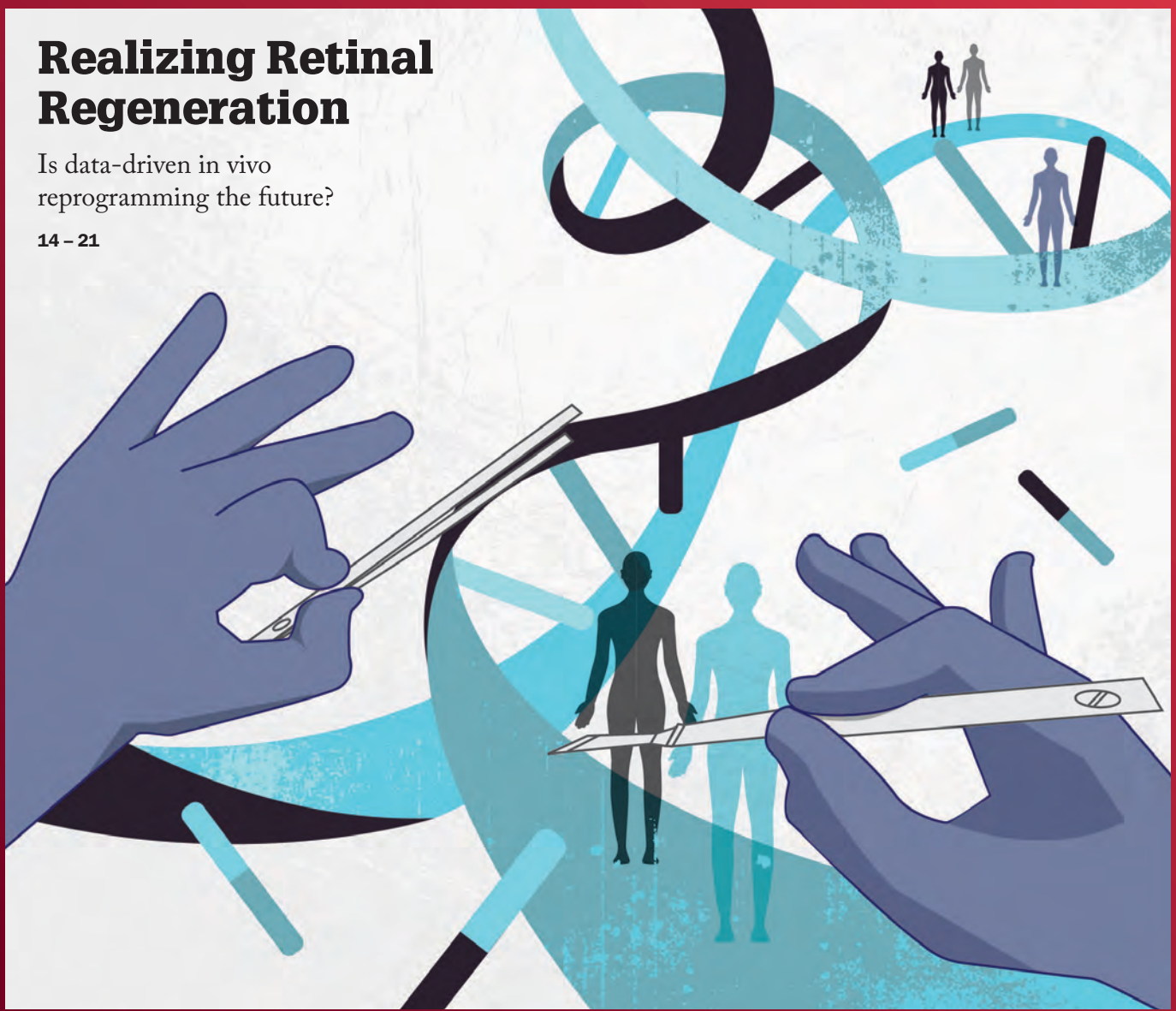
DECEMBER 2020 # 50

the Ophthalmologist™

50 ISSUES STRONG

Realizing Retinal Regeneration

Is data-driven in vivo reprogramming the future?



*In some patients with continued daily use. One drop in each eye, twice daily (approximately 12 hours apart).[3]

†Xiidra is an LFA-1 antagonist for the treatment of dry eye disease. **Pivotal trial data:** The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. **Use of artificial tears was not allowed during the studies.** The study endpoints included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0 to 100).[3]

A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease: ICSS (on a scale from 0-4; 0=no staining; 4=coalescent) was recorded at each study visit. At day 84, a larger reduction in inferior corneal staining favoring Xiidra was observed in 3 of the 4 studies.[3]

Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.
- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.
- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information about XIIDRA®, please refer to the brief summary of Full Prescribing Information on adjacent page.

References: 1. US Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). Accessed April 17, 2020. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1 **2.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628. **3.** Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2016

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

4 CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In five clinical trials of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had less than or equal to 3 months of treatment exposure. One hundred-seventy patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5%-25% of patients were instillation-site irritation, dysgeusia, and reduced visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare serious cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis have been reported. Eye swelling and rash have also been reported *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from premating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Data

Animal Data

Lifitegrast administered daily by IV injection to rats, from premating through gestation day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation

Risk Summary

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

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T2020-87

WORKING TO EMPOWER A NEW ERA OF

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> We might see a day in which the subjective portion of surgery is minimal and **we have more objective ways of lowering IOP**.
>
> **— Dr. Arsham Sheybani**

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Women of the Moment

The world is (slowly) turning over a new leaf – not on its own, but with our combined commitment to change

Just when you thought you were done with voting for this year(!), it's time to go back to the (virtual) ballot box: The Ophthalmologist Power List 2021 is now accepting nominations! But – before you rush off to nominate Ike Ahmed or Eugene de Juan (or both) – you need to know about a significant twist in The Power List plot. For the first time ever, we will be exclusively celebrating women in ophthalmology.

I've had quite a few conversations about the change of format for 2021 – all overwhelmingly positive. People have noted that, despite being as fair as we could make it, The Power List system (open nominations rated by an independent and varied panel of judges) has disproportionately affected women's chances of featuring on the Top 100 Power List. Implicit bias is still hard at work; even in 2020, women made up only 17 percent of our list (1). And only one woman, Carol Shields, featured in the Top 10 – albeit at the very top.

A recent study looked at ophthalmologists' compensation in the first year of clinical practice and found that women's mean salary was $33,139.90 less than that of their male colleagues. The authors concluded that such differences can lead to a "substantial loss" of earnings over the course of a female ophthalmologist's career (2). The problem persists in the good times and the bad; I don't have to look far to find evidence of the pandemic disproportionately affecting women in terms of income, opportunities, and mental health (3, 4).

But are times changing? According to an ASCRS Clinical Survey, though women make up only 8 percent of ophthalmologists with more than 30 years of experience, the figure is five times higher (40 percent) for those with fewer than five years of training or practice (5). The big question is whether this new generation of female ophthalmologists will stay and rise through the ranks or fall prey to the "leaky pipeline" frequently seen in STEM. Increased visibility of the right role models will certainly play a crucial role; as American civil rights activist Marian Wright Edelman said, "You can't be what you can't see."

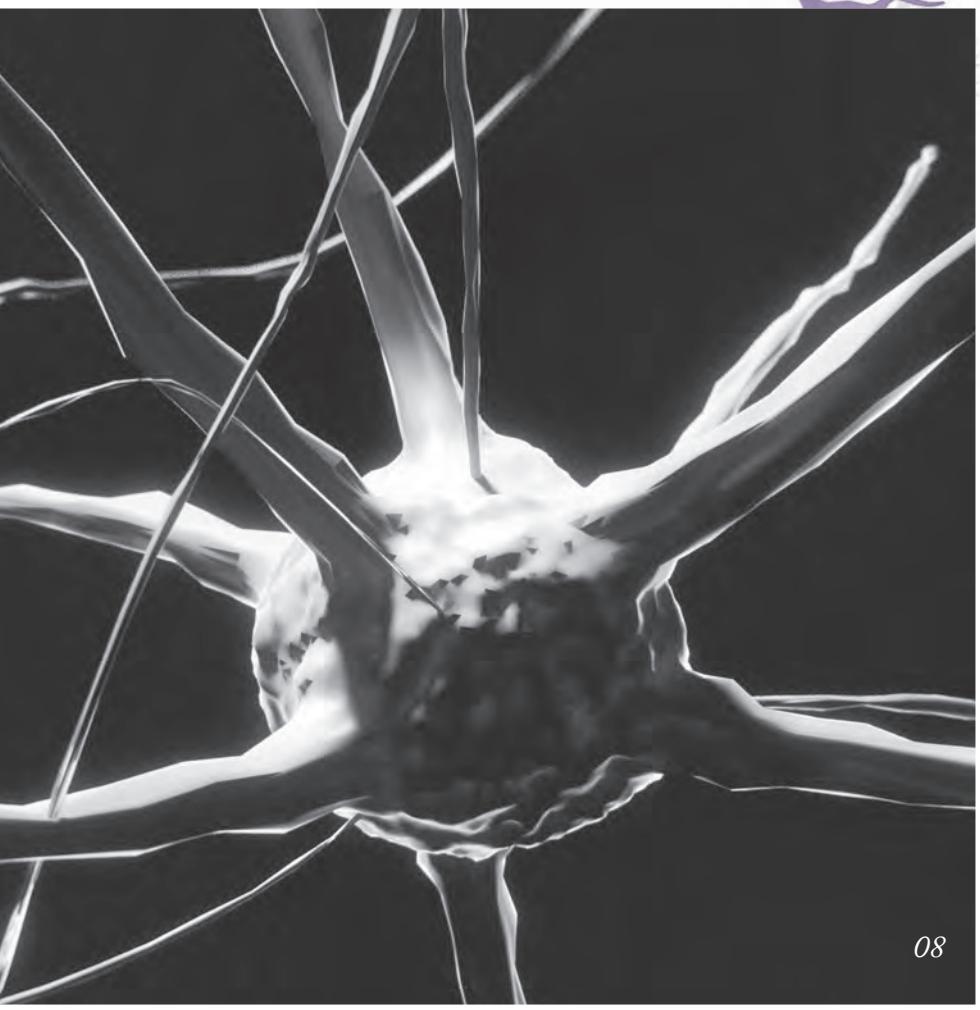
With that in mind, please take a moment to nominate the most influential and inspiring women in our wonderful field – and help make the change you want to see in the world of ophthalmology: theophthalmologist.com/power-list/2021

Aleksandra Jones
Editor

References

1. *The Ophthalmologist, "The Power List 2020" (2020). Available at: https://bit.ly/3fSEE40.*
2. *JS Jia et al., "Gender compensation gap for ophthalmologists in the first year of clinical practice," Ophthalmology, S0161 (2020). PMID: 33248156.*
3. *JK Silveris et al., BMJ Opinion, "COVID-19 and the effect on the gender pay gap in medicine" (2020). Available at: https://bit.ly/36jquGb.*
4. *M Zarefsky, AMA, "How COVID-19's affecting mental health of women physicians" (2020). Available at: https://bit.ly/2Jl7jTH.*
5. *ASCRS, "Clinical Survey" (2014). Available at: https://bit.ly/3fXo6Z2.*

