible material that resists degradation could help deliver more-sustainable benefits[3]

Hear from your peers and register for more information at
AdvancingGlaucomaSurgery.com

References: 1. Chan JE, Netland PA. EX-PRESS Glaucoma Filtration Device: efficacy, safety, and predictability. *Med Devices (Auckl).* 2015;8:381-388. **2.** Lee RMH, Bouremel Y, Eames I, Brocchini S, Kaw PT. The implications of an ab interno versus ab externo surgical approach on outflow resistance of a subconjunctival drainage device for intraocular pressure control. *Transl Vis Sci Technol.* 2019;8(3):58. **3.** Amoozgar B, Wei X, Lee JH, et al. A novel flexible microfluidic meshwork to reduce fibrosis in glaucoma surgery. *PLoS One.* 2017;12(3):e0172556. **4.** Agrawal P, Bradshaw SE. Systematic literature review of clinical and economic outcomes of micro-invasive glaucoma surgery (MIGS) in primary open-angle glaucoma. *Ophthalmol Ther.* 2018;7(1):49-73.

Sometimes, Simple Is Best

Progress in ophthalmology doesn't always come from increased complexity

At the turn of a decade, it's natural to wonder what progress will be made in science and medicine over the next 10 years – especially in a field like ophthalmology. Consider the countless strides made forward over the last few years alone – from the first FDA-approved autonomous AI device (IDx-DR) to the first US regulatory approval of a gene therapy to treat a retinal disease (Luxturna). Where will we be in 2030?

At The Ophthalmologist, we pride ourselves on exploring the likely impact of cutting-edge technologies; in this issue alone, we cover the use of an organ-to-cloud platform for glaucoma management (page 12) and provide an update on the RPE patch for macular degeneration (page 7). But, as Keith Martin remarked in our February issue, "In a world where cataract still remains the leading cause of blindness, it is worth remembering that it is not what we can do – it is what we actually do that matters" (1).

Tech-driven advances will always (and often deservedly) get a fair share of the limelight, but we must also celebrate the simpler, perhaps less glamorous solutions that save sight in patient populations across the globe – for they are no less impressive.

Having recently read Lucy Mathen's book "Outgrowing the Big," I found myself once again marveling at the striking simplicity of the Arclight. Designed with the desperate needs of developing countries in mind, the result is something so uncomplicated – and cheap – that it's hard to comprehend the full scale of its impact. And yet, armed with the Arclight and other essential technologies, Mathen and her team at SecondSight are able to work towards their goal of eradicating blindness in Bihar, India – one of the most poverty-stricken areas of the world. Here, simple (and cheap) works best.

But this focus on simplicity is also vital for new technologies. As the author of our cover feature, Ariel Cao, told us: "Simplicity is what makes our system beautiful – and, hopefully, what will also make it transformational."

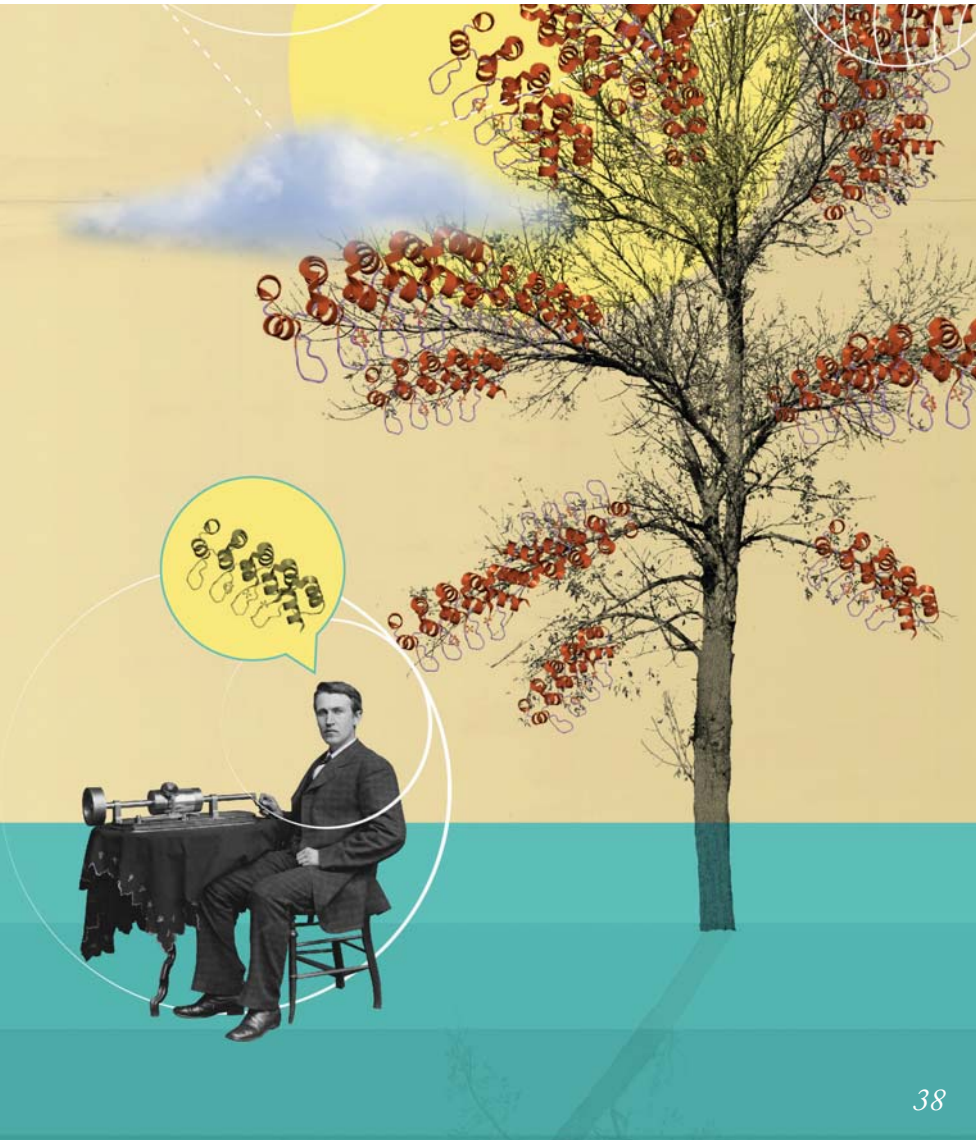
As organizations like the IAPB continue to work towards slashing preventable blindness worldwide, we must acknowledge that investing sufficient time, effort and resources into proper implementation of these simple solutions is crucial to progress in ophthalmology.

Lauren Robertson
Deputy Editor

Reference

1. *"A Pressing Matter", The Ophthalmologist (2020). Available at: https://bit.ly/2UFNxW7*

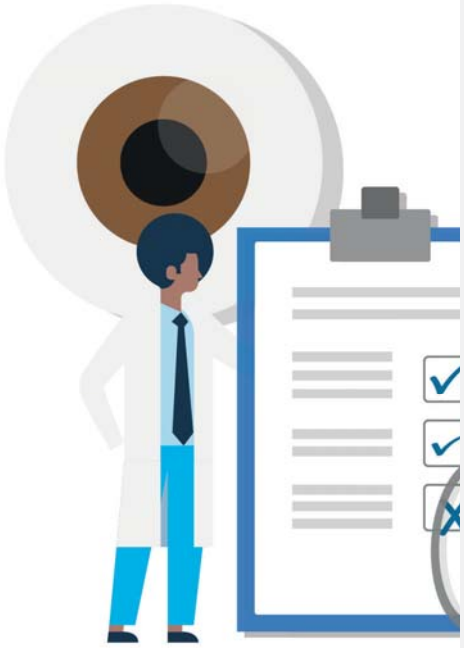
Contents



On The Cover

From eye to sky... enter the world of organ-to-cloud technology company, Injectsense

the Ophthalmologist



Feature

In Practice

NextGen

Profession

Sitting Down With

the Ophthalmologist

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Upfront

Research
Innovation
Trends

Monkey See?

A newly-identified mutation in monkeys could spur development of cell and gene therapies for BBS

Bardet-Biedl syndrome (BBS) – a rare form of retinitis pigmentosa (RP) that begins with degeneration of the macula – affects central vision and is therefore particularly debilitating, even in its early stages. Despite ongoing research, there is still no proven effective treatment for any form of RP, and so, beyond providing a diagnosis, clinicians can do very little for patients.

Now, a team of researchers at Oregon Health and Sciences University, USA, have identified a gene mutation associated with BBS in a family of rhesus macaques, which could kick off development of cell and gene therapies for treating the condition in humans.

Inspired by the success of Luxturna – the first gene therapy for retinal disease to achieve FDA approval – the team focused their attention on the lack of appropriate animal models for retinal diseases. They surveyed the retinal phenotypes of over 1,200 rhesus macaques, eventually identifying a family with a frameshift mutation in the BBS7 gene.

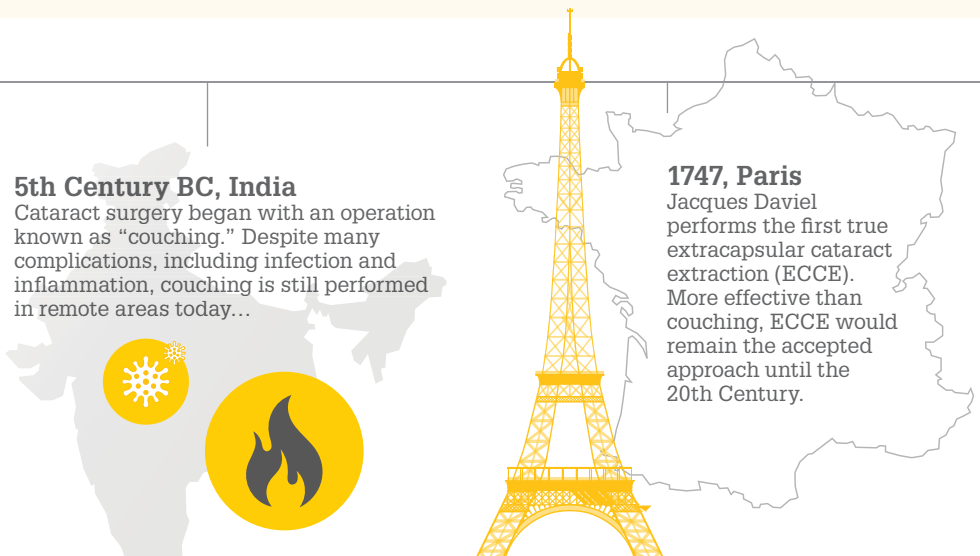
Although most cases of BBS are associated with mutations in the BBS1 and BBS10 genes, the team believe the rare BBS7 mutation can serve as a broader model for translational research. "Photoreceptor replacement therapy is an active area of research, and the information gained from our monkey BBS7 model is likely to generalize not only to all forms of BBS, but to all forms of RP and other photoreceptor degenerations," says Martha Neuringer, Professor of Neuroscience at the Oregon National Primate Research Center and Research Associate Professor of Ophthalmology in the OHSU School of Medicine.

With funding from Research to Prevent Blindness and the National Eye Institute, the team are now working to propagate the BBS7 model; "In the future, we hope to be able to establish a colony of animals as a valuable resource for testing a variety of therapeutic strategies, including gene- and cell-based therapies," adds Neuringer. "Our aim is to demonstrate the efficacy of such therapies, enabling them to be used in the clinic to preserve the sight of retinal degeneration patients."

TIMELINE

Cataract Surgery Through the Ages

One of the oldest, most common – and most successful – procedures in ophthalmology



BITESIZE BREAKTHROUGHS

The latest ophthalmology research – in brief

Complete (Corneal) Fabrication
Researchers at the University of Texas at Dallas have developed a technique for studying the eye's repair mechanisms. Using microfluidic devices, the team is fabricating fibrils to study the role of corneal keratocytes in repairing tissue. The research could help develop therapies to reduce corneal scarring and guide efforts to engineer tissue replacements (1).

Diabetes Gets Smart
A new "Smart LED Contact Lens" could revolutionize the development of wearable diagnostic and therapeutic devices for patients with diabetes, enabling the photonic diagnosis of diabetic retinopathy. The device not only enables monitoring of blood-sugar level in real time, but could also treat the condition (2).

The Signs of Aging
An eye movement test developed by University of Liverpool researchers could improve our understanding of how our brains age. Using an infrared eye tracker, the method investigates inhibitory control in the eye – which is related to the effects of aging (3).


Image credit of UT Dallas.

(No) More Tears
A self-moisturizing contact lens developed in Japan could help fight the symptoms of dry eye. The technology maintains a layer of fluid between the lens and the eye, using a current to move liquid up from the patient's tear reservoir to the surface (4).

Stopping Sight Loss in MS
New research has uncovered the process by which synapses in the brain are damaged in MS, and how this contributes to neurodegenerative symptoms. The study also shows the potential for gene therapy in preserving neural circuits, and protecting against vision loss caused by the disease (5).

References
1. *KH Lam et al., Biomed Microdevices, 1, 99 (2019). Available at: https://bit.ly/383N8AR*
2. *GH Lee et al., Nat Rev Mater, 149, 5 (2020). Available at: https://go.nature.com/2UwFdIe*
3. *PC Knox et al., Peer J, e8401, 8 (2020). PMID: 31942260.*
4. *S Kusama et al., Adv Mat Tech,* 5, (2020). *Available at: https://bit.ly/2UwGi2K*
5. *S Werneburg et al., J Immunity, 167, 52, (2020). Available at: https://bit.ly/2vPzZgl*

RPE Patch: What's New?

The retinal pigment epithelial patch edges closer to becoming a reality for dry AMD patients

Back in February 2019, we wrote about the use of an RPE patch to rescue retinal degeneration in animals and asked whether the research team's success would translate to humans. Since demonstrating the patch can be transplanted in animal models, the team have completed the phase I Investigational New Drug (IND) application and received FDA clearance to start a human clinical trial. "We hope our RPE-patch will be able to slow down disease progression and, if performed at the right time, even stop late-stage disease completely," says Kapil Bharti, Head of the NEI Unit on Ocular and Stem Cell Translational Research, who led the study. Results are expected 2-3 years from now. After this, the focus will be on making the technology available to the majority of patients, and developing more complex eye tissue patches.

Reference
1. *R Sharma et al., Annu Rev Pharmacol Toxicol, 60, 553 (2020). PMID: 31914900.*

1753, London
Samuel Sharp performs the first intracapsular cataract extraction (ICCE), removing the entire lens from the eye.

1949, London
After discovering wounded WWII pilots could tolerate plastic pieces in their eyes, Harold Ridley invents the intraocular lens, and performs the first successful implantation.

1957, Barcelona
Joaquin Barraquer uses alpha-chymotrypsin to dissolve lens zonules for ICCE, improving its popularity, but ECCE soon proves to be far more effective.

1967, New York
Charles Kelman revolutionizes cataract surgery with phacoemulsification. Initially facing resistance, phaco is now the preferred method in the developed world. (Developing countries tend to use the less resource-intensive SICS.)

Wild Thing

When it comes to brain mapping diversity, size – or rather, pattern – matters

Researchers are one step closer to understanding the origins of brain mapping diversity in eye dominance. A study has found evidence that the diversity of ocular dominance patterns relates to the amount of cortex available to represent each binocular point – something that varies between species as well as individual animals. The project, led by postdoctoral researchers Jianzhong Jin and Sohrab Najafian, and Jose Manuel Alonso, Professor at the College of Optometry, Laboratory of Visual Neuroscience, New York, USA, studied humans, macaques, and cats.

In humans and macaques, the cortex splits the map of visual space in intercalated pairs of stripes for the left and right eyes forming a Zebra pattern. In carnivores, the cortex splits the map in blobs forming a Dalmatian pattern. In rodents and lagomorphs, the afferents from the two eyes mix and do not form any specific pattern.

The researchers found that the pattern of ocular dominance columns in primary visual cortex was strongly associated with the amount of visual cortex devoted to process a binocular point across perpendicular axes of the visual field. "Our results predict that differences in the pattern of ocular dominance columns should be associated with differences in binocular processing. For example, stripe patterns should be associated with more pronounced differences in binocular processing across perpendicular axes of the visual field than blob patterns. However, these predictions have not yet been tested with psychophysical measurements," says Alonso.

But there was more. Alonso and his team noticed that when cortical resources decrease to represent points that are increasingly farther from the point of visual fixation, the half eye that is closest to the nose (nasal retina) dominates and gains access to more cortical space than the other half eye (temporal retina). Interestingly, this nasal retina dominance only increases with distance from the point of fixation within the focus plane, not across depth. "In other words, the nasal retina dominates vision when you fixate at one letter of this page, but read adjacent letters using peripheral vision," says Alonso. "The temporal retina never dominates, but its contribution to visual processing nearly matches the contralateral retina at the point of fixation." Alonso and his team are hoping to further their research by developing a model of cortical topography that aims to explain how the visual cortex represents and process multiple stimulus dimensions – including not only spatial position and eye dominance, but also light-dark contrast polarity, stimulus orientation, spatial frequency and direction.

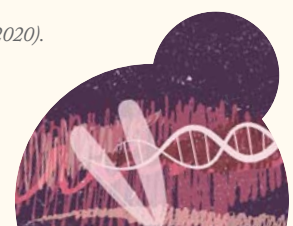
Reference

1. *R Mazade and J Alonso, "Thalamocortical processing in vision", Vis Neurosci, 34, E007 (2017). PMID: 28965507.*

A Golden Age

Could the ELOVL2 gene be the key to new therapeutics for age-related eye diseases?

Researchers at University of California San Diego School of Medicine have been working to establish whether a known biomarker of age, ELOVL2, has a central role in the aging process of mouse retinas. Dorota Skowronska-Krawczyk, Assistant Professor in the Viterbi Family Department of Ophthalmology at UC San Diego Shiley Eye Institute, says, "We believe our work is presenting a previously unknown molecular connection between aging and age-related eye conditions, such as AMD. The high demand for lipids and lipid membranes in photoreceptors allowed us to detect aging phenotypes in the eye and connect them to a particular gene – ELOVL2 – [which encodes a] key enzyme involved in lipid metabolism, previously described as one of the best biomarkers of aging." The team is currently working on potential strategies to help translate their findings into the clinic.



Reference

1. *D Chen et al., Aging Cell, 2 (2020). PMID: 31943697.*

IMAGE OF THE MONTH

{kornea:}

The first of four portraits of corneal researchers and surgeons, which make up the winning artwork of the European Eye Bank Association's 2020 Photo & Art Contest. To see the full project, as well as other submissions, go to https://bit.ly/2RWpPly.

Credit: Marie Burghardt, University Eye Hospital Halle, Germany

Would you like your photo featured in Image of the Month? Send it to edit@theophthalmologist.com

QUOTE OF THE MONTH

"These are exciting times for the cell therapy field. After years of effort, we are slowly starting to see clinical progress. I am hopeful that we will bring new treatments to patients that previously had no hope."

Kapil Bharti, Head of the NEI Unit on Ocular and Stem Cell Translational Research.

All Eyes on Coronavirus

Leading ophthalmic bodies warn that 2019-nCoV can be transmitted through aerosol contact with the conjunctiva

A recent Lancet study has stated that transmission of the Wuhan coronavirus (2019-nCoV) through the ocular surface must not be ignored (1). The statement comes after the American Academy of Ophthalmology (AAO) issued an alert on January 28 suggesting the virus can cause conjunctivitis and is possibly transmitted via aerosol contact with the conjunctiva – increasing the likelihood that ophthalmologists will be the first healthcare providers to evaluate patients potentially infected with 2019-nCoV (2).

Although the virus does not appear to have caused as many deaths as the SARS or MERS coronaviruses, there are already 1115 fatalities, including whistleblowing ophthalmologist Li Wenliang.

The AAO has recommended protection for the mouth, nose – and eyes – when caring for potentially infected patients.

As of February 12, there were 45,171 confirmed cases of 2019-nCoV globally, with 441 of these outside of China, and the total death toll stands at 1115.

References:

1. *Cheng-wei Lu et al., "2019-nCoV transmission through the ocular surface must not be ignored", The Lancet, (2013). Available at: https://bit.ly/2UK0LRL*
2. *AAO, "Alert: Important coronavirus context for ophthalmologists", (2020). Available at: https://bit.ly/39ukbON*

In My View

Experts from across the world share a single strongly held opinion or key idea.

Top of the Tree

CEDARS ASPENS is an active network with clear mission in the anterior segment sphere: building knowledge, providing education, and fostering innovation

By Jennifer Loh, cataract, refractive and ocular surface specialist, founder of Loh Ophthalmology in Miami, Florida, USA, and the 2019 President of CEDARS/ASPENS

The idea of CEDARS/ASPENS was born from the concept that collaboration among colleagues to improve patient care should be not only rewarding, but also fun. CEDARS (which is an acronym for Corneal External Disease and Refractive Surgery) was the first branch of the group, and was first developed by a group of male ophthalmologists who enjoyed working together professionally, but also shared a strong bond of friendship. As their collaborations in the field grew, they realized there would be many benefits in forming an official society. I entered the ophthalmology meeting scene in 2013, and after learning about this great group of ophthalmologists I was really impressed by the support and guidance they gave each other and how much they learned from one another. I realized how beneficial this could be to female ophthalmologists, and was inspired to create our own similar group. I was fortunate enough to know many great pioneering and successful female ophthalmologists, and by collaborating with Sheri Rowen and Alice Epitropoulos, and many other others, we set about creating the ASPENS (American Society of Progressive Enterprising Surgeons). While we were not officially related to CEDARS at that time, we began to work together as two synergistic groups. With time, both groups came to the conclusion that we needed each other, and so we formalized our relationship and merged the societies to what is now known as CEDARS/ASPENS. Together, we form a not-for-profit society of surgeons that is passionate about advancing the anterior segment area of expertise.

The society is made up of pioneers in the field, who practice, give lectures, conduct clinical research, and write papers. We highly value the opportunity of networking within the group, as well as using our collective strength to foster excellence in the wider anterior segment sphere. We believe that industry relationships are critical to moving the field forward, and introducing new technologies and treatments – ultimately, to benefit our patients. And so we are actively engaging in discussions with the industry, participating in clinical trials, and testing the latest innovations. But these partnerships work both ways – industry leaders often ask for our opinion or develop innovative products or procedures based on our ideas and recommendations.

Teaching is extremely important to CEDARS/ASPENS. A few times a year we offer mentorships and seminars for up-and-coming ophthalmologists – recent graduates, residents. We have new specialists joining our society every year, and we currently have around 85 members, including the biggest names in the anterior segment. We host an annual two-day conference, where the first day is focused on academic discussions and industry involvement, and the second day is a physician member meeting, where members discuss techniques to improve patient care and practice management.

It seems to me that, over the last few years, a small idea has grown into a great organization. We have strength in numbers, but also a family feel; I feel comfortable discussing concepts and ideas with our group that I might not be willing to share at large. It helps me foster innovation in my own practice, and create collaborations to achieve goals that would not be possible if I was working alone.

My vision for the future? To grow as a society that helps advance patient care, to collaborate with industry on technology innovation that improves surgical and medical outcomes and to continue to support the next generation of ophthalmologists in becoming leaders in the field. We have already come far. We've proved that the formula works really well for our field – and for all the individual members. The momentum is there, and I am very excited about the future of CEDARS/ASPENS.

Burden of Proof

The glaucoma subspecialty is now at a turning point. But new approaches, including MIGS, must be based on high-quality evidence – and that means more randomized controlled trials.

By Kaweh Mansouri, glaucoma specialist, Consultant Ophthalmologist at Montchoisi Clinique, Lausanne, Switzerland and Department of Ophthalmology, University of Colorado, Denver, USA

The "gold standard" of glaucoma treatment – trabeculectomy – is anything but golden. Although the procedure is 60 years old, it has largely remained unchanged, despite many attempted modifications. It is a type of surgery no ophthalmologist looks forward to performing, as its outcomes are very unpredictable – there are a host of possible early and late complications, which can be devastating for the patient.

When MIGS devices were first introduced, the idea was to provide a surgical procedure that is much safer than trabeculectomy, but has at least modest efficacy. A change of mindset was needed: suddenly we weren't necessarily aiming for maximum efficacy, but for maximum safety.

Glaucoma specialists are a conservative group – and extremely data-driven when it comes to new treatment options – so we didn't all throw ourselves straight into the surgical innovation pool. I am speaking in general terms when I say that "we" expect to see pilot studies, case studies, and a great deal of prospective data; of course, there are always pioneers who are prepared to take some risks.

The discussion at glaucoma meetings over the last five years has been focused on whether MIGS devices are just a fluke – a novelty that will fade and leave no trace – or if they were here to stay.

In my opinion, 2019 was the first year when the tone of these discussions shifted. Most of the controversy about using MIGS devices seems to have been left behind, as we now have a growing body of evidence to confirm that i) MIGS devices are safe, ii) procedures are easy to perform and can be done in an ambulatory setting, so the specialist's time is reduced, iii) patients' quality of life is improved as the recovery process is fast, and iv) the devices are at least modestly efficacious. These points have been nicely summarized in the World Glaucoma Association's 2019 Consensus Series Book on glaucoma surgery.

That last aspect largely depends on the surgeon's skills and experience, and the patient's specific needs: for one patient, requiring just one regular medication is a great outcome; for another – who might be suffering from chronic dry eye – stopping medication altogether will be the improvement in their quality-of-life that they want to see.

What we are still lacking is the highest level of evidence: randomized controlled trials (RCTs), comparing MIGS outcomes with the glaucoma gold standard. These trials are not exactly forthcoming: there are still very few quality MIGS RCTs. And they might only be applicable to a specific patient setting or population.

If there isn't a huge body of evidence available, the results might be skewed by the surgeon's bias, preference, or level of experience. And that's why we need more high-quality, quantified data from RCTs – and relating to various MIGS devices available on the market – which can be independently reviewed in a large volume. Thankfully, device manufacturers realize this as an imperative, and we are seeing an increase in RCT numbers in the MIGS field.

"If there isn't a huge body of evidence available, the results might be skewed by the surgeon's bias, preference, or level of experience."

We live in an era of constant change in glaucoma, and it is vitally important to adapt our practice to current procedures – and let the datasets change our mindsets and guide our clinical decisions. Pioneering work is important, but we should always be mindful of any adverse effects of novel treatments that we hear about. Now is the time to truly focus on acquiring and consolidating as much data on MIGS as we can, and coming up with universally-accepted standards and guidelines towards a new "gold standard" for glaucoma.

Relevant disclosures

Santen (C), Fabrinal (C), Alcon (S), Allergan (S), Optovue (S); ImplanData (C), New World Medical (C), Oertli (C)

HEAD *in the* CLOUDS

ORGAN-TO-CLOUD TECHNOLOGY IS HERE – *and it has its sights set on glaucoma. Offering a stream of* OBJECTIVE, UNCOMPROMISED DATA, *it could* REVOLUTIONIZE THE GLAUCOMA SPACE... *But for it to work, we need to* RETHINK *the way we* ASSESS THERAPY EFFECTIVENESS *under our current* TREATMENT PARADIGM.

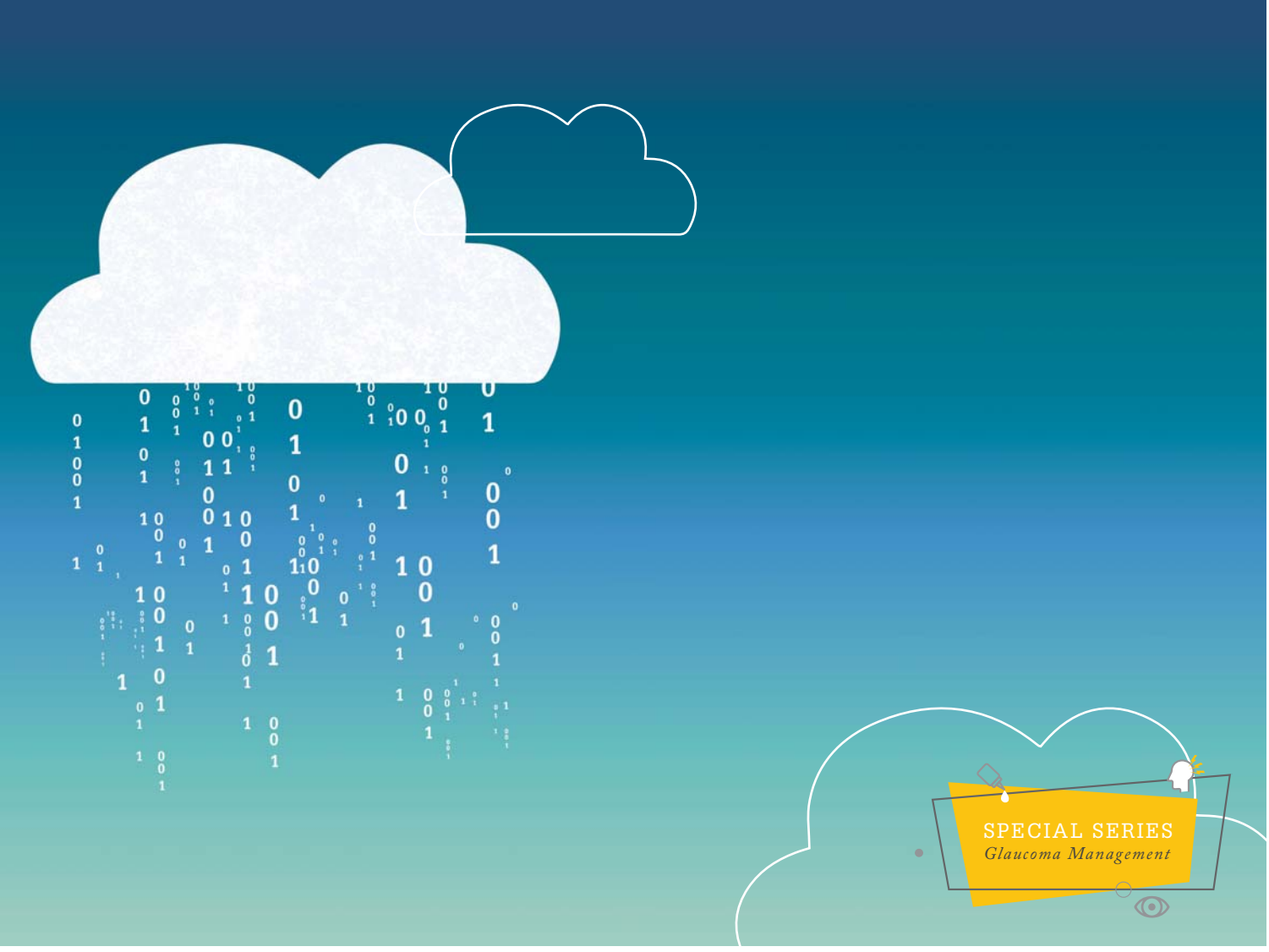
BY ARIEL CAO

When was the last time you bought a CD? I'm guessing it was a long time ago. Nowadays, you probably pay nine dollars a month for a music streaming service that lets you listen to whatever song you like, whenever you like, on whatever device you like – amazingly, with minimum fuss.

Given the choice, I doubt you would go back to CDs. Why? Because streaming makes sense. We live in an era of constant connection, where we can access the information we need anytime, from anywhere. Real-time event updates mean we can predict and plan for change. Yet, somehow, this does not translate to the medical field. An ophthalmologist treating a progressive disease like glaucoma can't be anything but reactive; critical data on a patient's disease state is only collected during sporadic office visits, yielding only a few single data points to interpret past trends and assess long-term risk – often with harmful results.

Patients are paying for therapies without knowing whether they are actually having the desired impact on their intraocular pressure (IOP) – and some are going blind as a result. Under our current treatment system, if a therapy doesn't work, the patient doesn't pay. But who benefits from this model? Not the patients – they don't see an improvement in their condition. And it's not the drug companies – they are being penalized by the reimbursement system for ineffective therapies. It is clear to me that it's time for a new treatment paradigm – one that proves outcome with evidence. But how do you know if a therapy actually works? Easy – you follow the data. And that's where we come in.

We are Injectsense – a sensor-enabled digital health company – and we have developed an organ-to-cloud data connection that enables clinicians to assess glaucoma therapy effectiveness at any time. A self-anchoring system is inserted into the vitreous base – the best place to measure pressure on the optic nerve – where it safely and autonomously collects pressure readings. This aspect is important: patient intervention has been shown to be the least effective pathway to improved glaucoma outcomes (1, 2). The device automatically syncs to the cloud every week, offering physicians unprecedented visibility into the patient's IOP profile and into previously unobserved changes that may affect glaucoma progression.



Once the device is implanted in the eye, it lies dormant until it takes an IOP reading. It is not affected by atmospheric pressure – the patient could go to the bottom of the ocean or the top of Mount Everest and the device will continue to work. Once a week, the data is sent to the cloud for the physician to access. So we have the data – what happens next?

Let's go back to CDs and music streaming. CDs contain data. The servers of the music streaming service contain data. What makes music streaming so special is how that data can be presented and used. A music streaming service doesn't just give you access to the CDs (or tapes or vinyl records) you used to own – or the music you want to own – it opens up a whole world of music. It makes recommendations, enables you to share songs or entire playlists with friends on the other side of the world, it allows you to discover something new. Music streaming has reinvented the way we consume music – and it has all but killed the traditional music store...

What if we started to treat glaucoma management like a streaming service? What if a patient doesn't buy a therapy, but subscribes instead? They could choose a treatment that suits their specific medical needs and budget, and if it doesn't work – and with our device, they will actually be able to tell – they try something else. The premium IOL market has proven that patients are willing to pay out of pocket for improved outcomes – and we are in the position to provide them with evidence of efficacy. A product like ours has the potential to guide drug and device development based on efficacy; no more wasted dollars for the industry and no more pointless treatments for patients.

We have already had success with the device, having recently completed our first in-vivo animal study. We safely collected a week's worth of readings – in agreement with tonometry measurements –and reported no device-related adverse events. If everything goes well, we will begin our first controlled human study at the end of 2020. From there, the sky's the limit.

THE ORIGIN STORY

Eight years ago, my parents were affected by glaucoma. My mother was prescribed topical drops but they stung her eyes, so she stopped taking them, and even omitted to tell the physician about her situation. As a result she lost her eyesight in one eye. Around the same time, Enrique Malaret, our COO and co-

founder of Injectsense, had also come up against the disease. We decided we would do what we could to help. The challenge spoke to us as individuals, as much as engineers. How do we determine whether a treatment actually works? Our solution was a continuous monitoring device, taking the form of an injectable ultra-miniature sensor coupled with a secure digital health platform. We spent the next three years fleshing out the concept and securing funding – once we had enough, we began to scale.

As you can imagine, creating an organ-to-cloud system is not easy. It takes time to develop a premium product, especially one that draws from several domains – such as medicine, semiconductors, fluid interactions, and electronics. Putting together a team that could connect these disciplines without leaving gaps was critical. We made sure to pick people with overlapping skills, and ensured we worked as one collective entity. The team now stands at 10-plus full time employees, alongside a pool of contractors. We choose to keep our team small because, the more people you bring in, the less efficient you become. Staying small keeps us agile. It has also makes it easier for everybody to know their roles, which is important, as two-thirds of the start-ups fail because of internal conflict. We made a policy of looking for people who are hands-on, team players, with proven multidisciplinary expertise, and who are motivated well beyond simple monetary payback. We have stuck to it. Together, we have built a team that has developed a solution to be proud of.

So how does it work? First, the implant is delivered in-office via an injection, leaving a self-anchoring sensor in the vitreous base. The implant begins to measure IOP at a series of times predetermined by the physician. Once a week, the patient is reminded to upload the data by putting on a pair of glasses – this notification will come from an app on the patient's phone. Uploading takes less than a second. At this point, the data is sent to the cloud, where it is ready to be mined by our software. We start by removing data that has no purpose (such as IOP increases caused by blinking) and instead, look for information that is actionable, which is to say, pressure readings that exceed a certain value over a given period of time. The idea is to build a histogram representative of the pressure exposure. The physician can then access the data and see which patients, if any, have exceeded their set target. We also provide physicians with the option to decide how often patients are sampled – for example, once every ten minutes or once an hour. The next time the patient uploads data via the glasses to the cloud, the new sequence will be automatically downloaded.

The whole system requires very little effort from the patient. Minimizing human error was one of our core aims, as patients are often the weakest link in the treatment process. Every physician can provide an example of a case where patient non-compliance has resulted in less than ideal outcomes. This issue is particularly common in glaucoma, where patients do not necessarily see an immediate benefit in taking their medication but may experience side effects. The patients also may not see the urgency, as they don't experience pain, and the disease typically progresses very slowly. Imagine how many people's vision could be preserved if there was a way of showing them how their treatment program was working. Crucially, the system also requires little physician time. By 2025, 50 percent of the ophthalmic workforce will have retired – but the number of students entering residency is dropping off. Devices like ours will play an important role in tackling the increasing treatment burden, made worse by an aging population.