Contents



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In My View

On The Cover

Following cell and gene therapy successes, we look at in vivo reprogramming for retinal and optic nerve degeneration

the Ophthalmologist

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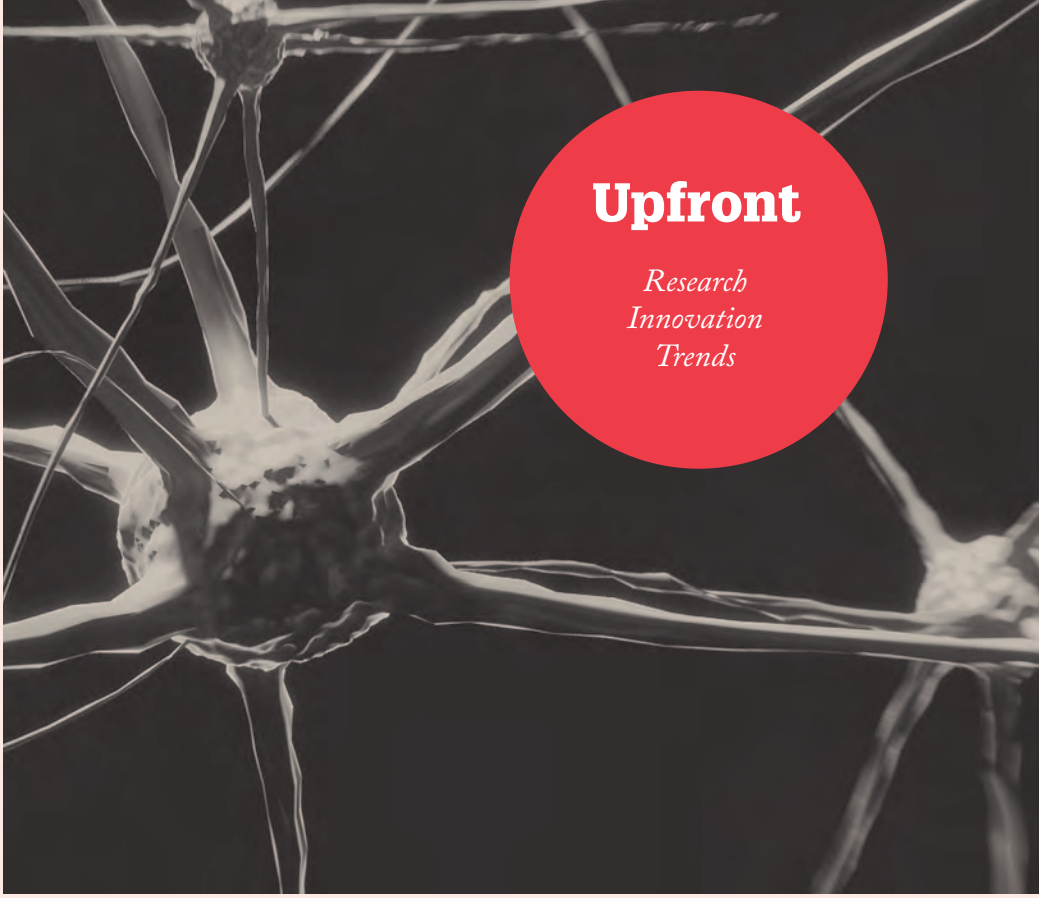

Upfront

Research
Innovation
Trends

(Re)Generation Game

A molecule capable of regenerating damaged nerve fibers may offer hope for glaucoma patients

Retinal ganglion cells extend their axons (nerve fibers) to the brain via the optic nerve to process visual information. When these axons are injured, the damage is usually irreversible – but it may be possible to stimulate regeneration with the help of the adaptor molecule protrudin. Researchers at the University of Cambridge used a cell culture system to grow brain cells in a dish, then injured the axons and analyzed the response using live-cell microscopy. Their findings? Increasing the amount or activity of protrudin in these cells vastly increased their ability to regenerate.

To investigate whether protrudin plays a protective role in glaucoma, the team employed gene therapy to increase the amount of protrudin in the optic nerve, using a viral delivery system that packaged the molecule within a deactivated outer shell. "The system works like a Trojan horse – the cells recognize the viral coat and engulf it, allowing the [protrudin] to be expressed within the cell," says first author Veselina Petrova, a PhD student in the University of Cambridge's Department of Clinical Neurosciences. Though the process of axon regeneration has been studied for decades, our understanding of the exact mechanism of successful regrowth after injury remains limited. "We showed that protrudin, which is part of the transport machinery in the cell, promotes axon regeneration after injury, strengthening the notion that the trafficking of growth components around the cell plays an important role in regeneration" explains Petrova. "Protrudin's interaction with the endoplasmic reticulum is essential for this effect. These findings bring up a novel idea about the involvement of the endoplasmic reticulum in axon regeneration, providing a platform for the development of innovative therapeutics." The team are now working toward testing the safety and efficacy of the therapy in human cells in hopes that, if the treatment is successful, they can soon move onto clinical trials in glaucoma patients.

Reference

1. *V Petrova et al., Nat Commun, 11, 5614 (2020). PMID: 33154382.*

TIMELINE

Influential Black Ophthalmologists

A series of firsts: we explore Black figures who shaped the field


Solatium
The Trustees of Columbia University
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David Kearny McDonogh
Doctor of Medicine

David Kearny McDonogh *(1819-1893)*

Born as an enslaved person, McDonogh trained at Columbia University and practiced at the New York Eye and Ear Infirmary. He was the first Black ophthalmology specialist in the US, even though he was prevented from receiving his medical degree.

Charles Victor Roman *(1864-1934)*

Roman founded the Department of Ophthalmology and Otolaryngology at the Meharry Medical College, and was one of the founders and the fifth president of the National Medical Association and the first editor of the Association's Journal.

BUSINESS IN BRIEF

The latest industry news – in 60 words or less

- Apellis Pharmaceuticals has announced findings from its retrospective database study on geographic atrophy (GA) secondary to age-related macular degeneration. Based on data from AAO's IRIS Registry, the study highlights the significant impact of GA progression on vision and underscores the unmet need for treatment in clinical practice.

- Biopharma company Oxurion has strengthened its intellectual property portfolio governing THR-687 – an integrin antagonist for the treatment of DME – by gaining two new patents. (The European Patent Office and the US Patent and Trademark Office's new composition-of-matter patents will expire in 2039.)
- The EMA has adopted a positive opinion recommending approval of the marketing authorization of Aerie Pharmaceuticals' Roclanda (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%. Roclanda is indicated for primary open-angle glaucoma or ocular hypertension patients who have not achieved sufficient IOP reduction with prostaglandin or netarsudil monotherapy.
- Samsung Bioepis has announced positive one-year results from its Phase 3 study on SB11, a proposed biosimilar to Lucentis (ranibizumab), in patients with neovascular age-related macular degeneration. The data were presented at AAO 2020 and have since been accepted for Biologics License Application review by the FDA.
- Bausch + Lomb has published investigational in-vitro data showing that two benzalkonium chloride preserved eye drops – Lumify (brimonidine tartrate ophthalmic solution 0.025%) and Besivance (besifloxacin ophthalmic suspension) 0.6% – completely inactivated SARS-CoV-2. The results were presented at the 2020 Ocular Microbiology and Immunology Group 54th Annual Meeting.

Newfound Neurons

Could a recently unearthed group of neurons help treat strabismus?

Can you see in 3D? If so, you can thank disjunctive saccades – eye movements that result from eyes rotating mostly in the same direction by different degrees. But, despite their importance, the neural control mechanism that powers disjunctive saccades has proved elusive. Now, however, Julie Quinet's team at the University of Alabama in Birmingham, USA, has found a novel neuron population near the midbrain region: 18 saccade-vergence burst neurons, which produce a burst of activity during disjunctive saccades, but don't fire during other types of eye movements, such as conjunctive saccades or symmetrical vergence movements. Researchers hope that the newly discovered neurons could help find modern treatments for strabismus.

Reference

1. *J Quinet et al., Proc Natl Acad Sci USA, 117, 29123. PMID: 33139553.*

William Harry Barnes (1887-1945)
Having earned his scholarship to the University of Pennsylvania Medical School, Barnes later became the first African American tenured professor there. He served as the 37th president of the National Medical Association.

Patricia Bath (1942-2019)
The first African American to complete residency in ophthalmology, Bath co-founded the American Institute for the Prevention of Blindness and received a patent for the Laserphaco Probe.

Eve Higginbotham (1953)
The first woman to head an ophthalmology department of an academic medical center in the US, MIT-educated Higginbotham became Professor and Chair of University of Maryland's Department of Ophthalmology and Visual Sciences in 1994.

This list is by no means exhaustive. If you would like to suggest ideas for similar content, email aleksandra.jones@texerepublishing.com

Connect 4

Moran Eye Center's researcher Rebecca Pfeiffer on the first pathoconnectome for early-stage retinitis pigmentosa

Last month, we wrote that the NIH-funded Marclab for Connectomics at the John A. Moran Eye Center at the University of Utah, had published a paper presenting the first ultrastructural pathoconnectome of early neurodegeneration (1). Though the pathoconnectome has been modeled on early-stage retinitis pigmentosa (RP), its implications go far beyond the eye and could be helpful in developing treatments for conditions including epilepsy, Alzheimer's, Parkinson's disease, and amyotrophic lateral sclerosis. Rebecca Pfeiffer, a Postdoc Research Associate at the Moran Eye Center, tells us more about the project and its implications for the field.

How did you get involved in connectomics and can you explain your discipline for those unfamiliar with it?

Connectomics is the study of the connections between cells in a neural system. In our case, we look at the connections of retinal neurons. I got involved in it while doing my graduate work with Robert Marc [founder of the Marclab for Connectomics]. My PhD work was focused on metabolism in retinal degeneration, but I hoped to do a pathoconnectome (a connectome of pathological neural tissue). When I finished my PhD, Bryan Jones [director of the Robert E. Marc Marclab for Connectomics] offered me a postdoctoral position so that we could create a pathoconnectome. I've been working in his group for the last three years, focusing on this project.

Why was it based on a model of early-stage retinitis pigmentosa?

We looked at early RP because we want to understand the progression of RP from the initial loss of rod photoreceptors to the complete loss of photoreceptors that occurs later in the disease. RPC1 is the first of the series. Importantly for us, looking at the early stages gives us insight into the effect rod degeneration has on the inner retina before the rods are completely lost. The knowledge that the inner retina begins to rewire as the rods degenerate is important for designing therapeutics capable of interfacing with the degenerating retina.

How does the pathoconnectome help us understand the way neurodegenerative diseases alter neural networks?