"A PRODUCT LIKE OURS HAS THE POTENTIAL TO GUIDE DRUG AND DEVICE DEVELOPMENT BASED ON EFFICACY; NO MORE WASTED DOLLARS FOR THE INDUSTRY AND NO MORE POINTLESS TREATMENTS FOR PATIENTS."

INSIDE *the* INJECTSENSE

Jose Padovani, Senior R&D Engineer at InjectSense, explains how the device works.

Our design is based on proven sensor technology. The device is less than two cubic millimeters in volume, delivered by injection, and self-anchoring. The silicon sensor is self-packaged, meaning it requires no further encapsulation. As it relies on semiconductor manufacturing techniques, volume production can scale into millions of units per year. Each wafer has 14,000-plus devices, no different from cell phone components. Its size is one of its greatest advantages: the implant is so small the animals were unaware of its presence. With no intervention required for data collection, and using wireless data downloads weekly or daily, we were able to obtain highly accurate data over an extended period of time in a consistent manner. Data with a unique patient/animal ID was encrypted and stored in a cloud database.

The device itself is built with the same technology that lets you buy groceries with Apple Pay. A tiny antenna inside the implant is coupled with an external antenna, paired to a wearable reader – a mechanism we use to remotely deliver power to the device and extract data. It is ultra-low power, operating at a nanowatt power level, which makes it harmless to the body. Outside of its internal electronics, it is polymer-free, biocompatible (a well understood foreign body response) and fully hermetic, so that it can operate for decades inside the body. A physician can implant the device and will only need to remove it – a simple surgical explant procedure – in the event of a chronic infection. The design allows the device to be delivered in-office, avoiding the cost of an operating room procedure.

Our device may also have significant potential in terms of patient responsibility. Too many ophthalmologists are exposed to malpractice claims. Wouldn't it be helpful if they could arm themselves with the evidence that it was, in fact, the patient who hasn't complied with recommendations? That's not to say we are going to act as a mediator between insurers and patients – rather, our data can empower patients to take their medication as prescribed, and everyone – physicians included – can benefit from the results.

TACKLING COMPLIANCE WITH DATA

Our current gold standard method for measuring intraocular pressure – Goldmann applanation tonometry – is plagued by fudge factors. Although it's considered the "gold standard" with broad acceptance, for some cases it may seem more like a "random number generator." Due to the lack of consistent calibration, operator error and variability of measurement conditions, the value may not be 100 percent trustworthy. One day it's this, the other it's that and nobody knows why.

Ophthalmologists use tonometry as a relative measurement – but I believe we can do better. All it takes is a shift in mindset. We are lucky enough to have some incredibly influential figures on our advisory board – Ike Ahmed, Myron Yanoff, Arthur Sit, Richard Lindstrom – but what is reassuring is that once we start talking to them about the device is that within 10 minutes they play back the benefits that they perceive from their own experience. It's what they've been waiting for – to be more effective in their therapy management. Now they can personalize therapy for each patient and transform the relationship to contain the disease progression more effectively. After all, only 30 percent of glaucoma patients are compliant with medication use. Our device may help to gain an additional 5 percent, 10 percent, maybe even more, of those patients, and improve outcomes with a cost-effective drug regimen, by just taking the drug.

The device may also offer unparalleled insight into drug efficacy – separating the losers from the winners. Companies who sell drugs that don't work will have no place to hide. And though that sounds damning, it will ultimately be a positive thing. Instead of spending money developing drugs that don't work, we could funnel funds into ones that do.

MONETIZING THE DATA

People ask how physicians can use the system to operate within a viable business model. Simple – they charge for the data plan. The true value of this system comes from data-driven therapy management. For the first time, physicians will be able to check a patient's IOP outside of clinic hours. Whenever a patient has repeat IOP spikes throughout

Figure 1. Pictured holding devices: Ernesto Collazo, member of Injectsense Medical Advisory Board; Enrique Malaret, Chief Operating Officer and co-founder; Arthur Sit, member of Injectsense Medical Advisory Board; Ariel Cao, Chief Executive Officer and co-founder.

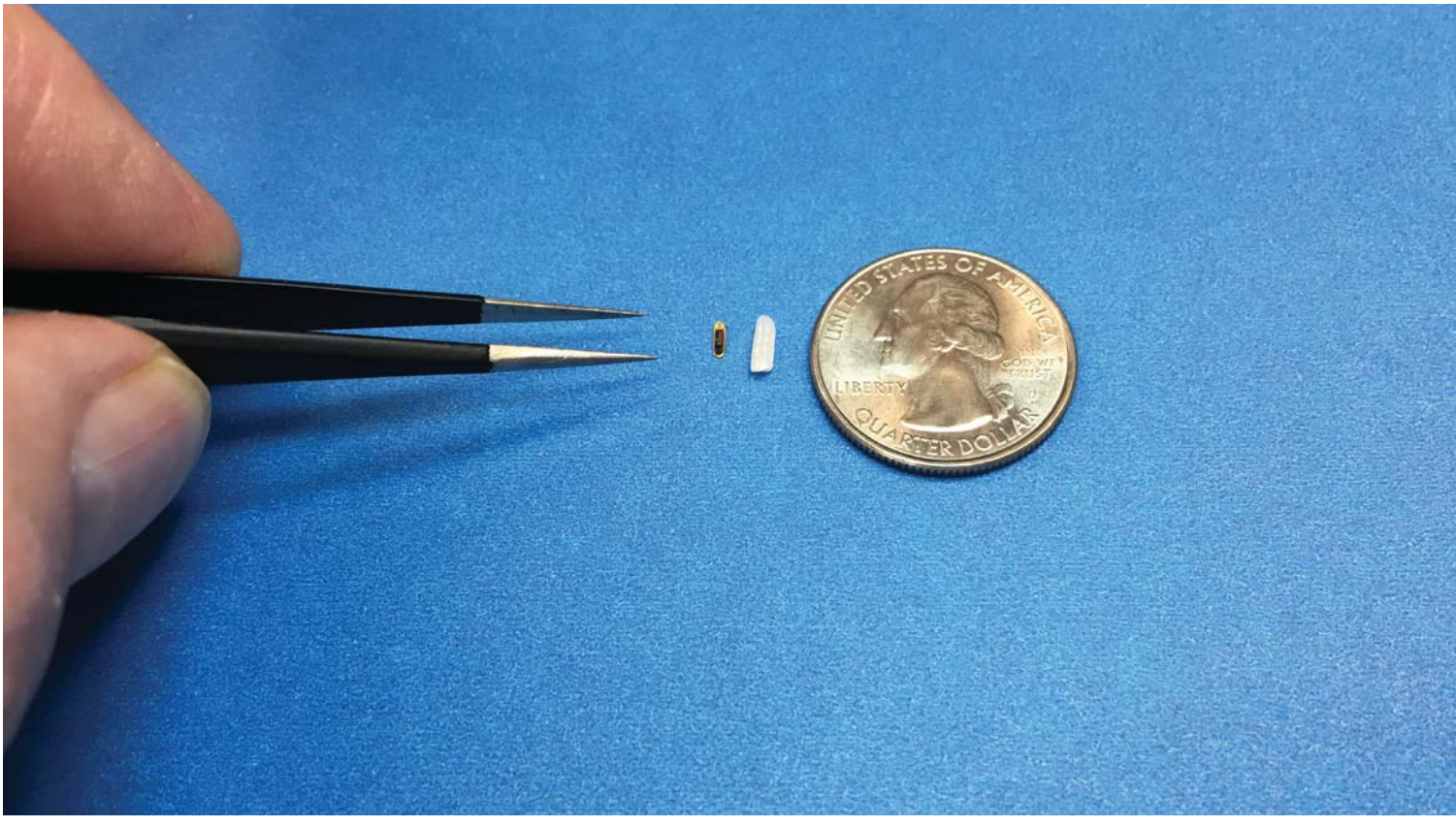


Figure 2. A prototype of the Injectsense IOP sensor used in animal testing, next to a grain of rice and a quarter.

different periods during the day, the system will alert the doctor. At the end of the week, they can download that data and decide on the best course of action for that particular patient. The benefits of this cloud-based system are two-fold. One: it is considerably cheaper – and easier – to move data than to move the person (to the doctor's office). Two: it eliminates unnecessary visits to the doctor's office, saving patients' – and physicians' – time and effort. When they do visit the clinic, it is for a justifiable intervention.

The idea is that providers receive a monthly fee for monitoring under a CMS reimbursement code, and more codes are being introduced every year. For some, this may seem like an unworkable business model – but it isn't. Medtronic, the world's largest medical technology company, began offering embedded advanced data analytics in its clinical monitoring software to enable cardiologists to identify and remotely monitor patients, allowing them to act faster on potential health risks. They understood what so many didn't: that the future of healthcare is data-driven – and we see it too.

We cannot claim to cure glaucoma but we can help patients manage it, by providing ophthalmologists with an objective, unambiguous body of clinically actionable data. The database could also become invaluable to research centers and public health organizations.

ERNESTO L. COLLAZO, OPHTHALMOLOGIST

On the subject of glaucoma, I often explain how difficult it is for ophthalmologists to manage a disease where our goal is to control IOP but we only get to measure that pressure at three or four points during the year. None of my internal medicine colleagues would ever try to manage the insulin dosage in a diabetic patient with only four measurements of blood sugar in a year, but we are forced to manage glaucoma that way. It was Enrique who suggested that some sort of miniature implantable device could potentially give us the ability to measure IOP throughout the day. I mentioned that the best place to implant the device would be the Pars Plana – the basic idea for what Injectsense is developing today was born at that moment. Once Enrique and Ariel founded Injectsense, they contacted me to become their first medical advisor and I recruited some of the other current members of the medical advisory board. The rest is history.

DIGITIZING THE FUTURE OF HEALTHCARE

Glaucoma is just the start. Sensor systems are renowned for both their stability – and their versatility. The device has the potential to be used in any field that measures fluid, from urology to neurology. Say a patient had brain cancer, we could put a reservoir next to the device to facilitate drug delivery. We could also replace the pressure sensor with an electrode to stimulate the nerve, for use in neuromonitoring and neurostimulation applications.

Our device is not a one-trick pony, it is a complete digital health platform. It may be diagnostic today, but could easily be extended to a therapeutic platform tomorrow. Even before initiating human trials, we plan to apply for theFDA's Breakthrough Device Designation that enables a waiver of the economic outcome study in order to set an early reimbursement value immediately. We fully meet all the criteria for this designation.

The mindset around medicine is changing. We, as members of the industry, have a responsibility to offer patients a better outcome, a better quality of service and a better quality of care. Glaucoma patients deserve a return on health – and we want to help make that happen. Our employees have invested years on this enterprise. When all is said and done, we feel that we have found the simplest, most elegant way of monitoring IOP, with tremendous flexibility to fit unanticipated needs.

Since our approach is inspired by intravitreal injections – now performed yearly in their millions, we have a path of least resistance with a simple injection for safe delivery of an IOP monitoring device.

Ariel Cao is CEO and Co-Founder of Injectsense.

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GO WITH THE (OUT)FLOW

Excise trabecular meshwork efficiently with MST's Excisional Goniotomy line

Goniotomy is considered an effective procedure to promote enduring IOP reduction by unroofing Schlemm's Canal (SC). Unlike MIGS stents, which require a targeted approach to allow aqueous outflow, goniotomy exposes multiple clock hours of SC and several collector channels. Goniotomy enables surgeons to visualize the white outer wall of SC, confirming completion of the procedure, in a wide range of disease states. Success, of course, depends on physician skill and – crucially – the device used. A common concern with the goniotomy technologies available on the market today is that they *may tear tissue*, rather than excise it. And that's understandably problematic, as remaining tissue can restrict aqueous outflow, which may in turn affect the IOP reduction. MST considered this carefully when *offering their range of premium excisional goniotomy devices.* The solution is a family of technologies engineered to excise trabecular meshwork (TM) effectively and efficiently: TrabEx, TrabEx+, and Trabectome.

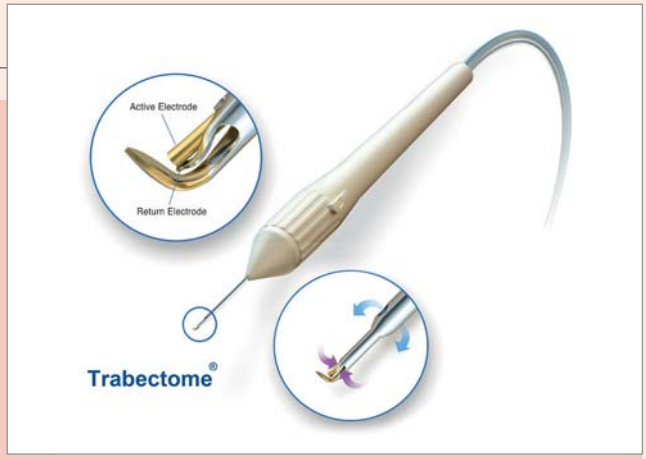
TrabEx features laser-honed serrated blades that promote tissue cutting, while a trapezoidal blade-head design adapts to varying patient anatomies, thus promoting more efficient TM removal. The TrabEx+ adds Irrigation/Aspiration (I/A) to enhance visibility to the anterior chamber, thus allowing better visual access to the angle (1). I/A also offers the major benefit of managing intraoperative blood reflux by maintaining appropriate pressure in the anterior chamber (1). Trabectome is a premium technology for electrosurgical ablation of diseased TM (2), with an established history of proven clinical outcomes with over 130 peer-reviewed articles of support. The device uses precise electrosurgical ablation for tissue removal, vaporizing TM more completely while minimizing damage to surrounding tissue.

MST's Excisional Goniotomy devices have been designed to treat the widest possible range of glaucoma conditions, from primary open angle and secondary glaucoma such as pseudoexfoliative or non-pseudoexfoliative glaucoma and more, in both adult and pediatric patients. These devices can also be used in conjunction with cataract surgery or as a stand-alone procedure.

In a meta-analysis in the British Journal of Ophthalmology, Kevin Kaplowitz and colleagues reviewed 64 studies on Ab Interno Trabeculectomy (AIT) – also known as goniotomy – with the Trabectome and came to the following conclusion: "AIT can be expected to lower the IOP by approximately 36 percent to a final average IOP around 16 mm Hg, while decreasing the number of medications by less than one"(3).

The MST Excisional Goniotomy family of devices were created with a purpose: to treat everyone, everywhere. To make that possible, the devices are offered at an affordable price and backed by strong reimbursement. TrabEx, TrabEx+ and Trabectome are sold individually. The Trabectome requires a generator console, which is sold separately.

MST Glaucoma Cases, Simplified™



BRIAN FRANCIS, ASSOCIATE PROFESSOR OF OPHTHALMOLOGY AT THE DOHENY EYE INSTITUTE, STEIN EYE INSTITUTES, UCLA, USA, SHARES HIS USE OF EXCISIONAL GONIOTOMY DEVICES FROM MST.

I started using the Trabectome in 2005 when it was still in the clinical trial phase, and started using it in my practice in 2006. I was also fortunate enough to perform the first combined cataract and Trabectome surgery in the world at that time, too. In the years since, I have helped design other instruments in the MST line, including the TrabEx non-powered excisional goniotomy blade – and I was the first surgeon to use it clinically. MST Excisional Goniotomy devices have been an important part of my practice for a long time now. It is worth remembering that Trabectome was the first ever angle-based MIGS procedure. Before that, we relied on trabeculectomy, tube shunts and cyclophotocoagulation. When Trabectome was introduced, it created a whole new category and I, for one, am grateful.

Goniotomy is the bread and butter of my practice. I use it for open angle glaucoma, anywhere from mild to moderate, as well as more advanced glaucoma cases – either standalone or combined with another procedure – that reduces aqueous production to achieve a lower target pressure. We've also published data on how the use of goniotomy after tube shunts or trabeculectomy can be effective in patients who have undergone failed glaucoma filtration surgery. I should point out that while goniotomy is suitable for most patients, not everyone is an ideal candidate. I exclude those with significant long-standing angle closure or elevated episcleral venous pressure glaucoma, as well as patients who require a very low target pressure, as this can only really be achieved with a trabeculectomy. Aside from these few exceptions, most are eligible for the procedure. The fact that goniotomy can be used as a standalone procedure, suitable for both phakic and pseudophakic patients, adds to its versatility. And it can be performed at the same time as phacoemulsification or cataract surgery, or alongside other minimally invasive or micro incisional surgeries.

The MST Excisional Goniotomy line has delivered a number of benefits to my practice: it has allowed me to offer surgery at an earlier point in the disease, reduce the medication burden on patients, and lower the risk of surgery for patients who don't necessarily need significant IOP lowering. This latter aspect is useful for individuals who have high pressure, but don't necessarily need filtration surgery. The other benefit is the design; to achieve optimum IOP lowering, proper removal of the trabecular meshwork is essential – and that means ensuring that tissue is cut, not torn, as tearing leads to bleeding and, in turn, scarring. This quality is what makes MST's devices so useful; they have been built with precision cutting in mind. In short, tissue cutting, not tearing, is a great advantage. I have also found that the constant irrigation is helpful in maintaining visibility and anterior chamber stability.

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In Practice

Surgical Procedures
Diagnosis
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Drug Drought

How will mitomycin C shortages affect glaucoma surgery?

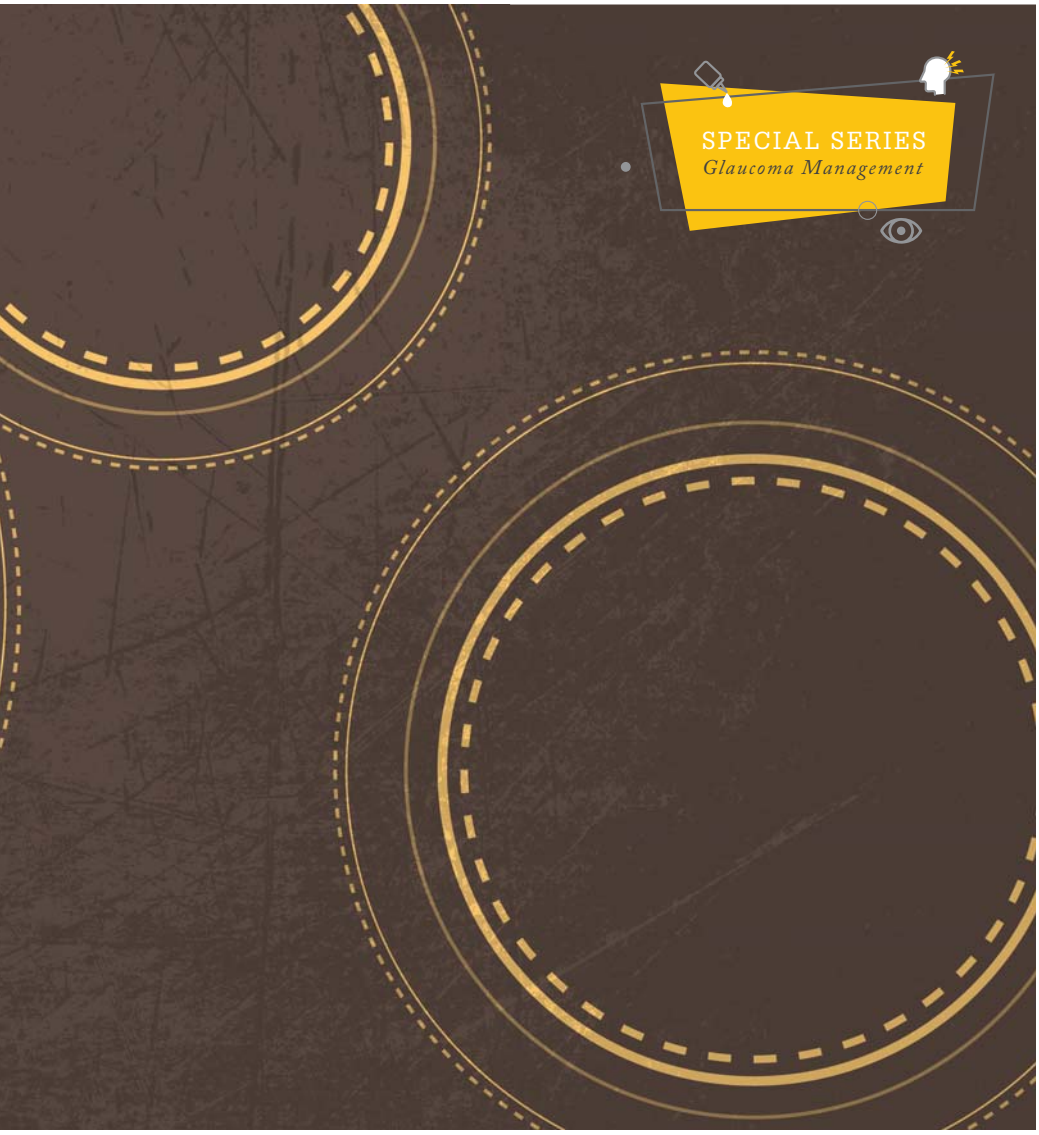
By Obeda Kailani, Claudia Quijano and Dan Lindfield

Europe and Asia are currently afflicted by a sudden availability crisis of mitomycin C (MMC). This is significant as the majority of trabeculectomy procedures performed in modern times utilize antimetabolites, and 63 percent of those use MMC (1). After an issue with the sterile processing of the drug was detected, Kyowa Kirin – a Japanese pharmaceutical and biotechnology company – ceased production of MMC pending investigation, and a Class 2 product recall of all shelf stock is currently underway. In the UK, Kyowa Kirin's drug is the only MMC product licensed for ophthalmic use. MMC licensed for intravesical application is still available in theory but supply is taken up by urological cancer requirements, leaving no surplus. Other routes of non-licensed supply were available, but the instant surge in demand meant those were quickly exhausted. This has left the UK, Europe and parts of Asia with no access to MMC, and hence trabeculectomy, tube shunt surgery and sub-conjunctival MIGS procedures (such as XEN or PRESERFLO) face significant challenges. The effects are expected to last at least until spring 2020.

5FU and filtration surgery

The wound healing response is the single most important determinant of the final intraocular pressure (IOP) after glaucoma surgery. Despite contemporary opinion holding that MMC is pivotal to surgical outcomes, only a decade ago MMC was viewed very differently. A UK survey in 2004 showed that 18 percent of trabeculectomy surgeons never used antimetabolites, 82 percent used them infrequently, and only 9 percent used antimetabolites routinely, with the preferred antimetabolite being 5FU. MMC was used in primary trabeculectomy by just two percent of all surgeons, with those who did use it reserving it for re-do surgery. In the US, between 33 and 55 percent of surgeons used MMC for first-time trabeculectomy in 2004 (2).

A recent Cochrane review compared 5FU with MMC in trabeculectomy surgery. It suggested that the risk of trab failure at one year was slightly lower for MMC than for 5FU, although this was statistically insignificant. Similarly, the review suggested that MMC was more effective at lowering IOP than 5FU in both high and low-risk participants but again did not reach statistical significance. No difference was found for the use of post-operative



Alternatives during the MMC drought

- Offer MMC-independent treatment modalities (SLT, Trans-Trabecular MIGS)
- "Hold" with oral acetazolamide
- Consider 5-Fluorouracil (5FU) augmented filtration surgery

"With no access to MMC trabeculectomy, tube shunt surgery and sub-conjunctival MIGS procedures face significant challenges."

medication between the groups (3). A Cochrane review on the use of MMC for tube shunt procedures gave a similar outcome (4). Evaluating safety across multiple studies reveals slightly more favorable outcomes using MMC, particularly with regard to the incidence of corneal epitheliopathy and hyphema. But there was a trend towards more bleb leaks, wound leaks, late hypotony and cataract formation in the MMC-treated group.

One Cochrane review compares postoperative use of 5FU versus no antimetabolite treatment. A significant reduction in surgical failure is seen in the first year after trabeculectomy in patients treated with 5FU; however, repeated post-operative injections were required (5). A further meta-analysis last year showed that MMC is more effective in reducing IOP and increasing qualified success rate compared to 5FU. However, a higher incidence of complications with MMC compared to 5FU – such as bleb leak, late hypotonia, narrow anterior chamber, endophthalmitis and cataract development – was also noted (6). Taken together, the evidence suggests that the safety profile of 5FU is no worse than MMC, and confirms that 5FU is still a viable option in antimetabolite augmented trabeculectomy surgery.

"Although the safety profile of bevacizumab seems comparable to MMC, the effectiveness of the drug in reducing IOP seems less certain."

(Unproven) alternative options

While MMC is currently the most effective antimetabolite used in glaucoma surgery, there is ongoing research into alternative agents that could augment surgical outcomes without the conjunctival thinning, bleb leak and endophthalmitis that MMC may predispose to. In a rabbit model of glaucoma filtration surgery, topical administration of silver nanoparticles resulted in improved bleb function when compared to MMC (7). The important role of VEGF in the cascade of wound healing, inflammation and angiogenesis has prompted numerous studies investigating anti-VEGF drug bevacizumab as an adjunct to trabeculectomy. Although the safety profile of bevacizumab seems comparable to MMC, the effectiveness of the drug in reducing IOP seems less certain (8). Another study suggested that the effect may be additive if multiple drugs are combined. Bleb morphology and IOP reduction were noted to be superior if MMC and ranibizumab were used concurrently (9). Beta-radiation has also shown significant promise in African populations and may translate well to more typical European/American demographic and conjunctival characteristics, but requires head-to-head comparison with standard MMC surgery (10).

Conclusion

The major confounding factor in comparing 5FU and MMC outcomes is the natural progression of surgical technique over time. Antimetabolite handling and conjunctival closure have improved greatly over the decades and, with the transition from 5FU to MMC occurring concurrently, we risk comparing the older 5FU technique to newer MMC techniques. We must account for this evolution when making comparisons, and care should be taken when directly comparing 5FU and MMC,

unless the technique is standardized.

We are yet to see how this drug shortage will affect the future of glaucoma surgery. Although we may not be enjoying this enforced "step backward" in pharmacological surgical augmentation, it's important to make the most of any positives in the situation. Maybe the MMC drought will allow for future direct comparison with standardized techniques, providing important data that we are currently lacking. It may even open the door for a paradigm shift towards other emerging options, such as beta radiation or combination antifibrotic/anti-VEGF approaches.

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Claudia Quijano is a glaucoma fellow at Guy's and St Thomas' NHS Foundation Trust, England, UK.
Dan Lindfield is a consultant ophthalmic surgeon at Optegra, and glaucoma lead at Royal Surrey County Hospital, England, UK.

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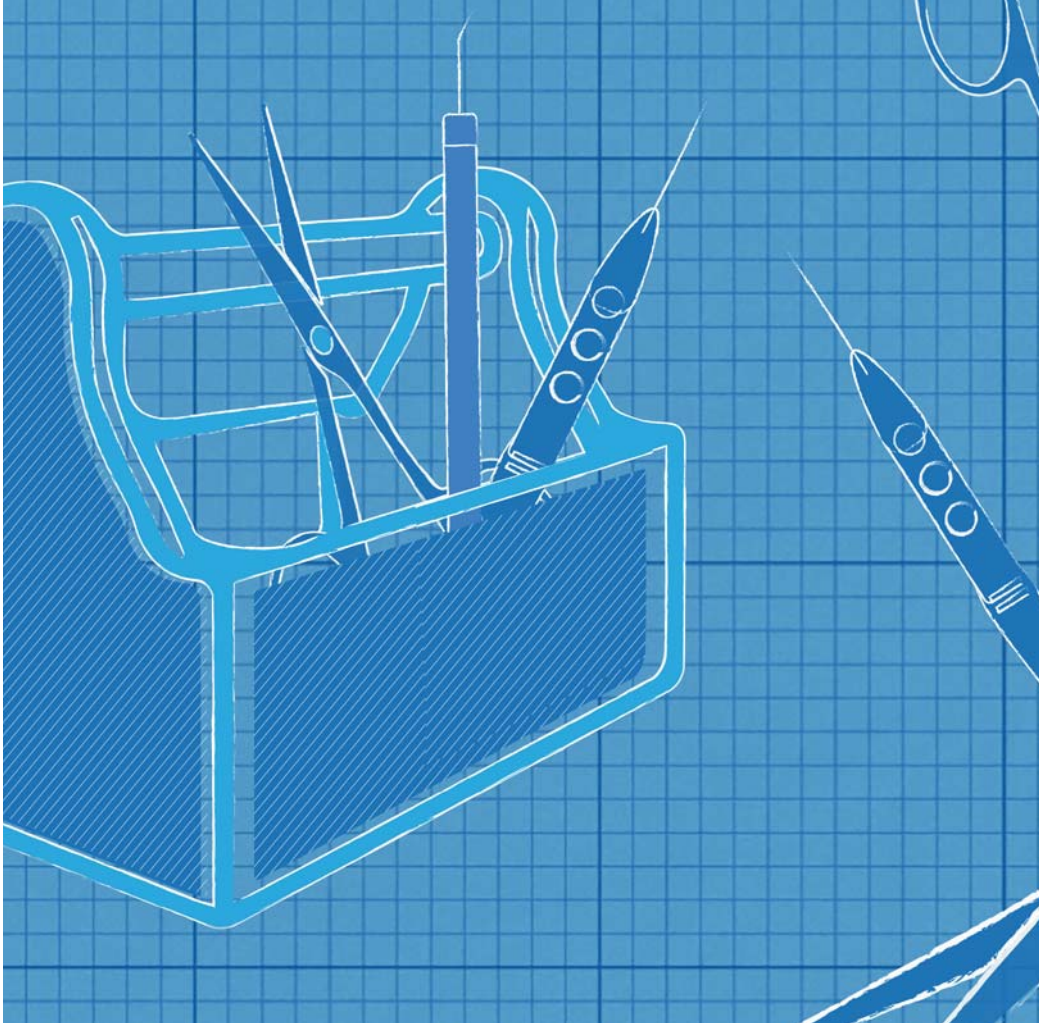


If You Think of It, Use It!

How surgical adjuncts can make cataract surgery safer – and minimize costs in the long run

By David Lockington

"Do you think I should use it?" is often heard in operating rooms from trainees regarding the use of surgical adjuncts when embarking on more complex cataract surgery cases. In the past, surgical adjuncts were often perceived as an unnecessary expensive luxury, and unfortunately these attitudes still persist today.

Here, we discuss how to minimize surgical complications with the appropriate use of surgical adjuncts – from pre-operative planning, simulation training, and strategic case selection for trainees derived from risk stratification. First, let's look at the evidence for challenging incorrect attitudes.

The Scenario Modeling Study

In a recent paper published in Eye, we modeled a common cataract surgery scenario (a white cataract with suboptimal pupil dilation) to evaluate the real-world equipment costs associated with using surgical adjuncts (1). We also modeled the costs of having to deal with the complication of posterior capsule rupture and vitreous loss in that scenario to illustrate the advantages of using preventative surgical adjuncts.

The results showed the profound advantages of spending a little early on, to save a lot later.

Unsurprisingly, significant costs were identified with the management of vitreous loss using the Anterior Vitrectomy Kit (anterior vitrector, triamcinolone, acetylcholine, corneal suture), which outweighed any initial cost saving from not using adjuncts. Moreover, the additional medical costs of further procedures (such as secondary IOL insertion) and extra outpatient follow-up visits (which are not often acknowledged in the surgical environment) were greatly significant. Our basic modeling suggests that an additional initial spend on surgical adjuncts of £137.47 ($178.96) could potentially prevent a further £1293.60 ($1,684, more than a 9-fold increase) in direct medical costs in the complication scenario.

The simple model used in the study demonstrated that the prevention of surgical complications through using appropriate surgical adjuncts, rather than the subsequent management of complications, should always be the preferred strategy. So, how do we go about ensuring a safe precautionary approach to ocular surgery? It must begin prior to the procedure.

Planning at the pre-assessment stage

For me, the surgical process begins in the pre-operative assessment clinic. I want to identify any risk factors that may make the operation more complex. For example, I am looking to positively identify or rule out corneal guttata or scarring, pseudoexfoliation, poor pupil dilation, poor capsule visibility or phacodonesis prior to encountering it intra-operatively. Has the patient had intravitreal injections before? Have they ever used systemic prostate medications? Is the cataract a posterior polar? This holistic approach enables appropriate well-informed patient consent, alerts the whole surgical team to be prepared for predictable complexities, and ensures precautionary adjuncts are readily available to minimize and/or manage potential complications, should they occur.

The potential for any "straightforward" case to develop intra-operative complications should be assumed, and

An example adjunct: my experience with the Malyugin Ring 2.0

The Malyugin Ring was designed by Boris Malyugin (Professor of Ophthalmology, and Deputy Director General at S. Fyodorov Eye Microsurgery Institution, Moscow, Russia) to reduce the risk of complications associated with small pupils. In my experience, the Malyugin Ring provides good reproducible pupil dilation and iris stability. In comparison with iris hooks, the ring's eight points of contact provide an evenly distributed tension on the iris, reducing the potential of "cheese wiring" through an atrophic iris. The spread of force and the lack of external attachment means the iris stays in the natural plane, so it doesn't tent up or get traumatized by instruments being introduced into the eye. The Malyugin ring is also effective in limiting Intraoperative Floppy Iris Syndrome (IFIS) behavior. It prevents iris prolapse because the pupil edge is mechanically restricted by the ring.

When faced with a poorly dilated pupil unresponsive to intracameral phenylephrine, I go straight to inserting a Malyugin ring. It is always safer to place this device early in the operation, before the iris starts to billow, and prior to the anterior capsule being opened.

Before the insertion of the Malyugin Ring, I inject the dispersive viscoelastic device (OVD) into the anterior chamber and beneath the iris. Then, entering through a 2.0-2.2 mm incision, I insert the Malyugin ring via the introducer, directly engaging the distal scroll first, followed by two lateral scrolls. With the use of a second instrument, I engage the last scroll behind the wound. Removal is very straightforward. I find releasing the distal scroll provides the space required to safely engage and retract the ring back into the introducer, and then withdraw the entire device from the eye.

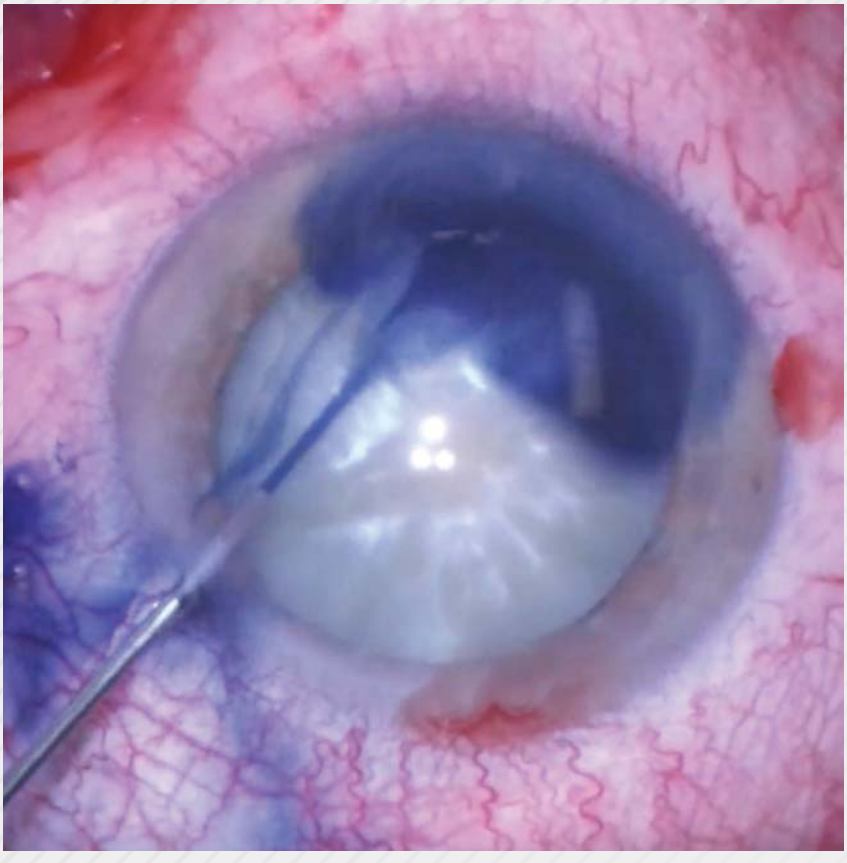


Figure 1. Trypan blue used to improve visualization in white cataract.