The retina is part of the central nervous system. Many processes found in late-stage neurodegeneration in the brain are also seen in neurodegeneration in the inner retina following prolonged photoreceptor degeneration. Also, many rules of synaptic wiring are likely similar between the brain and the retina. Therefore, finding a specific progression of events in downstream neurons triggered by early retinal degeneration may provide treatment targets to stop neurodegeneration in other diseases.

What's next for the pathoconnectome?

The pathoconnectome has many more networks that need to be evaluated. We are already looking into what happens to the next neurons in the network. And RPC1 is just the first in a series of pathoconnectomes; we have already captured and begun annotation of RPC2, which is based on a more advanced stage of RP.

Reference

1. *The Ophthalmologist, "Live Wires" (2020). Available at: https://bit.ly/38LWNiB.*

A Window to Neuro-degeneration?

Detecting neurodegeneration with a protein biomarker found in blood, CSF – and now the eye

Neurofilament light chain (NfL) is being investigated as a potential biomarker of neurodegeneration after it was found in cerebrospinal fluid and blood – but researchers at Boston Medical Center have also detected the protein in the vitreous humor.

Collecting eye fluid samples from ophthalmic surgery patients, they investigated the presence and association of NfL with known biomarkers of neurodegenerative disease. NfL was positively associated with t-tau, amyloid beta, and select inflammatory and vascular proteins in the vitreous humor. It was not associated with existing eye conditions, suggesting it is not influenced by eye disease.

Although further research is needed to validate whether ophthalmic NfL is a definitive indicator of neurodegeneration, the authors hope their findings will help detect disease before irreversible atrophy begins.

Reference

1. *ML Subramanian et al., Alz Res Ther, 12, 1 (2020). PMID: 32943089.*

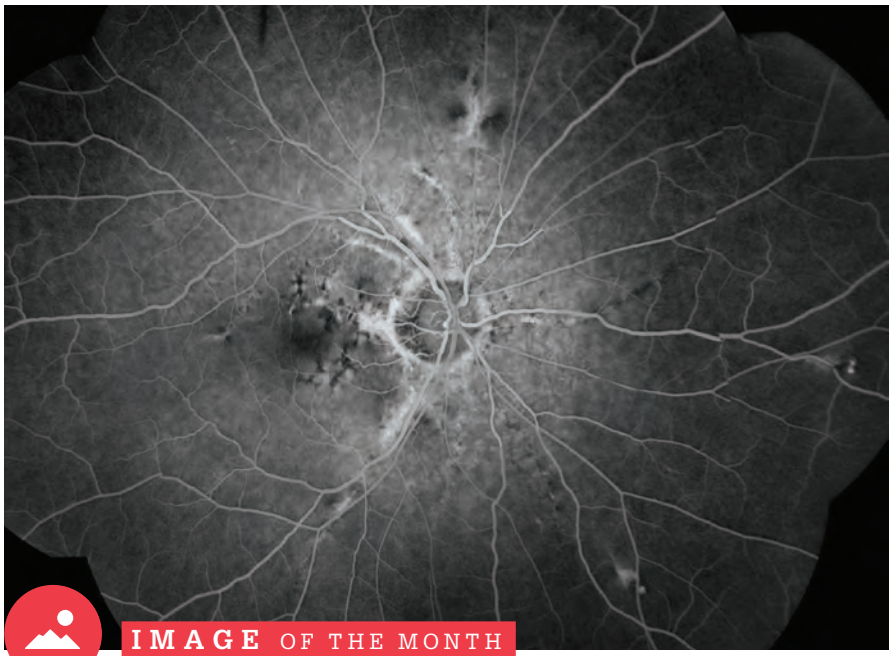


IMAGE OF THE MONTH

Uneven Break

This month's image shows angioid streaks – fluorescein angiography irregular radiations deep to the retina.

Credit: Denice Barsness, Technical Director, Ophthalmic Diagnostic Center at California Pacific Medical Center, Department of Ophthalmology, San Francisco, California, USA.

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

QUOTE OF THE MONTH

Malcolm Gladwell: *"Have the type of conversations that expose consensus."* Wonderful, thought-provoking closing session #AAO2020

Jennifer L. Lindsey, ophthalmologist from Nashville, Tennessee, USA, commenting on the AAO 2020 session, featuring Gladwell in conversation with Stephen D. McLeod, Ophthalmology Editor-in-Chief.

Rajendra Apte, Washington University School of Medicine.

Cornea Contra COVID-19

Unlike Zika and herpes simplex, SARS-CoV-2 does not replicate in corneal tissue

Some viruses, such as herpes simplex (HSV) or Zika, can infect the cornea and use this entry point to spread to other parts of the body – especially in immunocompromised patients. Does SARS-CoV-2 have this ability? Researchers weren't sure until a recent study by a team at Washington University School of Medicine in St. Louis showed that the cornea appears to resist infection from the novel coronavirus.

Led by Jonathan J. Miner, Assistant Professor of Medicine, Molecular Microbiology, and Pathology and Immunology and Rajendra Apte, Paul A. Cibis Distinguished Professor of Ophthalmology and Visual Sciences at Washington University School of Medicine, the team exposed mouse and human corneas to the virus and identified substances in corneal tissue that inhibited viral growth. That isn't a free pass to take off the eye protection – it's still unknown whether tear ducts or the conjunctiva are vulnerable to the virus – but COVID-19 is unlikely to be transmitted through corneal transplant or similar procedures.

Reference

1. *JJ Miner et al., Cell Rep, 33 (2020). PMID: 33147451.*

In My View

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

Of Surgery and Skiing

My memories of Alan S. Crandall – physician and friend

By Jim Davison, cataract surgery specialist at the Wolfe Eye Clinic, Marshalltown, Iowa, USA

I feel very lucky to have gotten to know Alan. He invited me to be a faculty member at his first Snowbird Ski Meeting in Utah, USA. It was a long time ago (in 1989) and there were only six of us lecturing that first year. We would give talks in the morning and help in the phacoemulsification lab in the afternoon. And then we'd ski. His idea was that once you were a faculty member, you were always invited back. And return I did – for the next 30 years.

I wasn't alone in this pilgrimage. Alan was so enthusiastic that he attracted many other people to participate at many levels. But it wasn't just his enthusiasm that drew us to him. He had a uniquely wonderful combination of curiosity, scientific passion, energy, diligence, honesty, humility, selflessness, generosity, and compassion. And he was a fun-loving guy with a great sense of humor, who feared nothing. His smile and laughter were infectious; we wanted to be around him, we wanted to work with him, and we wanted to have fun with him.

I learned more at that meeting than at any other and met so many fabulous people in the ophthalmology community there. Alan's open nature was the theme that permeated the meeting. Faculty, attendees, residents, fellows, industry representatives, and sponsors mixed as one – both in the scientific sessions and in afternoon recreation. The microphone was open to anyone. And the video sessions after hors d'oeuvres and hot tubbing became legendary. We all learned a lot and had great fun together.

Because of his essence, the meeting was successful and grew. He attracted wonderful people to attend and participate, most of them year after year, just like me. The gathering could have been called the Meeting of Future ASCRS Presidents; so many of the bright young people who came to be a part of those very special events were also destined to hold that position.

Alan was an awesome cataract surgeon and chose to specialize in glaucoma, probably the most difficult subspecialty in ophthalmology. The eventuality of blindness from glaucoma is extremely and continuously threatening to patients and substantially intimidating to physicians. Trying to save patients' sight from being extinguished by that disease required all of his best attributes. He was made for it. His surgical interventions were dramatically successful for many, but he helped countless more with his dedication, wisdom, and diligence. Taking care of those patients required years of tireless faith and commitment that most of us are not able to successfully muster. He also chose to dedicate a significant portion of his life to domestic and international mission work, helping those who would otherwise not have access to vision saving or restoring treatment.

We will all miss Alan, but we can continue to have our lives inspired by him – by remembering his work and the love that he had for all of us, as well as the love that we had for him.

Sit Down, Speak Up

With conferences no longer bound by geography, the spotlight can shift from "the West" to the rest of the world

By Valentina Gracia Rey, Second Year Resident at Universidad del Norte, Barranquilla, Colombia

Like most conferences, the World Ophthalmology Congress was held virtually this year. The event, which was supposed to take place in Cape Town, South Africa, still threw a spotlight on the country and the continent's great talent. Although the pandemic put a stop to people physically attending, I like to think it encouraged (virtual) attendees to consider what's going on elsewhere in the world; for example, Latin America.

Before the pandemic, Latin America showcased its talent and efforts through the Pan-American Association of Ophthalmology, which hosted monthly webinars from various countries. Though the webinars were very interesting, they took place at 6 or 7pm, when I was often too busy with patients or studying to benefit. Since Latin America went into lockdown, each country has been organizing its own webinar programs, starting with Peru – the first country to enforce a strict lockdown. And without surgery or school, I suddenly had time to watch them on an almost daily basis – and I found the content incredibly interesting.

Since then, other platforms have emerged. My favorite, from Oftalmo University, is called "Empty Chair" – a webinar that features a case or lecture from a different speaker every Wednesday. The best bit? Anyone can apply to become a speaker. By opening up the invitation in this way, Empty Chair gives a voice to many ophthalmology community members who would not usually have the chance to present to such a large audience – and these are huge webinars with hundreds of assistants – not niche shows for an exclusive group of professors. I love that everyone – even first-year residents – at least have the opportunity to present in an environment that is friendly and encouraging.

I had the opportunity to speak about a novel surgical technique in keratoconus. My application was accepted on the second try. Panelists are allowed to speak for a maximum of seven minutes and at the end of the session, the panel and the audience each chose a winner. I have to admit, I was nervous at first, but it was such a warm, safe space I just focused on doing my best.

Such initiatives seem to be having a really positive impact on Latin American ophthalmology. It has also united residencies all along the continent and the globe, letting us create a network of future ophthalmologists – something I hope continues long after the pandemic ends.

World Wide Web(inars)

The second wave is upon us and, as many countries go into lockdown, it is more important than ever to focus on the positives

By Atanas Yuliyanov Bogoev, Fourth Year Resident at the Vision Eye Clinic, Sofia, Bulgaria

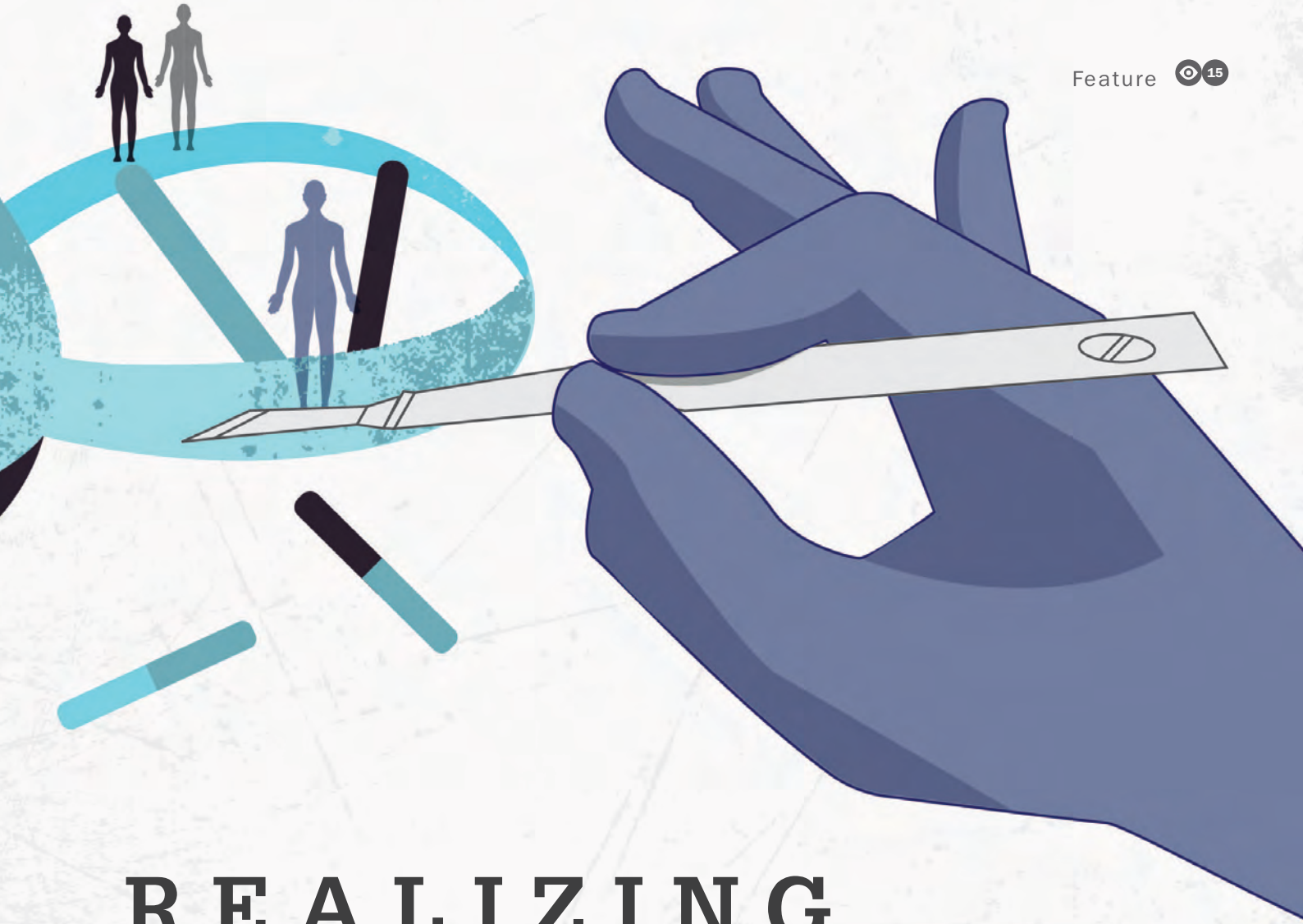
Webinars represent one positive aspect of the lockdown. Suddenly we have access to the world's best mentors, just as they

finally have the time to share their skills and wisdom. Even better, we often gain their time and insight for free – and we should definitely take advantage of it.

Although nothing can beat real surgical training, what we can do is focus on mastering the theoretical side of surgery. It is our job to seek out tips and tricks that we wouldn't be able to find anywhere other than conferences. (Even when at conferences, we are only there for a very limited time and the scale can be daunting). Having the opportunity to access all that information from the comfort of our own homes is amazing.

During the first lockdown, I helped host a big web meeting here in Bulgaria. A professor and I were inspired to act after a mandatory residency course actually got cancelled – we figured we could scale up the course. In the end, 70 percent of the residents in Bulgaria attended – a huge success! We had planned for a two-hour meeting but it continued for almost four hours, with countless questions and really positive feedback from attendees.

However dark the times feel, there are still positives – you just have to choose to find them.



REALIZING RETINAL REGENERATION

HOW CAN DATA-DRIVEN IN VIVO REPROGRAMMING BE USED TO TREAT RETINAL AND OPTIC NERVE DEGENERATION?

By Evdokia Paza, Alice Lightowlers, Tim Landy, and Geraint Parfitt

Approximately 1 in 2,000 people worldwide are affected by inherited retinopathies (1) but few treatment options are available for retinal degeneration. There is also no cure for glaucoma, which affects 60 million people worldwide (2) and is caused by degeneration of retinal ganglion cells (RGCs) and their axon bundles that form the optic nerve. The FDA's 2017 approval of Luxturna to treat inherited retinal degeneration caused by biallelic mutations in RPE65 has established viral vectors as a viable clinical therapy to monogenic retinal disease. Furthermore, advances in pluripotent stem cell techniques have enabled retinal pigment epithelium (RPE) to reach clinical trials as a cell therapy for treating AMD (3). Now it is time to talk about in vivo reprogramming: a novel therapeutic approach that will circumvent the issues with subretinal transplantation of cell therapies and the challenge of targeting every monogenic condition with gene therapy.

A REFRESHER IN HOW THE EYE WORKS...

To enable vision, photoreceptors in the neural retina absorb photons and cascade a signal through isomerization of 11-cis retinal and conformational changes in membrane-bound opsin proteins. This phototransduction causes hyperpolarization and closure of cGMP-gated cation channels, and the signal is propagated to bipolar, horizontal, then RGCs in the retina. The photoreceptor outer segments, where opsins are densely populated, are phagocytosed by the underlying RPE. The RPE monolayer forms a blood-retina barrier, which means there is an immune privilege for retinal cell therapies. Typically, RGCs are responsible for transmitting the visual information from photoreceptors to the brain; however, a sub-population of RGCs have been shown to be photosensitive and involved in the regulation of circadian rhythms. The axons of RGCs form the optic nerve which is responsible for transmitting visual information from the retina to the occipital lobe.

Out of the two photoreceptor types, rods represent up to 95 percent of the photoreceptor population and are responsible for low light and peripheral vision, while cones occupy only 5 percent of the total photoreceptor population and enable central vision and color perception (4). Rods express rhodopsin protein, whereas cones express S/M/L opsins and are primarily found in the fovea for central visual acuity. NRL is a transcription factor that defines rod cell identity, whereas CRX is highly expressed in both rods and cones (5). MITF is well-established as a transcription factor found predominantly expressed in RPE (6), whereas RGCs express ATOH7 and BRN3a/BRN3b transcription factors (7). By harnessing the power of transcription factors to control retinal cell identity and trans-differentiation, data-driven cell conversions can lead to the development of new cell therapies and in vivo reprogramming approaches to treat retinal degeneration.

DEGENERATION OF THE RETINA AND THE OPTIC NERVE

Let's go through different types of retina and optic nerve degeneration and discuss what place in vivo reprogramming may have in addressing them.

AMD is the most common form of retinal degeneration and affects up to 170 million people worldwide (9). There are many causes and no approved treatments that can reverse the degeneration of both RPE and photoreceptor layers. Treatments for wet AMD include anti-VEGF therapy that prevent the formation of new blood vessels. Human embryonic stem cell (ESC)-derived RPE has been in phase I/II clinical trials to evaluate safety and efficacy (9); however, there remains no approved cell or gene therapy to prevent, and potentially reverse, the progression of AMD.

Inherited retinal degenerations are heterogenous diseases that result in a progressive loss of photoreceptors and visual acuity. Retinitis pigmentosa (RP) is a group of phenotypically and genetically variable inherited retinal disorders that

affect up to 1 in 4,000 people in the US and worldwide (10). RP is typically defined by mutations in key photoreceptor genes, with over 50 genes known to be affected (10), including rhodopsin, RPE65, USH2A, PDE6A, and PDE6B. Mutations in rhodopsin are the most prevalent cause (accounting for under 18 percent) of autosomal dominant RP (11). Less commonly, RP can be autosomal recessive or X-linked recessive, as in the case of RP2. Cone-rod dystrophies are estimated to affect 1 in 30,000–40,000 people and ABCA4 mutations are responsible for 30–60 percent of autosomal recessive cases. Meanwhile, mutations in GUCY2D and CRX genes are responsible for up to half of the cases of autosomal dominant cone-rod dystrophies (12). Gene therapies have already proven successful in treating monogenic RP and there is substantial commercial interest in retinal gene therapy, while cell therapies also have the potential to treat all RP subtypes. However, in vivo reprogramming has the potential to be a more efficacious approach to late-stage retinal degeneration as photoreceptor integration and synaptic connections are more likely than with cell therapy approaches.

Glaucoma involves degeneration of the optic nerve that connects the retina to the brain and accounts for 12 percent of global blindness, making it the second most common cause of blindness worldwide (13). It is characterized by RGC death – most often caused by elevated intraocular pressure that results in deformation of the lamina cribrosa pores located at the optic nerve head. The lamina cribrosa is a porous extra-cellular matrix where the RGCs exit the retina; their axons form the optic nerve (14). Mutations in the MYOC gene are the most common genetic causes of primary open-angle glaucoma (15). Current treatments focus on lowering of intraocular pressure to slow progression of glaucoma; however, cell and gene therapies offer the greatest hope for reversing the damage to vision caused by glaucoma.

CELL THERAPIES FOR RETINAL DEGENERATION

Why has the eye proved to be well-suited for cell and gene therapies? It is easily accessible, immune-privileged, and well suited for clinical imaging because of the transparent cornea and lens. For example, the retina can be clinically monitored using imaging techniques such as optical coherence tomography and fluorescence adaptive optics scanning light ophthalmoscopy imaging (16). In this way, engrafted cells and retinal structure can be monitored after therapy, without termination of the study. Therefore, the safety and efficacy of cell and gene therapies can be readily assessed over time in animals and human clinical studies.

ESCs and induced pluripotent stem cells (iPSCs) are clinically valuable as a source of retinal cell types for research and application.

How does our PLATFORM *work?*

Our technology was developed to identify the key regulatory switches, such as an optimal combination of transcription factors, required to drive cell identity. The platform can be used to enhance existing stem-cell forward reprogramming methods or to bypass development pathways, affecting a direct transdifferentiation between a mature cell type and another mature cell type.

Firstly, gene expression levels are compared in the source and target cell types (consisting of FANTOM5 and other proprietary data). This step determines the changes in the gene expression levels that are needed to achieve the conversion. Secondly, transcription factors are scored compared with the required changes in gene expression levels by both direct and indirect influences (using the MARA and STRING databases); this includes the regulatory network information on protein-DNA interactions as well as protein-protein interactions. Thirdly, local transcriptomic regulatory networks are built to calculate the effect of the transcription factors on gene expression levels. Lastly, the optimal combination of transcription factors is predicted to maximize network coverage, while avoiding redundancies, to achieve the necessary changes in gene expression for the cell conversion to occur.