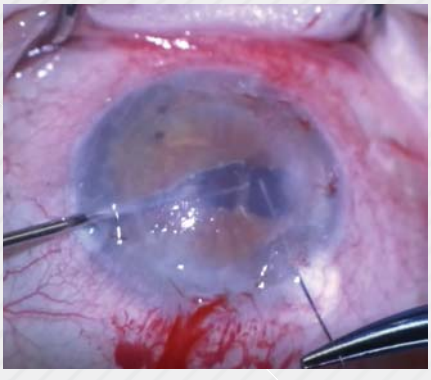


Figure 2. Intraocular forceps.

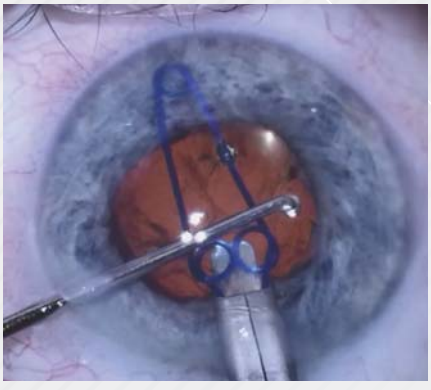


Figure 3. Malyugin ring insertion; using the second instrument to protect cornea on withdrawal.

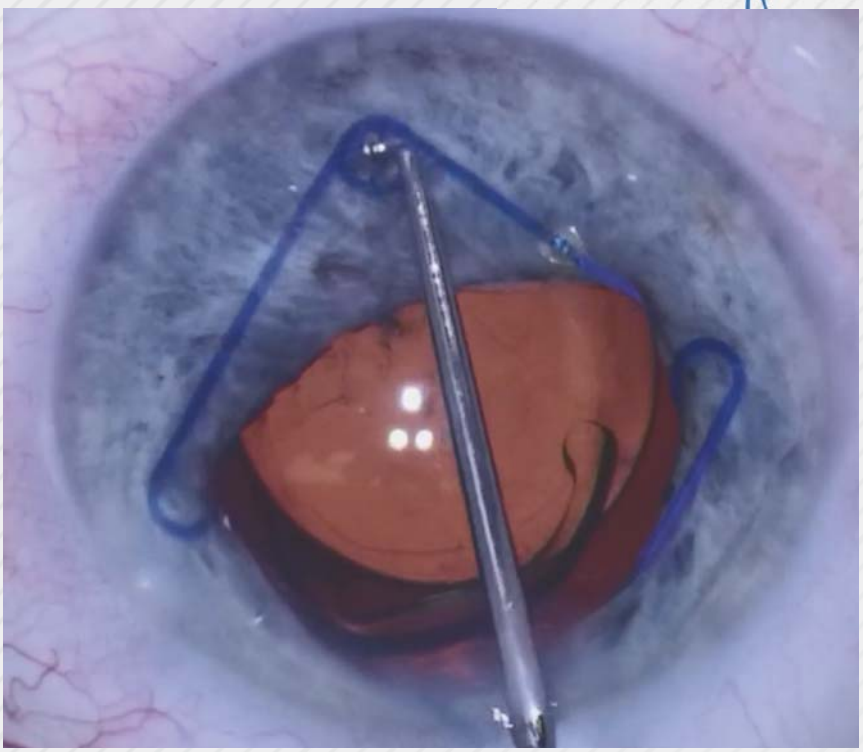


Figure 4. Release of distal scroll.

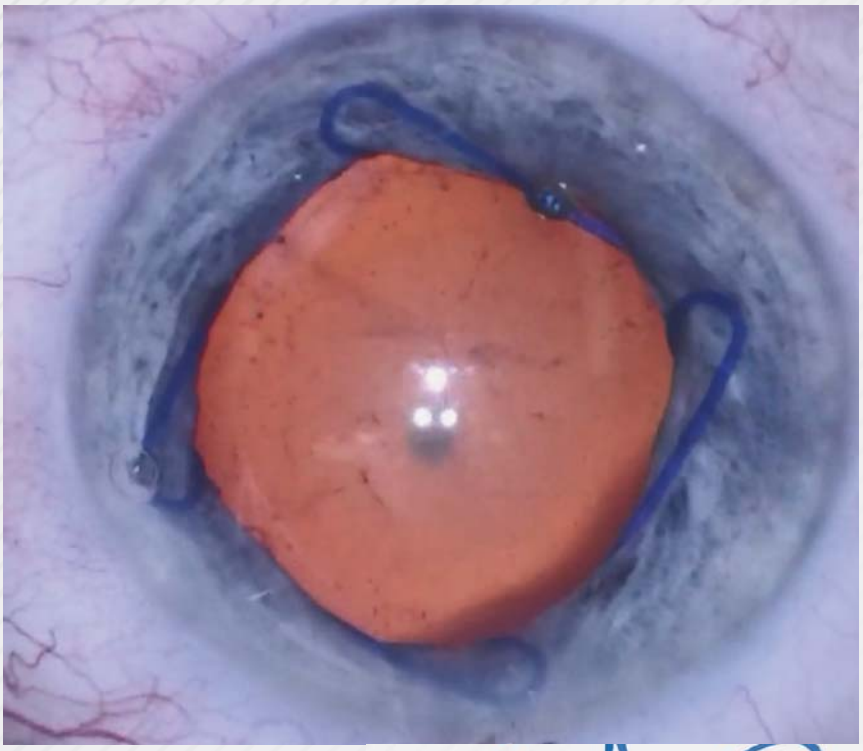


Figure 5. Final position.

the risk mitigated through appropriate pre-operative planning. Surgical adjuncts and the necessary equipment used to manage this risk need to be present and available in theater for safe and efficient use. Adopting this "think-ahead" strategy maintains high standards in theater for all staff and promotes confidence in the surgeon and the patient.

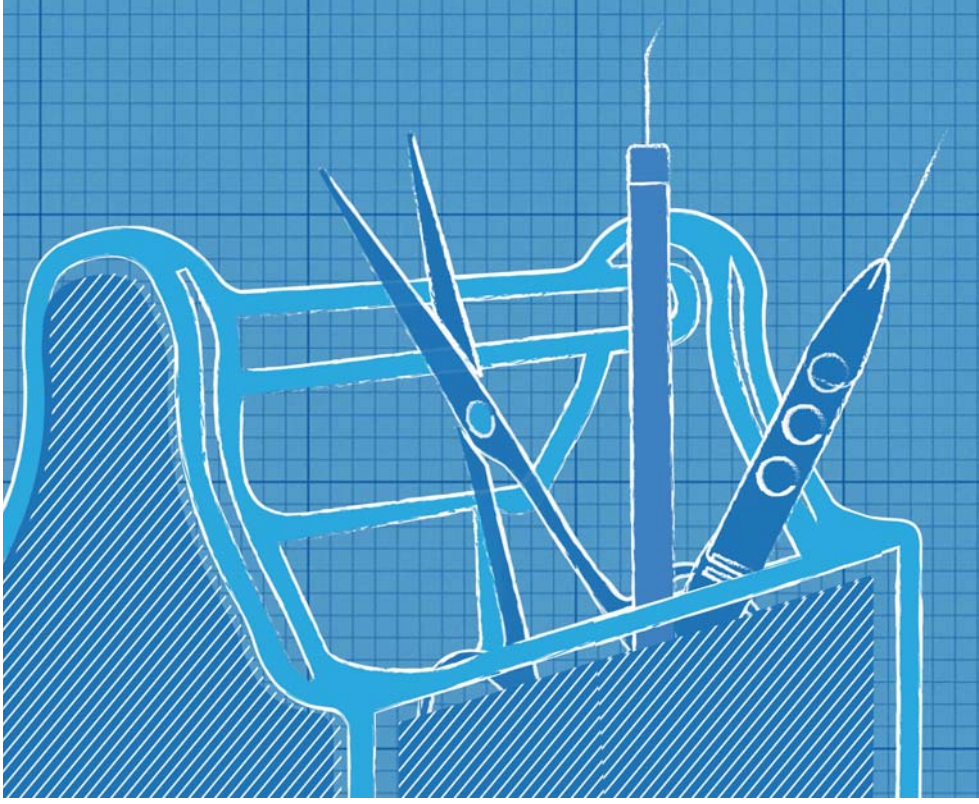
Challenging the existing mentality

Current theater management attitudes towards lean equipment levels could lead to lack of availability of surgical adjuncts, if one is facing an entire list of complex cases. Therein lies the temptation to just "chance it," and hope things will work out fine. Such an attitude is clearly not in the patients' best interests, and so should be resisted. It is safer to adopt a different mentality: "If you think you need a surgical adjunct, just use it", but this strategy obviously requires the adjuncts to be available at that point in time. If the whole theater team is educated to understand the importance of this principle, equipment stock levels will be at an appropriately high level; the true cost of not investing in adjuncts is the subsequent and much greater cost – to both the department and the patient – of managing a complication.

A strategy for success

We should all strive to make ocular surgery as risk-free and safe as possible, and I believe being armed with the necessary adjuncts helps achieve this goal.

There are already good studies demonstrating that Simulation Training provides effective exposure for trainees to learn and hone cataract surgery techniques, with an associated reduction in the rate of complications such as capsule rupture (2). Cataract simulators also provide management of common surgical complication modules, offering familiarity with these techniques prior to such events happening in real life.



These simulations include the use of surgical adjuncts such as trypan blue, triamcinolone, and pupil expansion devices, such as the Malyugin Ring. Effective Case Selection via risk stratification scoring combined with effective supervision ensures the trainee will be performing surgery on appropriate patients within their levels of competency. This approach also allows trainees to progress in a planned structure to more complex surgeries appropriate for their abilities. And it means they will reach the completion of their training with the breadth and depth of experience required to be independent ophthalmic surgeons.

Developing a lifelong learning attitude to engaging with new surgical developments through didactic teaching, expert videos, dry lab simulation, and hands-on wet lab training will help trainees learn new skills, and use surgical adjuncts and techniques effectively in the safe management of complex surgical scenarios.

One such example is the use of the Malyugin Ring 2.0, which is a device used to expand a small pupil. Small pupils can complicate cataract surgeries and there is a growing body of evidence supporting the use of the Malyugin Ring 2.0 in various complicated cataract surgery scenarios (3). If used properly, following appropriate training, this mechanical ring device helps to prevent small pupil complications, which can be costly both financially, and in terms of patient outcomes.

Trainees and consultants alike need planned approaches, with the freedom and confidence to use adjuncts whenever they require, in the quest for safe uneventful surgeries. Early use of surgical adjuncts, such as the Malyugin Ring, intracameral phenylephrine, and trypan blue capsular stain, might help prevent further long-term costs by preventing complications. Equally, appropriate use of other surgical adjuncts – triamcinolone (combined with an effective anterior vitrectomy and the familiarity and ability to place a three-piece IOL in the sulcus); capsule retractors for stability of the bag in patients with weak zonules; and bespoke micro-instrumentation to address issues such as errant capsulorhexis or intra-ocular suturing – can all minimize the risk of turning a complex situation into a much worse complication.

Conclusion

Cataract surgery can be made safer by preventing surgical complications with the use of surgical adjunct devices. The specific value of individual surgical adjunct use is unknown, but equally, the true cost and impact of a surgical complication to the patient is ill-defined, and goes far beyond the operating room costs.

One must acknowledge that the appropriate use of surgical adjuncts will not always prevent complications. Conversely, it is also possible to avoid the use of any additional aids in complex surgery and "get away with it." However, prevention rather than subsequent management of a complication should always be the favored approach. Adjuncts help deliver this strategy.

As a result of the findings in the published peer review paper, there should be greater confidence among trainees (and seniors) to go ahead and employ the necessary precautionary surgical adjuncts whenever they are indicated.

I believe that it is a failure of surgical planning if the surgeon says, "I wish I had used..." during the operation. I have never regretted using a surgical adjunct: if I think of it, I use it!

David Lockington is Consultant Ophthalmologist at Tennent Institute of Ophthalmology, Glasgow, Scotland, with sub-specialist training in cornea, cataract and anterior segment.

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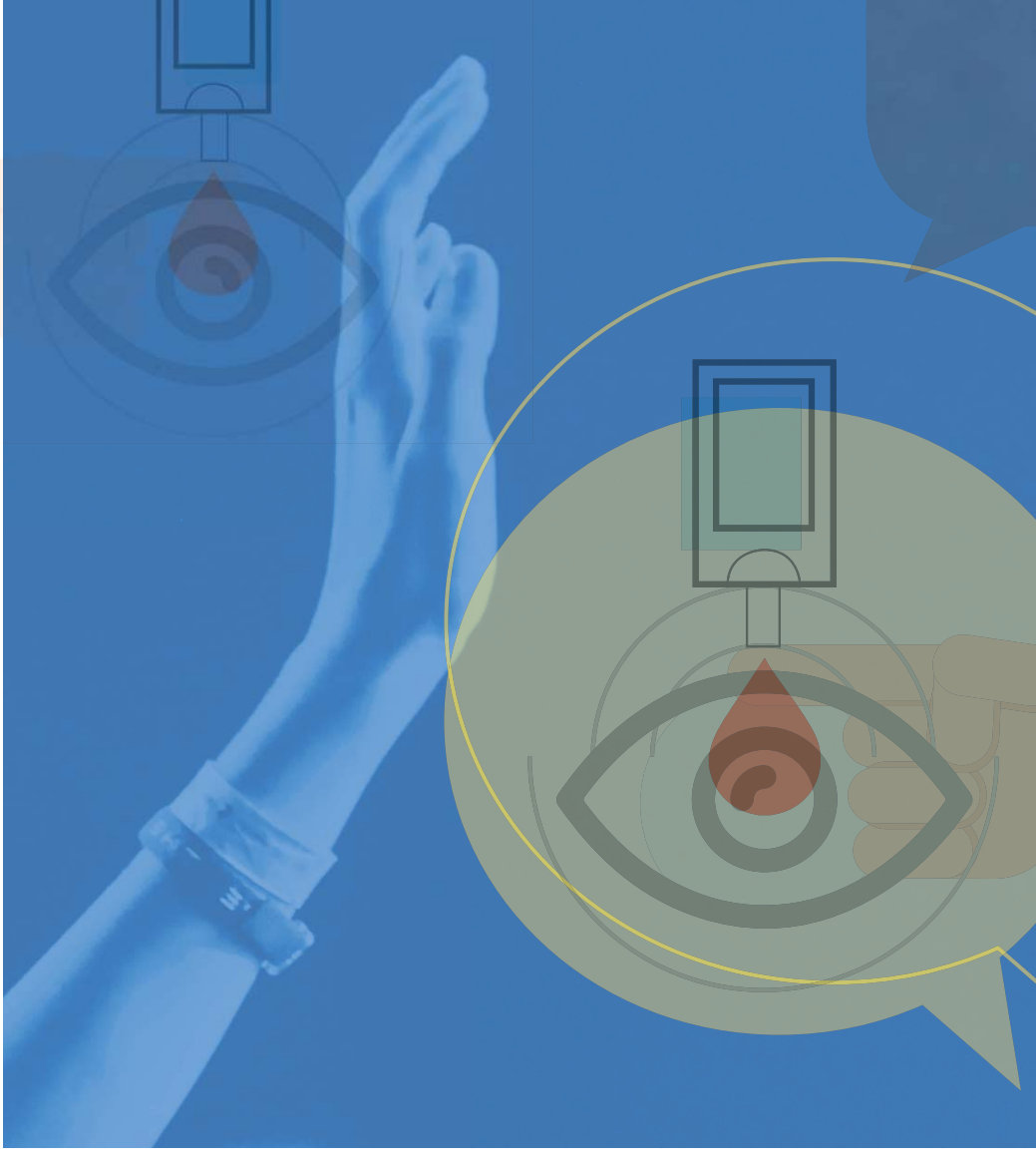
Connecting the Diabetes Dots

How important is a joined-up approach to caring for patients with diabetes and diabetic eye disease? We ask a diabetologist and an ophthalmologist – and their patient.

By Ralph Abraham



Diabetes has its own unique way of presenting itself to patients – or not presenting itself, as is often the case with this silent disease. Unlike so many other illnesses, where a patient suffers a symptom and seeks help from a doctor – diabetes often does not give the patient any such clues. Think about it: macular exudates, occluded coronary arteries, severe proteinuria, even neuropathic ulcers – more often than not, they do not "announce" themselves to the patient in the typical way. And so, the medical approach has been to identify early signs of complications and then provide treatment that reduces the risk of progression of serious organ damage, which not only shortens life, but also reduces the quality of life.

Screening for diabetic retinopathy (DR) has been shown to be particularly useful in identifying early disease, and, in turn, has allowed early referrals and treatment to reduce the number of people going blind from diabetes. Although it is possible that such a service could be outsourced to smartphones in the future, all solutions appear to suffer a disconnect between the disease pathology (a raised blood glucose) and the organ damage (DR). And that is true of most of the complications of diabetes. Once a referral is made to a specialist eye unit, doctors do try and include associated specialists, but the nature of specialist medicine is that it is rare for ophthalmologists and diabetologists to be discussing a patient jointly in a clinic environment – even in private clinics, such as The London Diabetes Centre, where they work together.

So how does the referral process inform the patient? The screening test detects an abnormality and a referral is made. The patient is confronted with words they may not understand; "background retinopathy" is the most common, and the patient fears the worst: blindness. They are not informed of the treatment options; this discussion often does not occur until they see a consultant ophthalmologist. The ophthalmologist has the job – often confronted with information that suggests sight-threatening changes – of telling the patient that they require either laser photocoagulation or intravitreal injections.

"Unlike so many other illnesses, where a patient suffers a symptom and seeks help from a doctor – diabetes often does not give the patient any such clues."

The ophthalmologist's view

Samantha Mann, Consultant Ophthalmologist at Guy's and St Thomas' Hospital, and the London Diabetes Centre, London Medical, UK

Diabetic retinopathy (DR) is affected by the systemic control of diabetes. Progression is accelerated if patients have higher sugar levels and uncontrolled blood pressure – and might need a more invasive treatment as a result. It is important therefore that specialists involved in a patient's care have access to and share information. Not many patients have the luxury of having both the diabetologist and ophthalmologist working together, based on the same site.