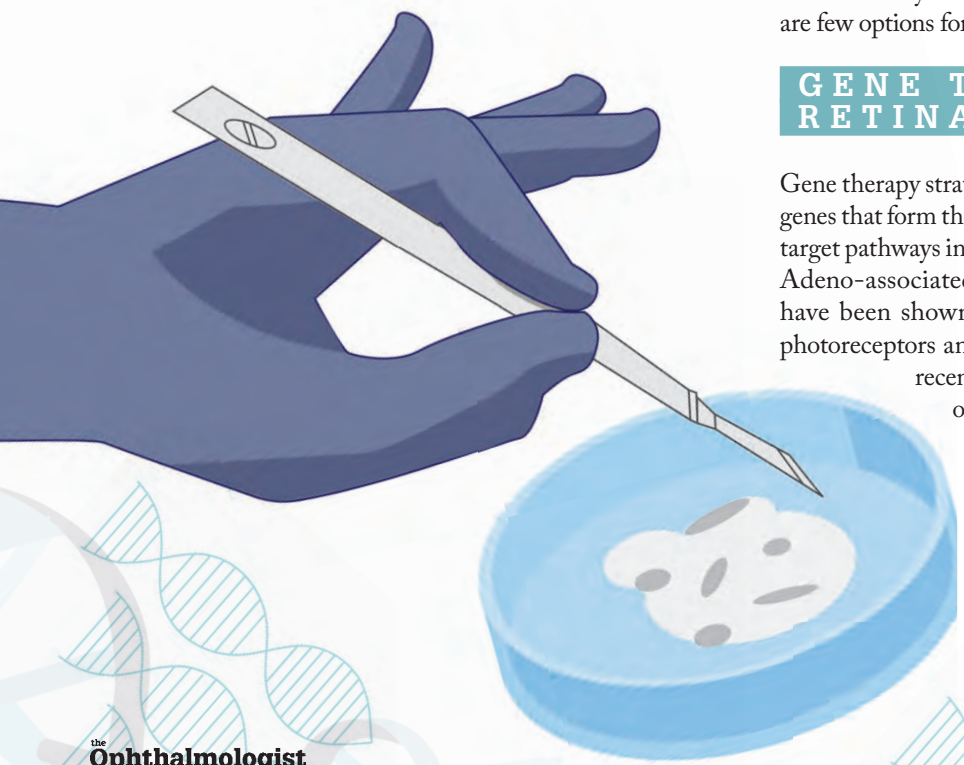
In addition to identifying transcription factor-driven cell conversions, small molecules that are known to affect the expression of the key predicted transcription factors can be identified from published literature to create a small molecule conversion cocktail. This approach has the added benefit of not requiring the transduction of transcription factors and consequently holds greater potential as an in vivo reprogramming therapy.

Retinal organoids generated from these cells have helped to significantly advance the understanding of retina development (17, 18), and they have also provided an effective tool to study photoreceptor isolation and transplantation (19). There have been several clinical trials to test the safety and efficacy of RPE derived from ESCs/iPSCs for the treatment of AMD (3). RPE can be spontaneously produced from iPSCs by removal of FGF2 from pluripotency media, or more efficiently generated by the addition of small molecules such as nicotinamide and activin A (20, 21). The delivery of RPE can be as a cell suspension or as a cell sheet through subretinal implantation. Several studies have also tried to transdifferentiate fibroblasts to RPE for clinical transplantation, using transcription factors including MITF (22, 23). Clinical trials have reached phase II for RPE transplantation to treat AMD and several strategies are being developed to more effectively deliver RPE generated from pluripotent stem cells.

Cell therapies are an attractive option for treating inherited retinal disorders as they have the potential to treat all variants of RP mutations by regenerating photoreceptors. Importantly, allogeneic therapies would not carry the host mutation and there is a blood-retina barrier formed by the RPE that grants immune privilege. Recent efforts have focused on generating Müller glia that can be isolated from organoids for sub-retinal transplantation and improvement of RGC function (24), while cone photoreceptor density can be increased in organoids so they can be isolated for transplantation (25). Fetal retinal progenitor cells (RPCs) are currently in phase I/IIa clinical trials (26), and have shown promising results in a phase IIb clinical trial for the treatment of RP (27). The use of RPCs as a cell therapy continues to be an exciting prospect for the treatment of inherited retinopathies.

"WHILE RGC THERAPY IS CHALLENGING, IT OFFERS A VERY REAL PROSPECT OF OPTIC NERVE REGENERATION AS THERE ARE FEW OPTIONS FOR GENE THERAPY."

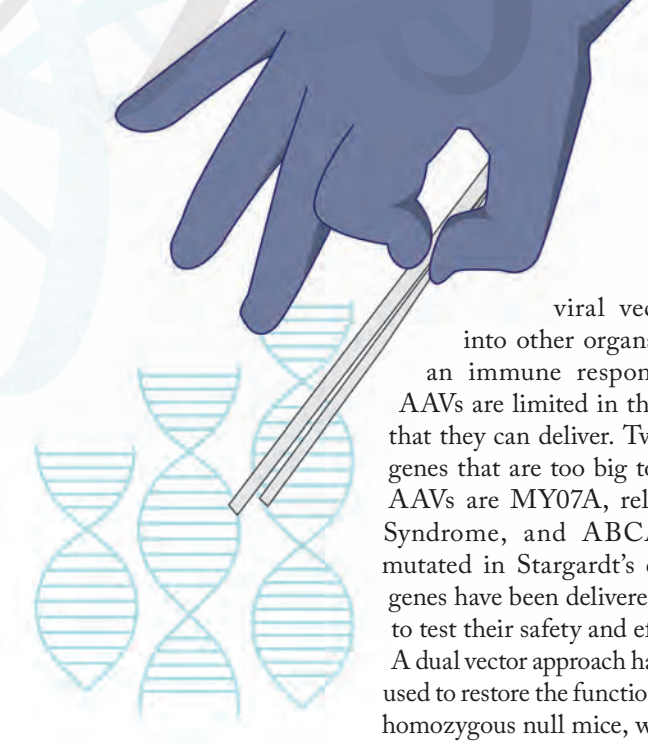
There are several published protocols for the generation of RGCs from iPSCs and retinal organoids (28), and they arise early in retinal development. Their application as a cell therapy remains difficult because of the axonal length required to connect the retina and visual cortex in the posterior region of the brain. For RGC cell therapies to be successful, the elevated intraocular pressure and lamina cribrosa defects also need correcting to prevent further damage to the donor RGCs. Though RGC therapy is challenging, it offers a very real prospect of optic nerve regeneration as there are few options for gene therapy.



GENE THERAPIES FOR RETINAL DEGENERATION

Gene therapy strategies aim to silence, replace, or repair defective genes that form the basis of inherited retinal diseases, or they may target pathways involved in inflammation or visual transduction. Adeno-associated viruses (AAVs) are non-pathogenic and have been shown to effectively target retinal cells, such as photoreceptors and RPE, after subretinal injection. The FDA recently approved LUXTURNA for the treatment of inherited retinal disorders using AAV vectors (29). Specifically, it is used for the treatment of Leber's congenital amaurosis (LCA) or RP caused by confirmed biallelic RPE65 mutations. The approval has led to great interest in the development of AAV gene therapies for inherited retinal disorders.

The blood-retina barrier formed by the retinal pigment epithelium helps to prevent



viral vector diffusion into other organs and eliciting an immune response. However, AAVs are limited in the size of cargo that they can deliver. Two examples of genes that are too big to package into AAVs are MY07A, related to Usher Syndrome, and ABCA4, which is mutated in Stargardt's disease. These genes have been delivered via lentivirus to test their safety and efficacy (30, 31). A dual vector approach has recently been used to restore the function of ABCA4 in homozygous null mice, which is a novel way to increase AAV vector capacity, but the level of expression may not be enough to elicit a therapeutic effect (32). Other strategies to deliver gene therapies include using antisense oligonucleotides for transient expression, which have been used for CEP290 in LCA and QR-421a for LCA involving USH2A (33).

Retinal organoids have recently been used to model X-linked RP caused by RP2 mutations. Gene therapy delivered by AAVs can correct photoreceptor degeneration and thinning of the outer nuclear layer in RP2-mutated organoids from patients (34). RPGR has also been targeted by AAVs for a gene therapy approach to treating X-linked RP (35). To protect cone photoreceptors in a mouse model of retinal degeneration, microglia have been stimulated with TGF-β1 using AAVs. In three mouse models of RP carrying different mutations, AAV-mediated delivery of TGF-β1 rescued degenerating cones. The results suggest that TGF-β1 can protect vision and may benefit patients with neurodegeneration (36).

A novel gene therapy approach to AMD blocks inflammation caused by the complement system. Here, AAVs are used to deliver a proprietary protein after vitrectomy; phase I/II trials commenced in January 2019 to test the safety and efficacy of this gene therapy in humans for treating dry AMD, with no safety concerns to date (37). There is also evidence that gene therapies may also help glaucoma patients by targeting aquaporin-1 in the ciliary body using CRISPR-Cas9 to reduce intraocular pressure (38). Other research highlights a CRISPR-Cas9 approach to gene editing MYOC that has been able to lower intraocular pressure in glaucomatous mouse eyes (15). Cell and gene therapies have the potential to restore vision after retinal degeneration; however, the delivery and integration of these approaches remains problematic and the number of approved advanced therapeutic medicinal products is few. Here, we evaluate in vivo reprogramming of Müller glia as an innovative approach to treating late-stage retinal degeneration.

Who is behind MOGRIFY?

The emergence of Mogrify as a start up with commercial aspirations follows years of scientific work. As there are around 2,000 transcription factors and 400 human cell types, the science of direct cell reprogramming is likely to advance slowly if it relies on educated guesses of the best combinations of conversion drivers.

Based in Cambridge, UK, Mogrify wants to make the identification of the combinations more scalable and efficient using a computational framework that makes predictions based on gene expression data and regulatory network information. In 2016, Mogrify co-founder Julian Gough – Programme Leader at the MRC Laboratory of Molecular Biology in Cambridge – and his collaborators discussed their progress toward that goal in a paper detailing the ability of their framework to correctly predict the transcription factors that facilitate two then-novel transdifferentiation mechanisms (42).

Back then, Mogrify had applied the framework to 173 cell types and 134 tissues and validated it by correctly predicting known and novel transdifferentiation routes. In 2019 and 2020, Mogrify secured funding and multiple awards, including Innovation Award at PharmaIntelligence Scrip Awards, and the AstraZeneca Life Science Innovation award from the Business Weekly Awards. This year Julian Gough received the Cambridge Enterprise Academic Entrepreneur of the Year award in recognition of his work as a life science innovator and founder of Mogrify.

IN VIVO REPROGRAMMING FOR RETINAL REGENERATION

Since the discovery that OCT4, KLF4, SOX2, and cMYC transcription factors can reprogram somatic cells into induced pluripotent stem cells (39), there has been great interest in direct reprogramming for the development of new cell therapies. Examples of direct reprogramming include fibroblast conversion to neurons (40) and cardiomyocytes (41); however, it is difficult to predict the required reprogramming factors for cell conversion. Big-data approaches, such as the algorithm we developed (42), predict the transcription factors required to convert any cell type using RNA sequencing. Transcription factors are then ranked according to their influence over the target cells' gene expression profile, and the optimal transcription factors are then used to convert cell types in vitro and in vivo. There is precedent for reprogramming of retinal cell types, such as fibroblasts to rods (43) and in vivo reprogramming of Müller glia to rods (44). Thus, the application of transcription factors directly for in vivo reprogramming of retinal cell types is an exciting new therapeutic approach to photoreceptor degeneration.

Müller glia represent the best potential source in the retina for in vivo conversion to photoreceptors as they are the primary support cell of the retina and activate on injury. In the zebrafish retina, Müller glia cells have been shown to regenerate other retinal cell types after injury and this finding suggests they have a progenitor capacity (45). The ASCL1 gene was shown to be up-regulated in Müller glia that contributed to the regeneration of neurons. In rodents, Müller glia are not associated with retinal regeneration (suggested to be a result of epigenetic repression), but they have been stimulated to generate neurons by ASCL1 overexpression and use of a histone deacetylase inhibitor trichostatin A (46). Another method to reprogram Müller glia is by cell fusion with hematopoietic progenitors, which has been shown to stimulate their conversion to photoreceptor precursors (47). More recently, the transcription factors OTX2, CRX, and NRL have been used to reprogram Müller glia to rod photoreceptors in Gnat1rd17Gnat2cpfl3 double mutant mice (44). This study used beta-catenin to drive proliferation of Müller glia before subsequent reprogramming to rod photoreceptors in the mice that lack functional photoreceptors. Overall, there is significant promise in the potential of converting Müller glia to photoreceptors to reverse retinal degeneration.

RPE has been shown to have stem cell properties in vitro and is another candidate to regenerate photoreceptors, as it is adjacently located to them in the outer nuclear layer (48). However, RPE is a quiescent monolayer, and cell conversions of RPE to photoreceptors may be counterintuitive given its fundamental role in photoreceptor homeostasis.

In vivo reprogramming is also attractive for the regeneration of RGCs and the treatment of glaucoma. One strategy has been developed to convert amacrine interneurons into RGCs by overexpressing Atoh7, Brn3B, Sox4, Sox11, and Isl1, which are established transcription factors in RGC development (49). There is also evidence that Ascl1, Brn3b, and Isl1 transcription factors can convert mouse fibroblasts into induced RGCs (50). Br Overexpression of KLF4 has also been shown to induce the regeneration of RGCs in vivo, even though it is not essential for their development (51).

By using a systematic data-driven approach, we will be able predict optimal transcription factors sets for the conversion of retinal cell types, to generate cells for therapy, and as a gene therapy for in vivo reprogramming.

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THE INNOVATORS

AS ONE OF THE MOST INVENTIVE FIELDS IN MEDICINE, OPHTHALMOLOGY IS OFTEN AT THE FOREFRONT OF CUTTING-EDGE TECHNOLOGIES AND TREATMENTS. HERE, SOME OF THE LEADING INNOVATORS FROM THE OPHTHALMIC SPACE PRESENT THEIR LATEST OFFERINGS: FROM IMAGING AND DIAGNOSTICS, TO REFRACTIVE SURGERY AND GLAUCOMA CARE.

SMARTER DSAEK SURGERY

Transform endothelial keratoplasty cornea transplant procedures with the preloaded EndoSerter-PL by CorneaGen

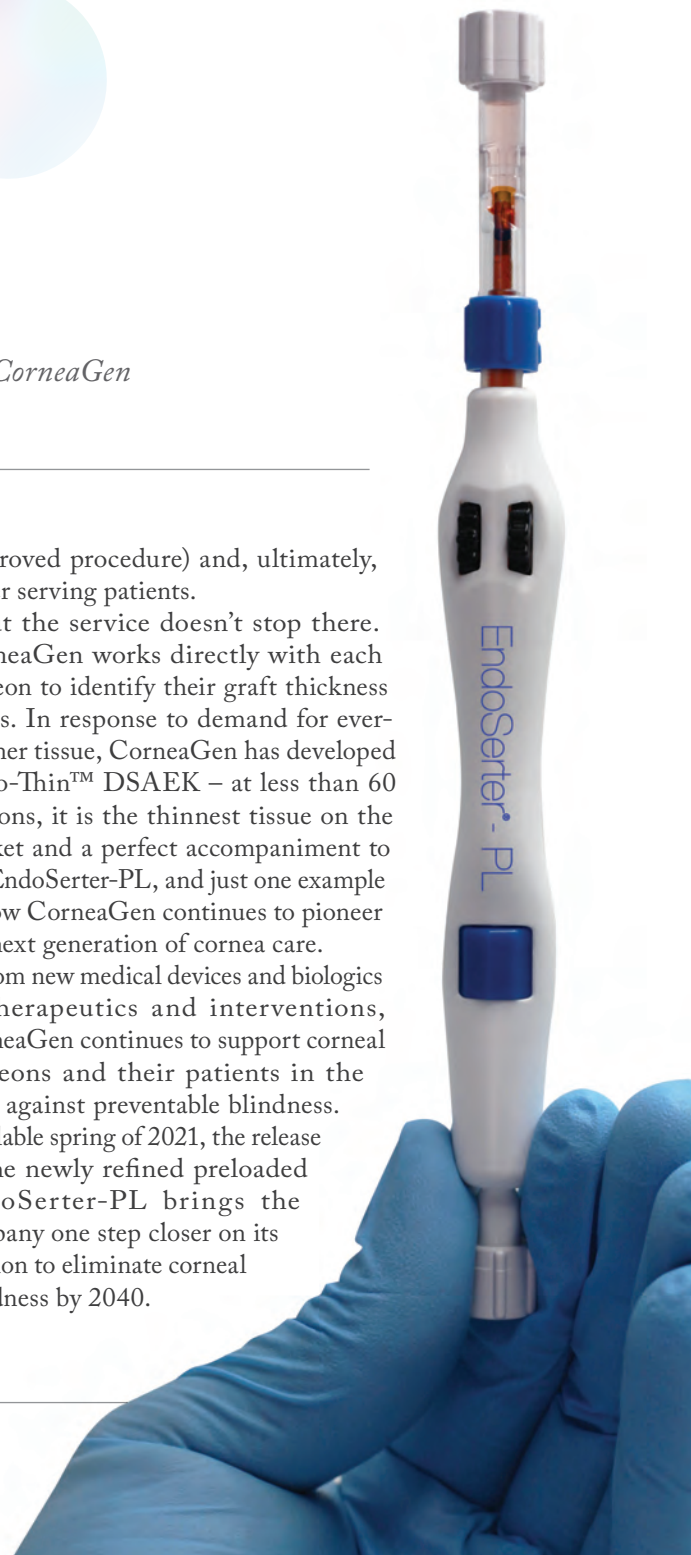
CorneaGen first released its EndoSerter Corneal Endothelium Delivery Instrument in 2011, providing surgeons with a sterile, single-use device that offered a controlled method of delivering and positioning the donor allograft into the anterior chamber of the eye during Descemet's stripping endothelial keratoplasty (DSEK). Donor tissue is inserted through a tight 4 mm clear corneal incision, reducing the need for sutures. The EndoSerter's intelligent design allows coaxial irrigation, eliminating the need for a separate chamber maintainer. Unlike conventional insertion devices, the EndoSerter does not push or pull on the fragile allograft tissue and endothelial cells; the allograft is simply uncovered during deployment.

Unsurprisingly, the EndoSerter was well-received by the ophthalmic community – and expectations are high for its successor. The latest device, the preloaded EndoSerter-PL, has been designed with automated procedures in mind – procedures which now represent the largest segment of all domestic corneal transplant cases in the US. The all-new EndoSerter-PL streamlines the process by acting as both a shipping container and insertion device. CorneaGen processes the tissue to the surgeon's exact specifications and loads the graft into the EndoSerter-PL, saving precious time in the OR.

In short, the preloaded EndoSerter-PL simplifies the DSAEK surgical procedure – better serving surgeons (improved procedure) and, ultimately, better serving patients.

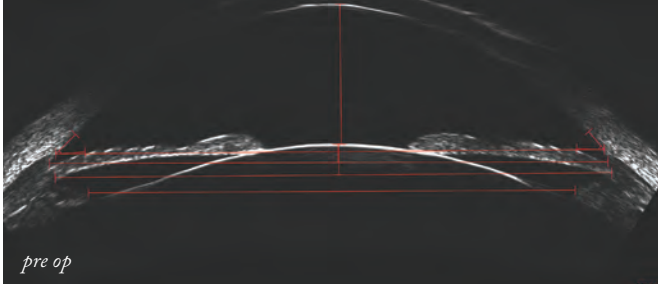
But the service doesn't stop there. CorneaGen works directly with each surgeon to identify their graft thickness needs. In response to demand for ever-thinner tissue, CorneaGen has developed Nano-Thin™ DSAEK – at less than 60 microns, it is the thinnest tissue on the market and a perfect accompaniment to the EndoSerter-PL, and just one example of how CorneaGen continues to pioneer the next generation of cornea care.

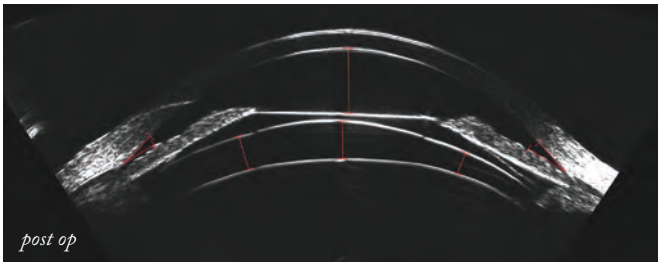
From new medical devices and biologics to therapeutics and interventions, CorneaGen continues to support corneal surgeons and their patients in the fight against preventable blindness. Available spring of 2021, the release of the newly refined preloaded EndoSerter-PL brings the company one step closer on its mission to eliminate corneal blindness by 2040.



SAFE AND (ULTRA)SOUND

Boost your implantation success rate using the ArcScan Insight 100's ICL sizing capability





Selecting the right implantable phakic lens just got safer. The ArcScan Insight 100's ICL sizing capability allows clinicians to reduce the risk of size-related complications by selecting a lens based on direct measurements of the posterior chamber. By producing crystal-clear "HD" images (versus the "analog" efforts of other ultrasound biomicroscopy systems), measurement accuracy is assured to within 1.0 µm at the cornea and 0.12 mm laterally behind the iris. How? Thanks to the ArcScan Insight 100's ability to maintain a consistent perpendicularity and distance from the eye with its robotically-controlled transducer, and its automatic focal depth settings. Each preoperative imaging scan set includes seven meridians to cover the desired area of the lens footplate location. And the resulting images not only help determine the exact lateral space, they can also be used to detect the presence of ciliary cysts or other pathologies, aiding surgical planning.