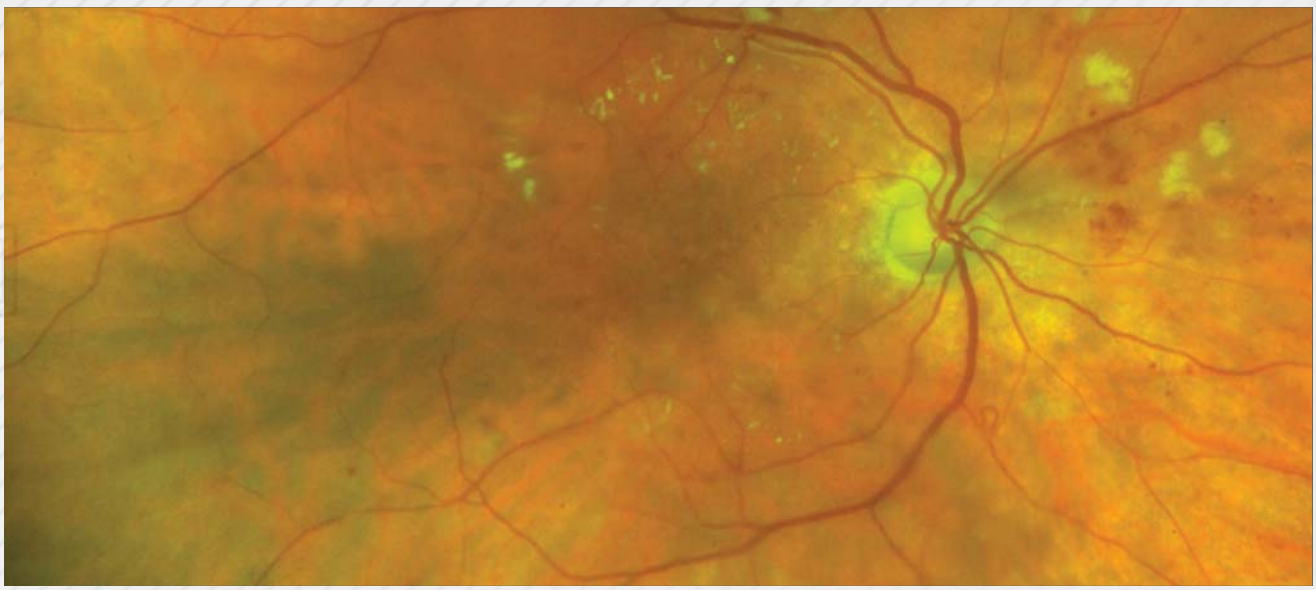
In my practice, we offer a screening service, which helps to pick up asymptomatic diabetic eye disease changes quickly and efficiently, which speeds up the treatment, and improves outcomes.

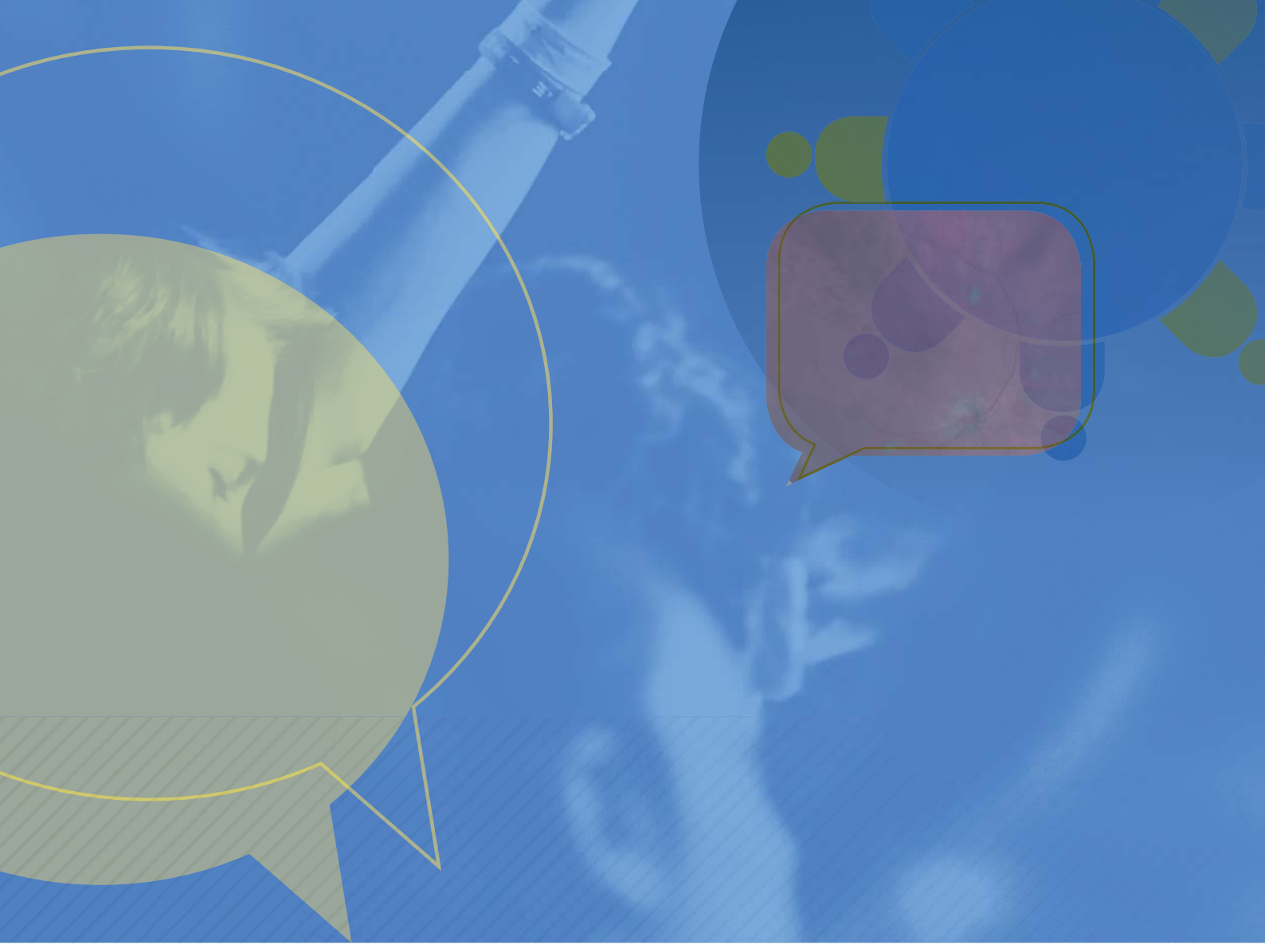
Some patients may only require improvement of systemic control to prevent worsening of their eye changes, but it's important to develop a realistic management plan with the diabetologist, so that this is not done too rapidly. This could have the opposite effect and actually cause progression of the maculopathy or retinopathy. If systemic control is not enough to prevent the disease from developing further, laser treatment may be required or in more severe cases of maculopathy, a course of intravitreal injections; this revolutionary treatment allows us now to improve the vision of patients with diabetic maculopathy – something that simply wasn't possible a few years ago.

Despite its ability to reverse retinal swelling, patients rarely like the idea of having monthly injections in their eyes – and some have a great fear of the procedure. This may help initially to incentivize our patients to try to manage their diabetes better with the assistance of the diabetologist to see if they can, avoid anti-VEGF injections.

If injections are inevitable, I try to explain the process very clearly, talking about the risks and benefits, but also what it is likely to feel like. Once they start the treatment, patients usually see a substantial improvement in vision over the first few months, and can see the reduction of the swelling on their OCT scans when they come back for further treatment.

It is also important to make sure that patients undergo regular eye screenings even if they have good diabetic control and no symptoms, to pick up diabetic changes at the earliest opportunity. Once referred, I also feel it is good practice for the ophthalmologist and the diabetologist to have access to the results including the retinal images and OCT scans to share these with the patient to make them part of the decision-making process. This way the doctors can clearly explain the impact that diabetes control has on the patients' eyesight, using the images to illustrate the problem.





Fatima Ahmad and the patient experience

I had gestational diabetes, which went away after my pregnancies, but then I developed type 2 diabetes when I was older.

In public healthcare settings, the care I received was somewhat fragmented, and the way I was informed about the preferred course of treatment for my diabetic eye disease – anti-VEGF injections – was quite abrupt. I was told that it was the only thing I could do not to lose my sight, without a clear explanation of what the process involved. It was quite a scary experience, and I felt a lot of anxiety associated with it.

I decided to change my diabetologist. I met Ralph Abraham, who scanned my eyes, and directed me to the ophthalmologist, Samantha Mann, even though I did not have any ocular symptoms at the time. I have been in their care for two years now, and they guided me step-by-step through the gradual process of managing my diabetes. I got all the information and reassurance I needed before agreeing to a treatment of intravitreal injections. And that meant I felt comfortable and relaxed.

Every time I undergo the treatment, everything is clearly explained. Thanks to the doctor's attitude, I remain calm and it is a stress-free experience. Based on my experience of different types of setting, it seems to me that, for the patient, it is very important that the diabetologist and ophthalmologist work together in an empathetic way, making the patient feel like their experience matters.

"Many years of clinical contact with patients has taught me that they like to see those changes in their body that signify disease."

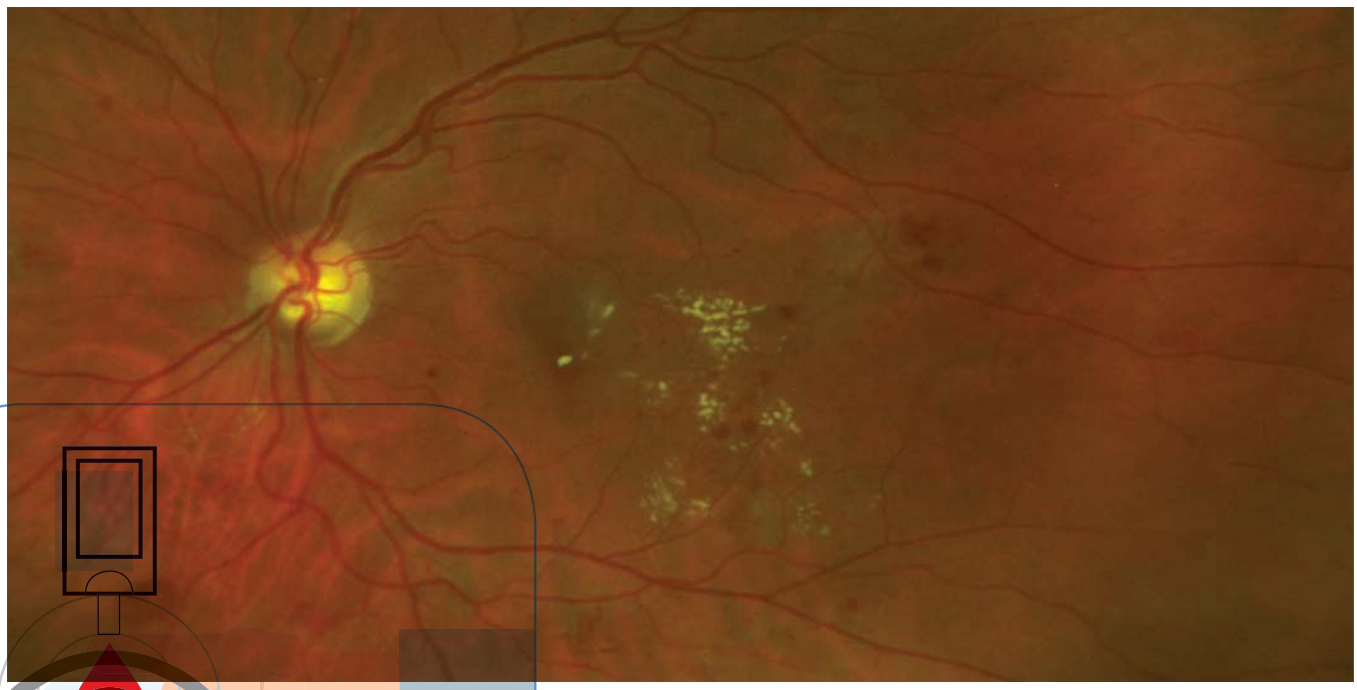
Explanations of what these do, their potential side effects, how procedures are performed, and what their vision will be like later on – all of these conversations must happen in a limited time, in a busy clinic. It's therefore likely that these conversations are not optimal.

Here, I wanted to present the opinions of a patient and retinal specialist to see if there are knowledge gaps in the treatment of DR – ones that can cause patients discomfort or even fear. Should the diabetologist be more involved? In the National Health Service in the UK, once general screening identifies a problem, an appointment is made directly with the ophthalmology department – GPs do not have time for counseling on intravitreal injections, nor do they have the expertise. Is there a role for appropriate application of the Internet to help inform patients before their appointment?

In my clinical practice, I have the luxury of seeing fundus photographs of my patients on the screen in my room during consultations. It is one benefit of working with a team of ophthalmologists. Many years of clinical contact with patients has taught me that they like to see those changes in their body that signify disease. And they want to receive a relevant interpretation from a specialist. It helps them better understand the course of chronic disease, and aids compliance with therapies. If a patient is shown their fundus photographs every time they attend their diabetes clinic – with a reminder that their blood pressure, glucose and lipid control is key to keeping them out of trouble, they try harder to overcome the problems generated by chronic disease management. And they are better able to cope with recommendations for treatment that may be invasive or destructive. Once I show patients hemorrhages or macular swelling on an OCT, I have smoothed the process of referral to my retinal specialist colleagues, with a view to treatment being timely and compliant.

We must remember to ask our patients how we are doing. We must deliver not just on outcomes, but also on patient-reported outcomes. Dealing with patient fears and ignorance is an essential role of the modern diabetologist.

Ralph Abraham is a diabetology and endocrinology specialist and a consultant at the London Diabetes Centre, London Medical, UK.



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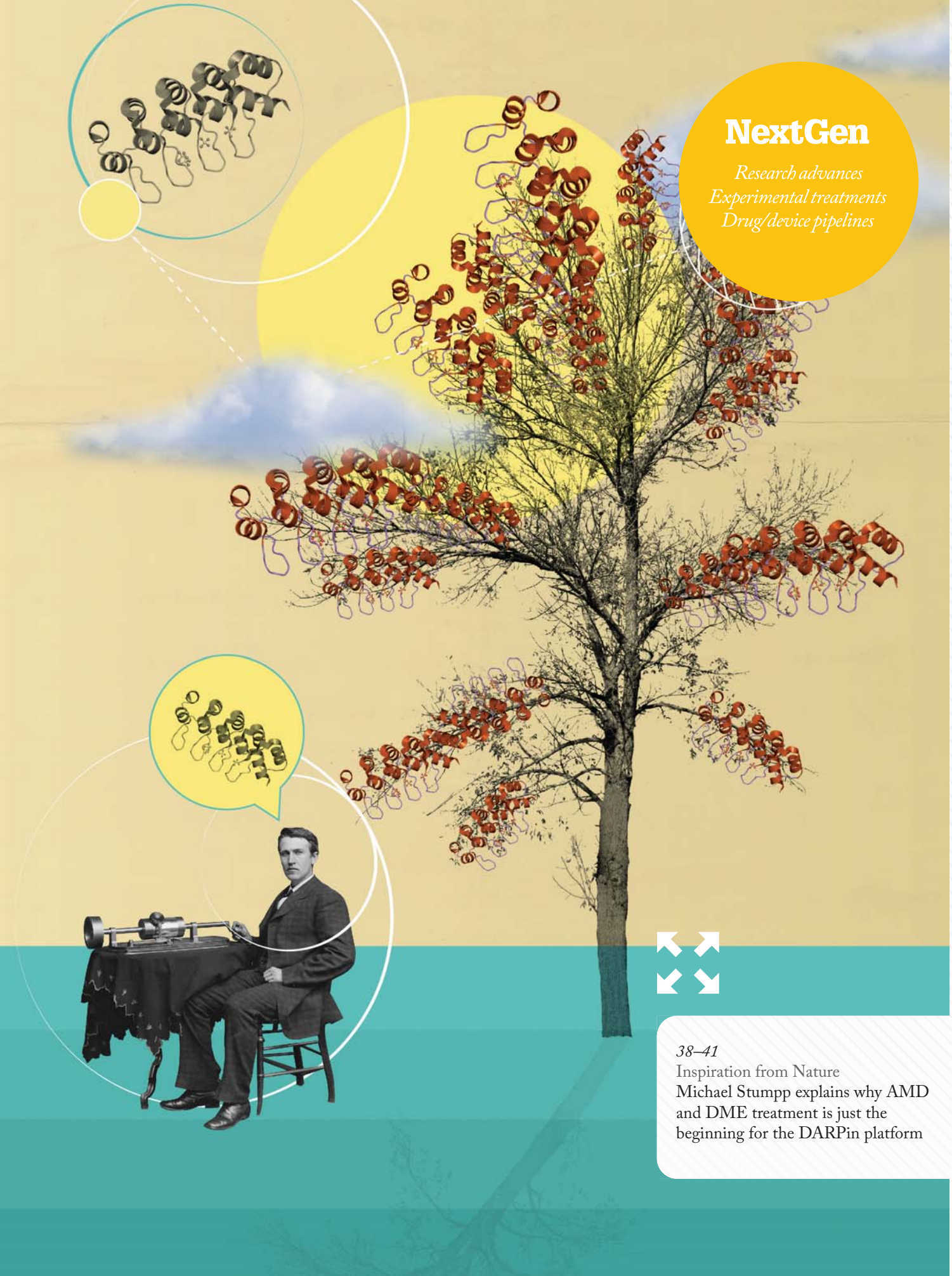


NextGen

Research advances
Experimental treatments
Drug/device pipelines

Inspiration from Nature

The DARPin platform has the AMD and DME treatment burden firmly in its sights – but that's only the beginning

By Michael Stumpp

In the latter half of the 1990s, medical science and biotech in particular were asking a big question: "What comes after antibodies?"

Antibodies have a strong and successful history and have diverse uses, including drug targeting, diagnostic and research applications. For a time, antibody utility and availability dissuaded people from looking elsewhere – that was until a certain post-doctoral researcher, Patrik Forrer, a co-founder of Molecular Partners, made an enlightening observation: nature also uses a very different class of proteins to achieve the same goal as antibodies. These so-called repeat proteins ultimately provide an immune system that is independent of antibodies. The reality is that immunity to pathogen infections is provided by different mechanisms in plants and animals – and there are surprising similarities and informative differences between the two.

"The reality is that immunity to pathogen infections is provided by different mechanisms in plants and animals -- and there are surprising similarities and differences between the two."

Specific problems – specific solutions

We observed that repeat proteins frequently occur in nature as multi-domain constructs, and therefore have several functions included, which is very different than antibodies. Antibodies have traditionally been designed to target one protein with high specificity, and this has led to the development of targeting drugs. However, the concept of multi-specificity allows a drug to be designed with a number of properties, each one having a "specificity" tailored to its purpose. For example, designing a drug to target a cancer in the brain has to include the chemical properties to allow it to enter the brain specifically (maybe even a particular area or function of the brain), and then to search and find the tumor specifically, before killing the tumor without destroying the neighboring healthy tissue. The challenge was to move from an antibody, which is commonly extremely good at blocking one single pathway, to a multi-purpose molecule, without losing any of the critical specificity required to localize its activity.

Nature is continually faced with complex problems, which it addresses with its armory of proteins. Diseases present as multifaceted problems, where multiple things can go wrong simultaneously. To investigate whether multi-specificity could be designed into new drugs, we focused upon the ankyrin repeat proteins, originally discovered in yeast, and developed the DARPin platform. DARPin (a registered trademark owned by Molecular Partners AG) proteins are genetically engineered, antibody-mimetic proteins. The success achieved within the academic world with DARPin molecules led us to consider how best to bring the platform to clinicians.

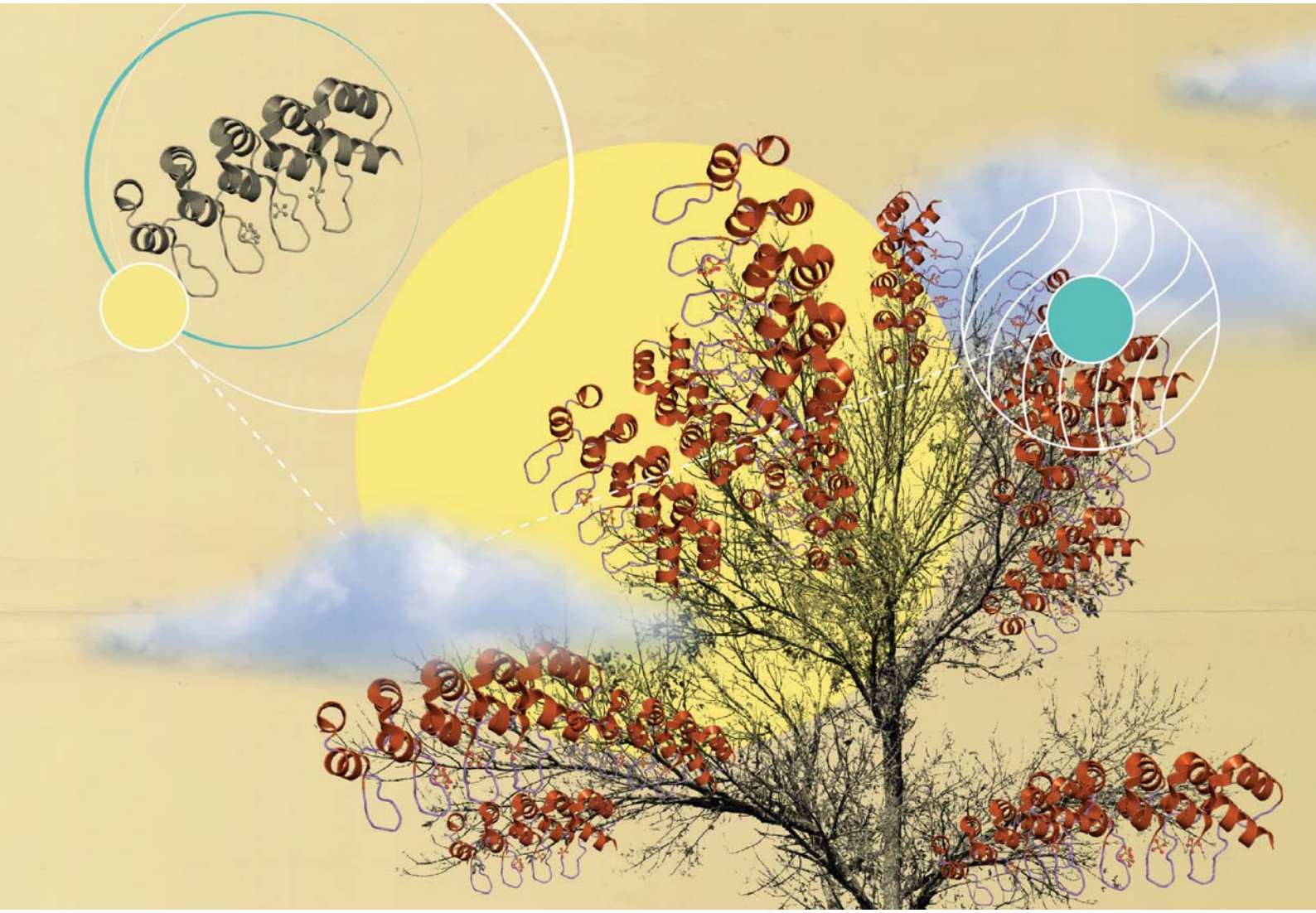
We set up Swiss-based biotech company Molecular Partners in 2004 to take early stage candidates through the first clinical trials. Today, Molecular Partners is 130-people strong and still focuses on bringing novel therapeutics to the patient from DARPin technology, obviating the need for complicated and expensive large biologicals. Notably, the platform also benefits from an ability to generate multiple molecules in parallel and to combine these with already-known drugs to improve their efficacy, duration, or targeting.

The eye as a testing ground

The next significant step in our story was inspired by Genentech's drug Lucentis (ranibizumab) – a humanized anti-VEGF antibody fragment indicated for the treatment of neovascular (wet) AMD, macular edema following retinal vein occlusion, diabetic macular edema (DME), diabetic retinopathy, and myopic choroidal neovascularization. Patients being treated with Lucentis were suddenly regaining sight. However, the frequency of injections was a burden for many patients. And so, we set about designing a DARPin-based compound that had the same therapeutic target but with a longer half-life.

We took the new drug design into the clinic to test whether the drug can last longer in clinical practice. In our first phase I trial, while looking at the safety aspects of the treatment, we were able to determine how long the beneficial effects of the treatment lasted. From this, we were able to test increasing doses using the optimum treatment schedule and investigate patient observations for improvement and duration, correlating these with objective measurements using OCT. The study was a success, not only in demonstrating safety but also determining that the effects of the drug could last beyond a three-month period.

Next, Allergan, the oldest company specializing in ophthalmic solutions, became interested in our work. Allergan had a very ambitious long-term plan to become leaders in the field of retinal diseases – and therefore represented an ideal partner that was able to take the new treatment to the marketplace. Allergan performed the design of the subsequent phase II trial, which comprised three parts: i) a traditional study to address efficacy and ii) an investigation into how much could be achieved with a single dose and iii) how much could be achieved with three loading doses. The trial results demonstrated that a loaded dose every three months compared favorably with monthly dosing of Lucentis, potentially reducing the time a patient would need to spend in clinic and the number of injections received. These results informed the design of the phase III study (see sidebar: "Shaking the AMD Tree"), where Allergan assessed safety and efficacy of 8-week and 12-week treatment regimens compared with monthly ranibizumab in treatment-naïve patients with nAMD, generating the data that allowed the first submission to the FDA for Market Authorization



How does DARPin technology work?

DARPin proteins are genetically engineered antibody mimetic proteins with binding surfaces. DARPin molecules are relatively small in size, with a molecular weight of around 15 kilodaltons. To put things into perspective – this is approximately one tenth of the size of a conventional IgG antibody, or one half of the size of an antibody fragment (scFv) – the smallest antibody fragment currently approved for therapeutic use.

DARPin proteins also have higher binding affinity against the desired target molecules than antibodies. Their small size affords them greater tissue penetration and their higher binding affinity in the picomolar range means that they are active at low concentrations.

The stability of DARPin molecules is also very high, making them ideal for drug development. The DARPin complexes that are formed are typically cleared by the kidney and removed rapidly from the circulation; however, their half-life in the eye has been prolonged by fusion to polyethylene glycol (PEG), to maximize the biological effect. They exhibit high specificity and have high affinity to the target and so represent an ideal platform for macular degeneration treatment.

Shaking the AMD Tree: what have the clinical trials shown?

Abicipar was studied in two identical phase III multicenter randomized clinical trials, CEDAR and SEQUOIA, which compared the safety and efficacy of abicipar with ranibizumab, in treating exudative AMD. The primary endpoint of the trials was stable vision (loss of fewer than 15 letters) at one year. The secondary endpoints were mean change from baseline in ETDRS vision, mean change from baseline in central retinal thickness on OCT, and the proportion of patients who gain three or more lines of vision. The studies ran through two years.

Both phase III trials together enrolled around 2,000 eyes of 2,000 patients. The patients were randomized to receive abicipar every eight weeks, abicipar every 12 weeks or ranibizumab every month.

Overall the studies met their primary endpoint: at week 52, abicipar (given every eight weeks or every 12 weeks) was non-inferior to monthly ranibizumab. The mean change in visual acuity between the three groups was similar (between 5.6-8.5 letters). The mean change in central retinal thickness was also similar between the groups. However, the incidence of intraocular inflammation was higher in patients treated with abicipar, than in the ranibizumab group. In the second year of the study, the incidence of intraocular inflammation was comparable in all groups.

We have seen in the past that biologics benefit from manufacturing improvements over time, which can lead to decreases in side effects, such as inflammation. As a result of a modified manufacturing process of the DARPin compound, in the most recent, MAPLE study, the inflammation rate was lower than in the previous two studies. We expect more information in the future on these cases, but the improved safety profile with the refined process is very encouraging.

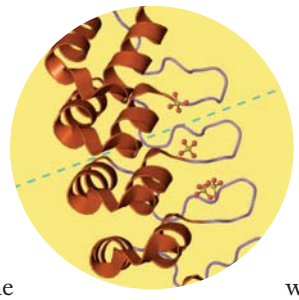
The studies have shown that abicipar is effective when given quarterly for the treatment of exudative AMD. This dosing schedule could greatly decrease the treatment burden for patients with exudative AMD.

(MA). Two parallel, identical phase III studies, called CEDAR and SEQUOIA were performed and enrolled a total of 1,800 patients around the world. Vision increases and the reduction of retinal thickness were the key outcomes. In brief, abicipar at quarterly dosing intervals turned out to be non-inferior compared to standard of care, ranibizumab, given monthly.

All of these studies focused upon AMD. However, a parallel track investigated use in DME, particularly in the familial or diabetic origin of the disease. The results of these studies have now shown that patients respond to loading doses followed by quarterly injections as well as to the monthly injections currently required for Lucentis.

What's next for the DARPin platform?

We are now waiting for the FDA to grant an MA, and we are continually supplying additional data to assist with this process. Allergan is continuing to work on future clinical trials to include DME. Once there is an MA in place, we hope the drug will be brought back to the EU and begin the process of reimbursement negotiations. Hopefully, we will see a drug on the market in 2020. Allergan will drive the commercialization of the product, extending to other markets, including Japan. I think it's important to note that i) the drug will be the first anti-VEGF therapy that can be administered quarterly to every patient and, as such, could become a leader in the field, and ii) it is also relatively easy to manufacture. These two points together make it a promising product for Allergan.



Having proved its clinical application in AMD, the future potential of the platform is very exciting. Because the platform does not generate antibodies, but instead smaller and simpler proteins with similar activities to antibodies, we can more rapidly design other multi-purpose drugs. We can certainly design monotherapies, but the really exciting aspect of the technology is the multi-specificity we can build into the molecules. And that is the direction we now want to take Molecular Partners for other drugs and indications, primarily in oncology. Furthermore, DARPin applications outside oncology can be pursued, mainly in partnership with other companies or academic groups.

Michael Stumpp is Chief Operating Officer of Molecular Partners, Switzerland.

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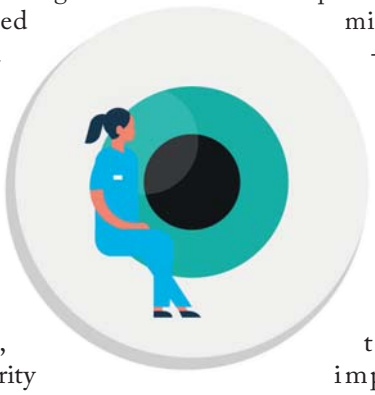
An End to Disparity

Ophthalmology needs a diversity boost – and minority mentoring programs could be the key

According to a study published in JAMA, racial and ethnic disparities in eye care are still prevalent in the USA (1). A higher proportion of blindness among minorities, an increased prevalence of glaucoma in African American and Hispanic patients, and a decrease in the number of minorities who have undergone necessary ophthalmic surgery all point to the need to eradicate these disparities. Furthermore, women and other minority groups remain underrepresented in the ophthalmic workforce despite an available pool of medical students (1).



We talk to Scheffer C.G. Tseng, Co-founder and Chief Technology Officer of Bio-Tissue, and its parent company TissueTech, about the Minority Ophthalmology Mentoring program that is a partnership between the American Association of Ophthalmologists (AAO) and the Association of University Professors of Ophthalmology (AUPO).

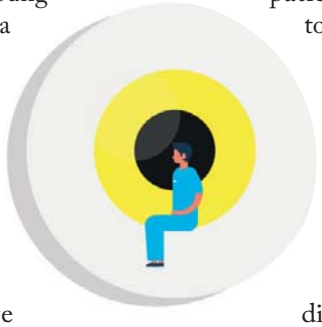
Tseng became involved with the Minority Ophthalmology Mentoring program during AAO's 2019 annual meeting when he was asked to meet with minority medical students and discuss opportunities in ophthalmology with them. "Increasing diversity in medical training may expose physicians-in-training to a wider range of different perspectives and afford them the opportunity to develop interpersonal skills that can result in higher levels of patient trust and satisfaction," says Tseng. "I applaud the American Association of Ophthalmologists and the Association of University Professors of Ophthalmology for working together to address health disparities through this program."

What is the main goal of the Minority Ophthalmology Mentoring program and how did you get involved?

The primary goal of the program is to increase diversity in the field of ophthalmology and encourage minority medical students – those who identify as Black or African American, Hispanic or Latino, and/or Native American – to become competitive ophthalmology residency applicants. Research has shown that access to care improves when the physician community reflects the population at large. Although underrepresented minority groups comprise 30.7 percent of the US population, they only make up 6 percent of practicing ophthalmologists (1).

How can minority mentoring programs make a difference to physicians and their patients?

These programs focus on increasing diversity and implementing change. By increasing diversity, young physicians are exposed to a wider range of different perspectives to develop interpersonal skills that can result in higher levels of patient trust and satisfaction. Programs also focus on implementing change within the healthcare education pipeline to bridge the gap between the racial/ethnic mix of URM healthcare professionals and the racial/ethnic mix of people who need healthcare services.