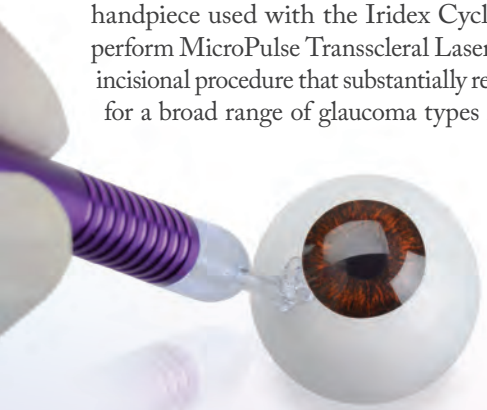
Dan Reinstein, MD, Founder of the London Vision Clinic and Chief Medical Officer at ArcScan, is the man behind the innovation. Here, he explains how the precise measurement capability of the Insight 100 increases confidence in ICL sizing: "OCT-based formulae with anterior chamber dimensions have improved on the STAAR recommended white-to-white formula, but posterior chamber dimensions have improved yet further the predictability of postop ICL vault. Lovisolo, Dougherty, and Kojima derived sulcus-to-sulcus based formulae, but the Reinstein Formula utilizes an even better predictor: the ciliary body inner diameter." The calculator can be found at iclsizing.com.

Roger Zaldivar, Founder of the Instituto Zaldivar, speaks highly of the device's new capability: "I can't emphasize enough how important the ArcScan is today in our practice for ICL sizing. It will soon be the global gold standard in sizing."

MICROPULSE P3® DELIVERY DEVICE FOR NON-INCISIONAL GLAUCOMA TREATMENT

A revised MicroPulse P3 fiberoptic handpiece features multiple design enhancements

The Iridex MicroPulse P3® Delivery Device is a fiberoptic handpiece used with the Iridex Cyclo G6® Laser System to perform MicroPulse Transscleral Laser Therapy (TLT) – a non-incisional procedure that substantially reduces intraocular pressure for a broad range of glaucoma types including primary open-angle, closed-angle, and refractory glaucomas. Since 2015, more than 120,000 patients have been treated globally with MicroPulse TLT. In the USA, the procedure is performed in 35 of the top 39 ophthalmology hospitals (1).



Earlier this year, Iridex revised its design of the MicroPulse P3 device to enhance stability, coupling, visualization, and fit. The enhancements include a smooth, scleral-matching footplate curvature to increase stability; a recessed fiber tip with an added fluid channel to enable constant fiber immersion in fluid to improve light coupling to the tissue – critical for the success of the procedure; an elongated stem to improve visualization of the treatment area and to function as a speculum if needed; and a reduced footplate for ease of placement in small eyes. Overall, the revised MicroPulse P3 device creates a more ergonomic-friendly handpiece to perform MicroPulse TLT – a versatile therapy to use prior to, in conjunction with, or following all other glaucoma treatment options.

Reference

1. *Iridex, "IRIDEX Cyclo G6™ Laser System for Glaucoma Treatment Used in Majority of Top US Ophthalmology Hospitals" (2018). Available at: https://bit.ly/3oYOeGW.*

REINVENTING PATIENT CARE

Innovations for building, managing and growing myopia, dry eye and refractive practices

Keeping pace with the ophthalmic industry's ever-changing landscape, Topcon Healthcare offers the latest integrated solutions, including advanced multimodal imaging, vendor-neutral data management, and ground-breaking remote diagnostic technology. The company's two most recent innovations are MYAH – for myopia and dry eye management and Chronos – for refraction and visual acuity testing.

MYAH is ideally suited to combat the increasing prevalence of both myopia and dry eye disease. Its versatility and ease of use allow eye care professionals to build a myopia service within their practice, educate patients on the implications of myopia and dry eye disease, manage their patients' conditions, and grow their service offerings.

MYAH combines optical biometry, corneal topography, pupillometry, meibomian gland imaging, and tear film analysis into a single compact, easy-to-use instrument. It also integrates progression reports to analyze treatment efficacy and a comprehensive suite of dry eye assessment tools. Additionally, MYAH features contact lens fitting software with a database of conventional RGP and ortho-K lenses. And from a patient satisfaction point of view, MYAH allows for rapid capture.

But don't take our word for it; thanks to its versatility, innovation and ease of use, MYAH recently received the Silmo d'Or Award in the Material/Equipment category.

As if that wasn't enough, Topcon Healthcare is proud to have developed the only all-in-one, fully-automated, binocular refraction system on the market. It features the all new SightPilot® – the guided refraction system that combines autorefraction, keratometry, and subjective refraction. Chronos occupies less than four square feet of space while combining both subjective and objective refraction using binocular testing protocols for a more natural exam. This multi-modal device provides a complete refraction test in approximately 3.5 minutes. The SightPilot® software guides operators through the entire process with a simple user interface and on-screen prompts at each step. Subjective tests include visual acuity charts, red-green comparison, cylinder axis adjustment, binocular balancing, and near addition charts.

The number of patients requiring comprehensive eye care is quickly outpacing the number of providers. Eye care professionals must find new ways to see more patients and focus their time on providing services that only a trained professional can perform. Chronos allows refraction tests to be conducted by anyone in the practice, allowing trained clinicians and technicians to spend their time providing advanced care.

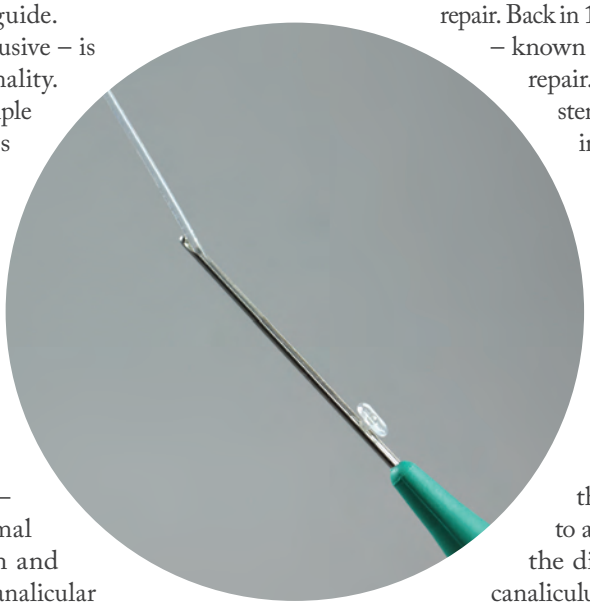
Please note that MYAH is not currently available in the US.

LOCKED AND (PRE)LOADED

The world's first injectable monocanalicular intubation stent

Entirely self-retaining, LacriJet® (FCI S.A.S., Paris, France) is a revolutionary injection system that has been specifically designed to reduce operating time – both in the intubation phase and removal. The world's first injectable monocanalicular intubation stent indicated for congenital or acquired nasolacrimal duct obstruction (NLDO) and canalicular laceration, LacriJet® consists of a single-use injector handpiece into which a silicone tube is preloaded inside a metallic guide.

The device design – an FCI-exclusive – is unique in both its form and functionality. But behind the smart design lies simple operation. First, the LacriJet® is introduced into the nasolacrimal duct; once in position, the sliding piston is retracted and the silicone intubation is released. The intubation is maintained in place at the punctum by a plug-like fixation head: no nasal retrieval, no knots, and no suture necessary. The device is available in seven lengths: five lengths for nasolacrimal stenosis – from 30 mm to 50 mm – to restore the patency of the lacrimal drainage system both in children and adults; and two shorter lengths for canalicular laceration – 15 mm and 20 mm – to prevent future canalicular obstruction due to scar tissue formation.



To understand why the LacriJet® is revolutionary, it is important to understand the condition it treats. NLDO, a blockage of the lacrimal drainage system, can be either inherited or acquired following trauma, viral conjunctivitis, acute dacryocystitis, or the use of topical antiviral medications. Since 1984, all FCI lacrimal intubations (monocanalicular and bicanalicular) have been designed to treat a specific obstruction: first, according to its location in the tear drainage system and, secondly, according to pathology severity. These multiple options enable surgeons to select the most appropriate device to treat their patients, in terms of techniques ("pulled" or "pushed"), preference, and usability.

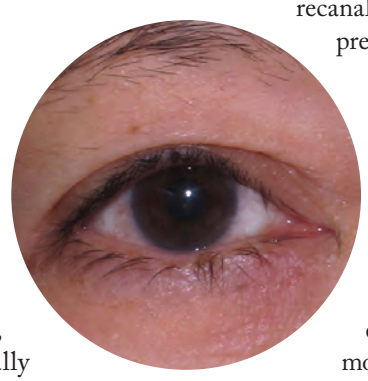
As a "pushed" technique, the LacriJet® is significantly less traumatic than "pulled" on the nasal mucosa as there is no need for retrieval. It is also more user-friendly for the patient, as the lack of knots or sutures means there is little-to-no blood loss during or after the procedure.

The device is equally effective when it comes to canalicular repair. Back in 1989, FCI invented the Mini-Monoka® – known as the gold standard for canalicular repair. This short silicone monocanalicular stent was specifically designed for repairs involving the external two-thirds of the canaliculus to avoid future blockage caused by scar tissue. However, the tube placement procedure was considered by some to be too complicated for some inexperienced doctors, as the silicone tube was soft and needed to be passed through the lacerations for suturing. The LacriJet® 15 mm and 20 mm have been specifically designed to facilitate the procedure, using a metallic probe to act as a catheterization guide between the distal and proximal portions of the canaliculus. The silicone tube is then released and left in place to avoid future scar tissue-induced blockages. Simple, yet effective.

The LacriJet®'s innovative design can be attributed to Bruno Fayet, MD, renowned oculoplastic surgeon, lacrimal field specialist, and long-time FCI collaborator. Fayet also contributed to the design of many existing monocanalicular lacrimal intubations from FCI, including the Mini-Monoka®, Self-threading Monoka® (Ritleng type), Monoka® of Fayet (Crawford guide), Monoka®, and Masterka®.

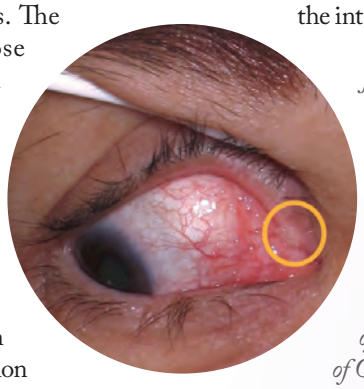
The products mentioned may not be registered in your country. Please contact your local distributor to find out what is available in your area.

Reynaldo M. Javate, Professor and Chairman at the UST Hospital Eye Institute, Chief of the Lacrimal, Orbital and Oculofacial Plastic Surgery Section at the University of Santo Tomas Hospital, University of Santo Tomas Espana in Sampaloc, Manila, Philippines, talks about his experience with the LacriJet®.