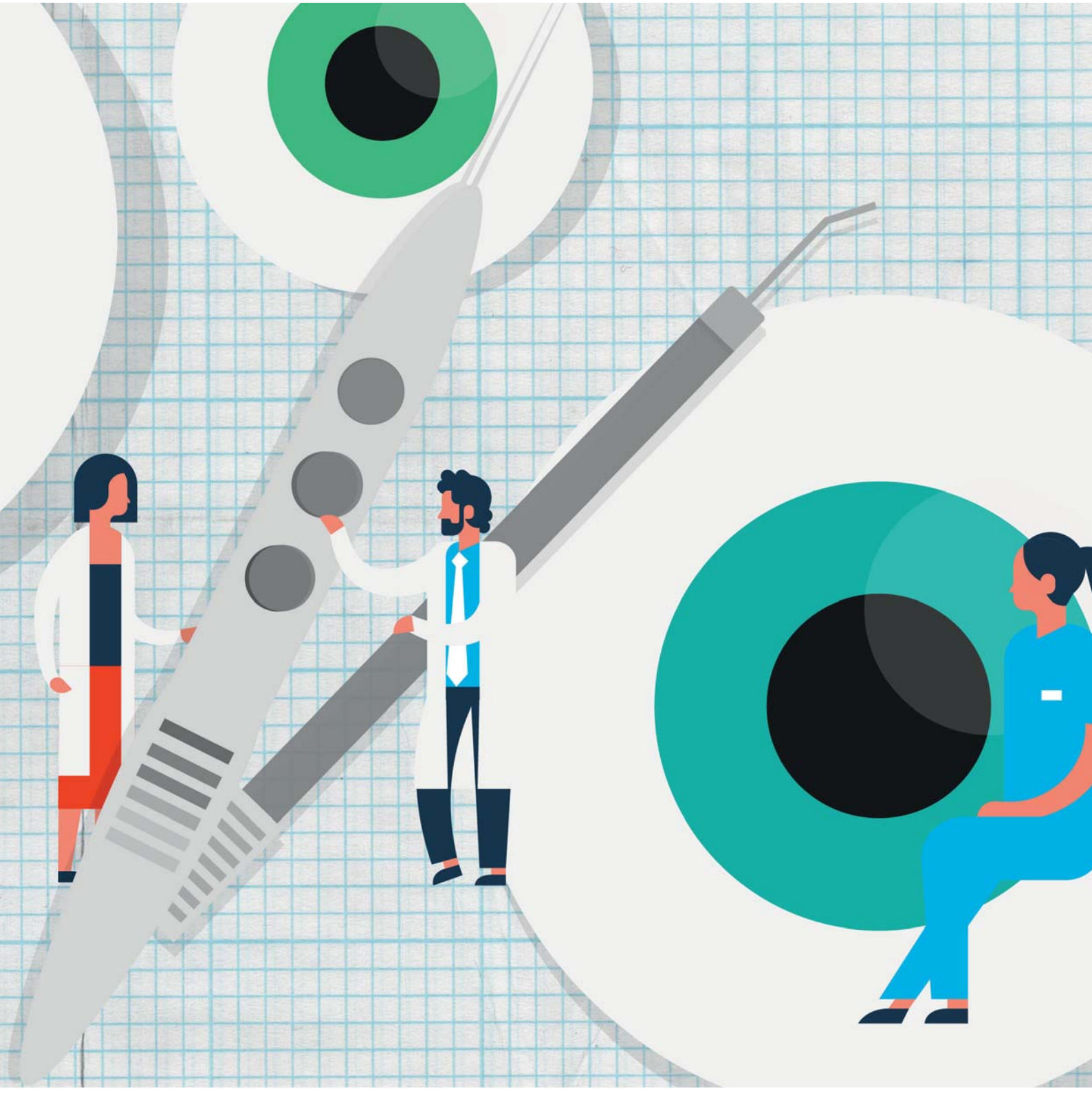


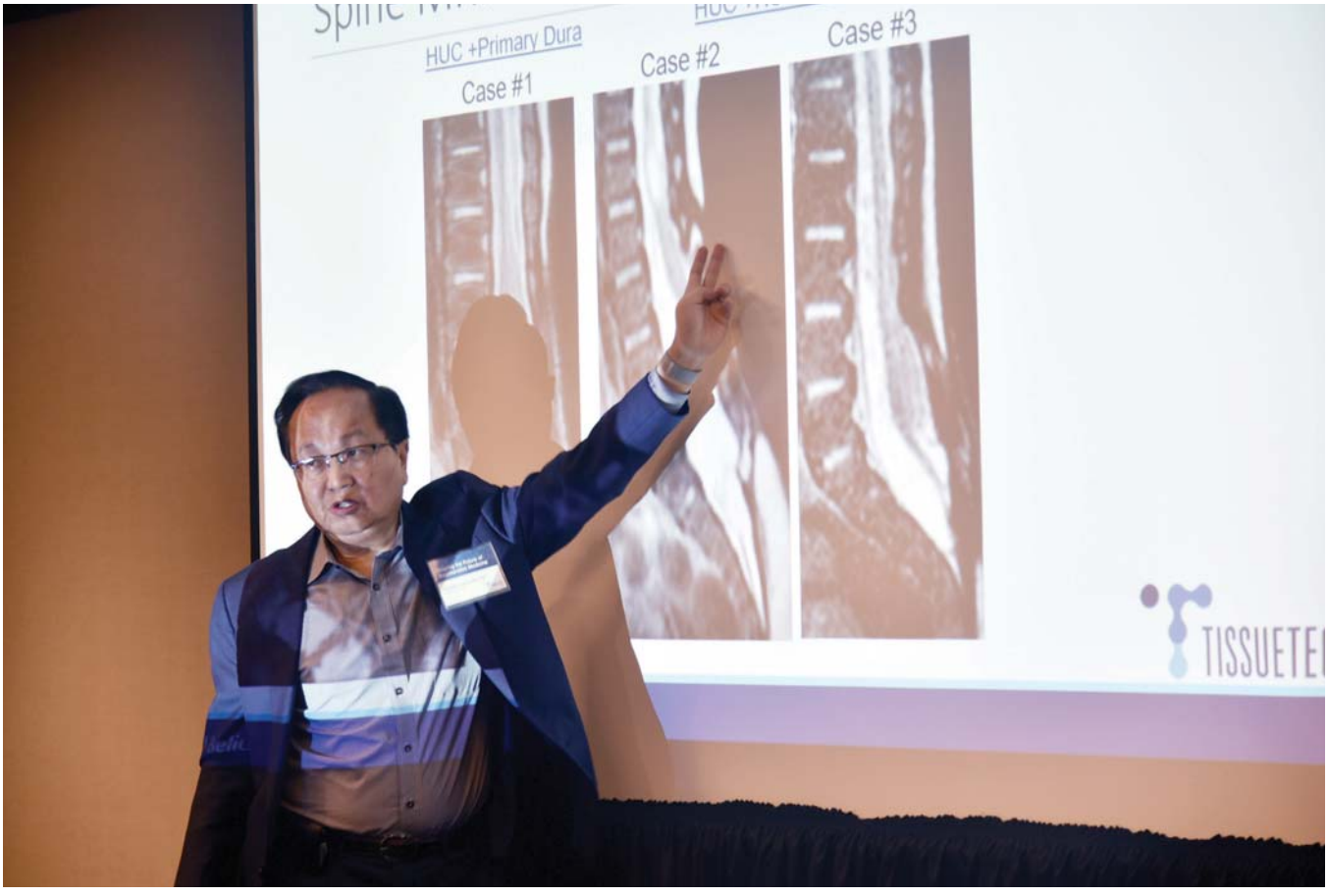
"Although underrepresented minority groups comprise 30.7 percent of the US population, they only make up 6 percent of practicing ophthalmologists."

These programs are critical to improving diversity and decreasing disparities in access to healthcare. They also benefit patients – URMs often speak the language of underrepresented minority patients and relate to them on multiple levels. Additionally, prior research has shown that patient-physician concordance of race, language, and social characteristics strengthen the patient-physician relationship to facilitate higher levels of trust and satisfaction during the patient's office visit (2).

What else can be done to reduce disparities in eye care?

In addition to increasing diversity and implementing





"I am deeply proud of the fact that Bio-Tissue has been awarded the Greater Miami Chamber of Commerce Minority-Owned Business of the Year."

change, more attention needs to be paid to ophthalmology-specific barriers faced by minority residents. In a survey conducted by AAO, researchers learned that insufficient interest, lack of exposure, and the field being "too specialized" were the main reasons why students, regardless of "underrepresented in medicine" status, did not pursue ophthalmology. These factors all need to be taken into consideration if we are going to succeed in growing the pipeline of future minority ophthalmologists and physicians (3).

Diversity is one of the factors that drew me to Miami, where I served as a Chair Professor at Bascom Palmer Eye Institute, University of Miami Miller School of Medicine before starting Bio-Tissue in 1997.

I am deeply proud of the fact that Bio-Tissue has been awarded the Greater Miami Chamber of Commerce Minority-Owned Business of the Year. We afford minority professionals with a unique opportunity to be on the cutting edge of regenerative medicine with our amniotic membrane and umbilical cord human birth tissue products for ocular surface disease. We will continue to encourage diversity in the workplace and supporting future AAO mentorship initiatives.

The Minority Ophthalmology Mentoring Program is seeking URM students in their first or second year of medical school or pre-medical students planning to enter

medical school. Find more information and apply online: www.aao.org/minority-mentoring.

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2. *RL Thornton et al., "Patient-Physician Social Concordance, Medical Visit Communication and Patients' Perceptions of Health Care Quality", Patient Educ Couns, 85, e201 (2011). PMID: 21840150.*
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Partnership Opportunities

One example of underrepresented minority mentoring is that of the provision of grants to educational institutions and employers to support any number of partnership opportunities, including:

- Workshops and conferences that expose URM students to URM health professionals to learn about healthcare careers and requirements for admission to training programs and licensure.
- Summer enrichment programs at health specialty schools to further help URM undergraduates prepare for admissions to graduate-level educational institutions interact with other URM students and faculty.
- Mentorship opportunities between minority faculty members and URM undergraduates during the academic year.
- Paid internships for undergraduate students to work in the healthcare sector as patient navigators, health coaches, or other positions in healthcare organizations.

An Australian Icon

In a new series, we present ophthalmology's most inspiring figures, as told by those closest to them – beginning with the unsurpassable Fred Hollows

By Ian Wishart

In 1968, Australian ophthalmologist Fred Hollows was in his Sydney eye clinic when two Aboriginal Elders presented with eye problems he'd never seen before. After treating the men, Hollows was invited to visit the camp where they lived – Wattie Creek – in the remote Northern Territory. He was shocked by what he saw: blinding trachoma, a disease he didn't think existed in modern-day Australia.

Fred Hollows was more than an ophthalmologist. He was a social and political activist who believed that the basic attribute of mankind was to look after each other. He was a no-nonsense, larger-than-life character who embodied the Australian values that everyone deserved "a fair go." It was these qualities that endeared him to the Australian public, and earned him the honor of "Australian of the Year" in 1990, three years before he passed away. To this day, almost 80 percent of Australians can still identify Fred Hollows, and the organization founded in his name remains one of the nation's largest NGOs.

The Fred Hollows Foundation continues its sight-saving work in the areas where Hollows' mix of medical outreach and advocacy started – in outback Australia, Vietnam, Nepal, and Eritrea. Over the past two decades, its scope has expanded rapidly, now extending to more than 25 countries. After seeing first hand the devastation of trachoma at Wattie Creek in 1968, Hollows gathered a team of eye health professionals and social activists, lobbied decision makers, raised money, and delivered the National Trachoma Program. Over two years from 1976 to 1978, the Program representatives visited more than 100,000 people in remote and rural Australia, treating people in 465 communities. Their hard work halved the rate of blindness for Aboriginal and Torres Strait Islander Peoples.

A recipe for success

The National Trachoma Program's success was based on the active involvement of Aboriginal and Torres Strait Islander Peoples in its design and implementation. This approach remains fundamental to the DNA of The Foundation, and drives its commitment to improving the eye health of Aboriginal and Torres Strait Islander Australians. In 1985, Hollows visited Nepal, Burma, Sri Lanka, India, and Bangladesh on behalf of the World Health Organization. Two years later, he visited Eritrea, whose people were then in the midst of a civil war. These experiences shaped Hollows' outlook. He understood the barriers to providing first-class eye healthcare globally, and decided on a plan to overcome them. He followed a

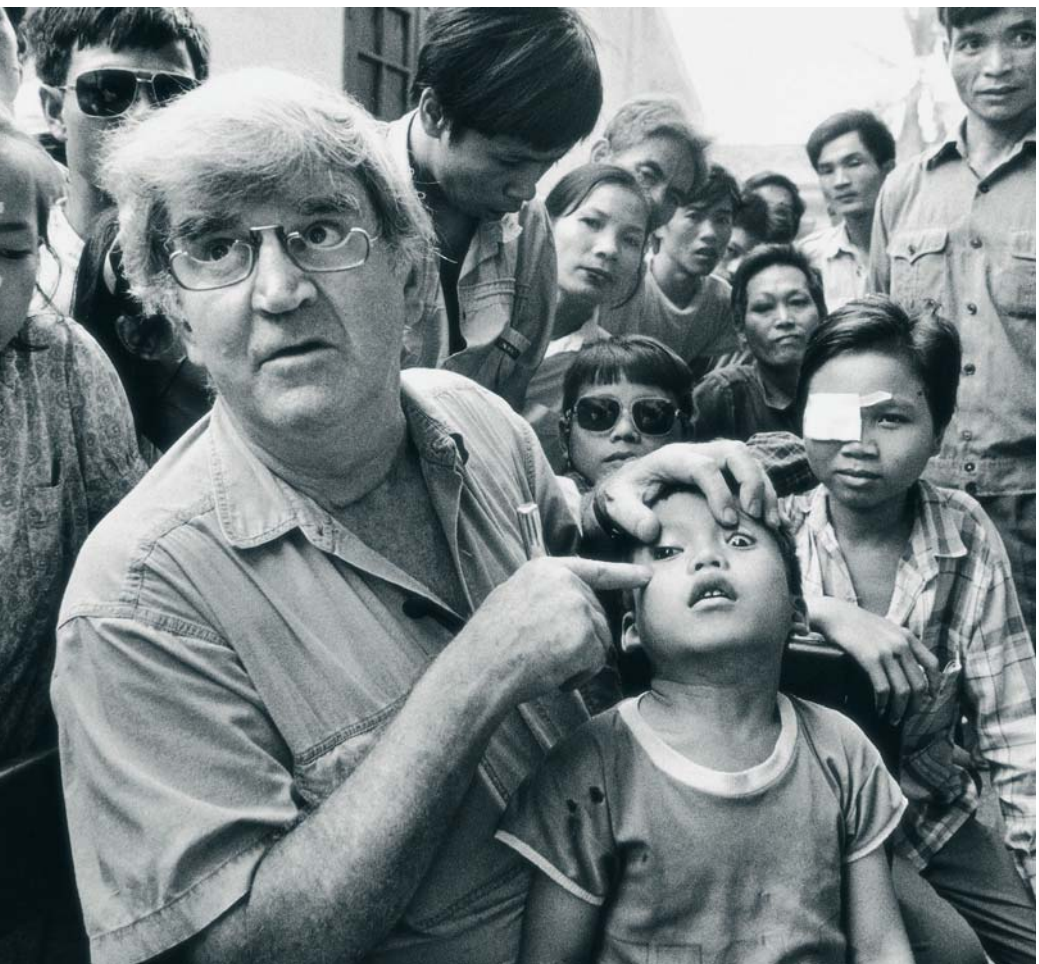
"He was a no-nonsense, larger-than-life character who embodied the Australian values that everyone deserved a fair go."

simple but effective formula that would quickly establish The Foundation as one of Australia's largest international development organizations.

The approach was straightforward: donating capital and skills, and training people to look after themselves. This model remains at the heart of The Foundation's work. Hollows' vision rested on two pillars. First was the development of intraocular lens (IOL) factories in developing countries like Nepal and Eritrea. These factories would develop affordable, high-quality IOLs, produced at a fraction of the cost of those made in industrialized parts of the world. Once established, the factories would also empower those countries to take the lead in developing an independent commercial enterprise that could earn valuable export income. Within five years, the factories were producing enough lenses for local demand, and were soon exporting to 39 other countries.

Second, Hollows invested heavily in training eye surgeons in developing countries in modern surgical techniques. In 1992, he went to Vietnam to learn more about the state of cataract surgery there. He reassured the eager eye surgeons that he would be back to train them in modern cataract surgery, and deliver equipment and surgical supplies. Hollows would never leave a job half-done, and despite fighting a tough battle against cancer, he checked himself out of hospital to deliver on that promise. By the time of Hollows' death in 1993, his "train the trainer" model had laid the foundation for the development of a considerable eye health workforce in Nepal, Eritrea, and Vietnam.

Delivering Hollows' vision fell to his wife, Gabi, and the band of committed fellow travelers who had convinced him to establish an organization with the strategy and financial capacity needed to achieve his goal of ending avoidable blindness. (The Foundation was established around the dinner table of the Hollows' Sydney home, with the first board meeting held at the back of the ophthalmology department at the Prince of Wales Hospital in Sydney.)



Today, Hollows' vision has become a global legacy. Over the past five years, The Foundation, working with its partners, has supported 3.6 million eye operations and treatments, trained some 303,000 surgeons, health workers and teachers, and provided $16.5 million worth of equipment and infrastructure. Empowering local people to deliver local services in partnership with health authorities and other partners – that's the vision I'm doing my best to uphold as CEO.

As the world's population ages, we are acutely aware of the challenges ahead. The Foundation's new five-year strategy is geared towards urgently scaling up efforts to end avoidable blindness – in particular, cataract and the increasing prevalence of refractive error. The Foundation also has a strong focus on improving women's access to eye health through a new initiative called "She Sees" (Editor's note: read more in our February 2020 issue), which places women and girls firmly at the center of our programing, service delivery, partnerships, and global advocacy work.

None of this would have been possible without Hollows. He was not a charity worker who handed out money, fixed eyes, and walked away. He was a social activist, who was wholly committed to creating sustained systemic change to ensure that the highest standard of care was available to those who could least afford it. He is gone, but he will never be forgotten.

Ian Wishart is the CEO of the Fred Hollows Foundation, Australia.

Holding Court

Sitting Down With… Melissa Hunfalvay,
Co-Founder and Chief Scientific Officer
at RightEye, USA

You started out as an athlete – how did you become a scientist?

I originally came to the USA from Australia on a college tennis scholarship. I turned professional but ended up getting an injury. I started coaching and doing graduate studies at the same time. A lot of my doctorate focused on motor learning: what it takes to learn a skill. Around that time, I came across an article talking about a new technology called eye tracking. It was really primitive – lab-based with heavy wires everywhere – but had offered some interesting results. In a comparison of experienced versus inexperienced soccer goalkeepers, researchers found that the experienced goalkeeper looked at the rotation of the leg and the foot before the ball was kicked and was therefore able to predict its trajectory. And that's similar to what I was seeing in tennis. In short, inexperienced players end up reacting to the ball, rather than being proactive.

This work led me to consulting for other sports, like Major League Baseball. I was brought down to spring training. Although it was a sport I was much less familiar with, I was able to give them a picture of where major league guys looked, which was a very narrow focus. The MLB players also looked at specific cues, or locations on the pitcher, in the same order, every time. In comparison, the minor league guys' visual cues were much less focused and distracted. I shared my findings with the staff and there was silence. Finally, the major league hitting coach, who's now a good friend of mine, slammed his hand down on the table and said, "I ****ing told you guys this was important!" We still laugh about it now.

Is it true you consulted for the military?

Yes. If police officers or soldiers think there is a threat in a building, they do what is called a "stack" – a tactical team enters, each member looking in a different place to clear the space as efficiently as possible. I was asked to profile members of the stack to work out whether individuals should be first, second or third in the line-up, since each position requires different skills. But instead of just establishing where each person was looking, the project grew, and I was asked if it was possible to determine a person's depth perception or dominant eye. The idea being, if we could determine their skills and deficiencies, they could potentially be trained to cross over to other positions. This made me take a broader look at vision. It wasn't just about visual search anymore (looking at the environment for cues to determine what to do next), but about fundamentals of vision.

What happened next?

Around 2000, eye-tracking technology became lighter and cheaper as parts were more readily available. I began moving from a consulting model, which was very time and labor intensive, to processing information automatically. In 2012, I was actually playing tennis one night with my now business partner, Adam Gross, when we decided to create a product that automated my consulting work and took me out of the equation altogether! Then cloud-based processing came along and changed everything. What used to take me three months to analyze, can now be done in a quarter of a millisecond! I used 18 different metrics in my doctoral dissertation, RightEye uses over 1,000.

What do you think the eye tracker of the future will be like?

Eye tracking is going the way of webcams – webcams started out as external devices and now they're built into laptops. Eye tracking is already available as a free app for iPhones and other devices, and while it does not have the accuracy of a clinical eye tracker, it can do some screening. It is even available as a feature in some cars. If the driver's eyes close for a period of time, the car will vibrate – what is known as haptic feedback – to wake them up. Eye tracking technology in the future will be built into every technological device you own from the phone and laptop to car, VR headset and even helmets.

You have been vocal about the social benefits of eye tracking. Can you give an example?

It can be as simple as identifying kids who have problems reading. Convergence problems directly affect early reading and learning. Many kids have never even had a basic vision assessment. In elementary school, they may be erroneously considered problem children because they (literally) can't focus on a book. Being categorized as disruptive may put them on a certain track, and certainly stop them from getting services that may help. There are many children, particularly minority children, who go without the help they need because there have not been tests that readily identify such issues.

How can eye tracking help?

Eye tracking is an unbiased way to alleviate the physician assessment and treatment burden. As a technology, it's much more specific than clinical observation. Tests tend to be based on white females and males, but aspects of vision are affected by ethnicity and gender. And that's why it's so important to have normative values specific to certain population groups – to avoid misdiagnosis.

Is that your goal?

If I want to leave a legacy – and I do – it's going to be for the social side of RightEye. Even if just one person benefits from the product, that's enough. I know what value our information has. As of this moment, 266,402 people have used our software. That's over 1.8 terabytes – 10 times 10 million data points – which blows my mind. We can mine that data to find trends and insights into human health and wellness that we could never have imagined without it.

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