Cases of nasolacrimal duct obstruction, epiphora and canalicular lacerations are usually referred to me by my colleagues and trainees. The most challenging epiphora cases are those with nasolacrimal duct obstructions from congenital bony anomalies, and with canalicular obstruction or stenosis with long distance occlusion (involving the proximal, middle, distal and common canalicular obstructions).

I have found FCI's LacriJet® very useful for patients with focal stenosis of the upper or lower canaliculus. I also use it for patients with focal or partial NLDO after doing a recanalization procedure, and for those suffering from a recurrence or reobstruction after a transcanalicular endoscopic lacrimal duct recanalization. The device is user-friendly, and it saves precious procedure time.



The LacriJet® is preloaded into an injector, which protects the silicone stent during insertion or injection into the tear ducts. It has a self-retaining punctal fixation, removing the need to secure the end of the tube in place in the inferior meatus with knots or sutures. Prior to inserting the LacriJet®, the punctum should be dilated, to allow for the introducer's external diameter of 0.9 mm. I have found the monocanalicular stent to carry less risk of injury to the intact canaliculus than a bicanalicular silicone stent.

Javate is Past President of the Philippine Society of Ophthalmic Plastic and Reconstructive Surgery; Founding President of the Asia-Pacific Society of Ophthalmic Plastic and Reconstructive Surgery; President of 10th International Society of Dacryology and Dry Eye; and Fellow of the American Society of Ophthalmic Plastic and Reconstructive Surgery.

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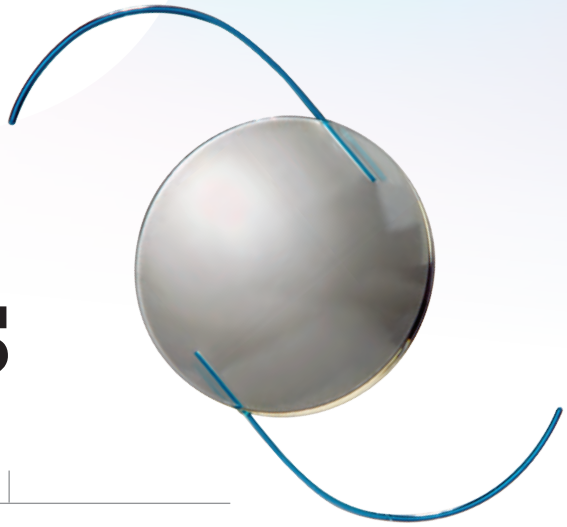


POWER DYNAMICS

Postoperative adjustment of IOL power is now a reality

A common challenge in premium cataract surgery is discussing vision optimization options with patients ahead of the procedure – it is not easy to demonstrate different visual outcomes to patients with cataracts.

As the lens power of traditional IOLs cannot be changed after implantation, physicians typically spend a great deal of time on preoperative measurements to estimate the most suitable lens power for the patient. Though outcomes of traditional IOL implantation are generally good, residual refractive error – even after premium cataract surgery – is common due to variations in postoperative lens position and wound healing. So what happens when patients are not happy with their vision outcomes? Until recently, additional surgery or lens removal was required to change lens power after implantation.

Enter the RxSight® Light Adjustable Lens™ (LAL) – the first and only IOL that can be non-surgically adjusted after cataract surgery, giving physicians the ability to customize the power of the implanted lens after the eye has healed. Instead of having to prescribe glasses after cataract surgery, the physician can simply apply the customized prescription that the patient has previewed directly into the adjustable IOL, using a series of 90-second in-office UV light treatments. With such precise refractive targeting, physicians can finally achieve the best possible vision for their patients.

An innovation indeed, but how does it work? The LAL contains photosensitive macromers distributed throughout the lens. When low-intensity UV light from the proprietary Light Delivery Device (LDD) is directed to a specific area of the lens, the macromers in the path of the light polymerize with other macromers. The remaining unpolymerized macromers then move to the light-exposed area. The movement causes a highly predictable change in the curvature of the lens – representing the refraction entered into the LDD by the physician.

The system is approved for cataract surgery patients with pre-existing corneal astigmatism (at least 0.75 D), who do not suffer from macular disease. FDA approval was based on results of a US randomized, pivotal study that evaluated the safety and effectiveness of the LAL and LDD compared with a commercially available monofocal lens in 600 eyes with pre-existing astigmatism (1).

The LAL allows for optimization on a clear and stable visual system. This way, if a patient is uncertain of their desired refractive target, the effect can simply be adjusted after cataract surgery, allowing surgeons to recommend premium options with confidence. For the first time, patients can "design" and achieve their own custom vision for all distances – near, intermediate, distance – and treat astigmatism with a single IOL.

Reference

1. FDA, "Summary of safety and effectiveness data (SSED)" (2017). Available at: https://bit.ly/3eQxInS.

A NEW ANGLE ON GLAUCOMA MANAGEMENT

The next innovative step in irrigating goniectomy

It is estimated that 76 million patients across the globe have suffered from glaucoma in 2020; the number is expected to grow to 111 million by 2040 (1). Finding simple, versatile, yet effective glaucoma solutions is increasingly important.

MIGS has been a fantastic innovation, giving cataract surgeons new tools with which to treat glaucoma – ultimately providing a way to treat the disease sooner and with a high safety profile. Nevertheless, some MIGS technologies, such as stenting and scaffolding, can present challenges in terms of surgical technique and reimbursement. And that's where MST's irrigating goniectomy with TrabEx Pro comes in.

Irrigating goniectomy is a new MIGS procedure that continues on from the legacy of goniotomy – a well-established procedure first described by Barkan in 1938 (2). Irrigating goniectomy, first introduced by the MST Trabectome in 2004, works by incising and opening trabecular meshwork (TM) tissue with the support of active IA, exposing Schlemm's canal and allowing aqueous to drain via several collector channels and the intrascleral venus plexus. Irrigating goniectomy is well supported with clinical literature. A recent meta-analysis states it "can be expected to lower the IOP by approximately 36 percent to a final average IOP around 16 mmHg while decreasing the number of medications by less than one. After 2 years, the overall average success rate is 66 percent. The rate of visually threatening complications is <1 percent." (3)

Traditional goniotomies create a single incision in the TM with a cystotome or keratome. Though effective in pediatric patients, they have a limited effect in adults because the lack of elasticity in adult TM can allow remaining tissue to reocclude the outflow system (4).

Irrigating goniectomy using the Trabectome removes a central strip of the TM with electrosurgical ablation with the aim of preventing reocclusion from remaining leaflets of tissue. TrabEx Pro works in a similar fashion but excises TM tissue with a trapezoidal bladehead that features serrated blades – tailored to varying patient anatomies. The result? Cleanly-cut removal of the TM: the "goni-ectomy".

Perhaps the greatest innovation of the MST Glaucoma portfolio is the incorporation of IA. The addition of irrigation pressurizes the anterior chamber to help prevent intraoperative blood reflux in the angle and provide maximum visibility during surgery, while aspiration assists in pulling the TM against the serrated blades and facilitating a precise and complete excision of tissue. The TrabEx Pro features the latest in irrigating goniectomy technology, a silicone infusion sleeve that maximizes the surgical benefit of IA and allows for use in varying incision sizes.

The instrument is indicated for both adult and pediatric patients and can be used in combination with cataract surgery or as a standalone procedure to treat open angle, narrow angle, pseudoexfoliative, pigmentary, mild, moderate, and severe glaucoma.

TrabEx Pro is best used in a 2.2-2.5 mm incision. And because it can connect to any phaco platform to incorporate fluidics for IA, it does not require any capital equipment investment. Moreover, it is backed by strong reimbursement, which allows the technology to be widely offered.

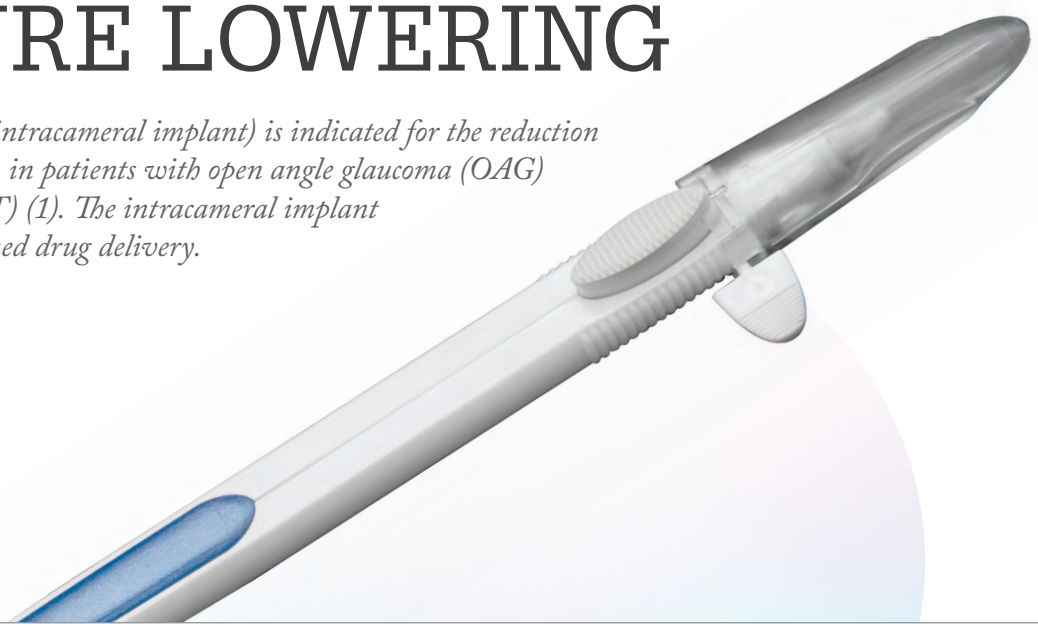
TrabEx Pro will be available in the US, Canada, and Europe in January 2021.

References

1. *YC Tham et al., "Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis," Ophthalmology, 121, 2081 (2014). PMID: 24974815.*
2. *O Barkan, "Technic of goniotomy," Arch Ophthalmol, 19, 217 (1938). DOI: 10.1001/archopht.1938.00850140059006.*
3. *K Kaplowitz et al., "Review and meta-analysis of ab-interno trabeculectomy outcomes," Br J Ophthalmol, 100, 594 (2016). PMID: 26733487.*
4. *J Liu et al., "Ab interno trabeculotomy: Trabectome[trademark] surgical treatment for open-angle glaucoma," Expert Review of Ophthalmol, 4, 2, 119 (2009).*

INNOVATIVE TREATMENT IN INTRAOCULAR PRESSURE LOWERING

DURYSTA™ (bimatoprost intracameral implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT) (1). The intracameral implant is making the case for sustained drug delivery.



INDICATIONS AND USAGE

DURYSTA™ (bimatoprost implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

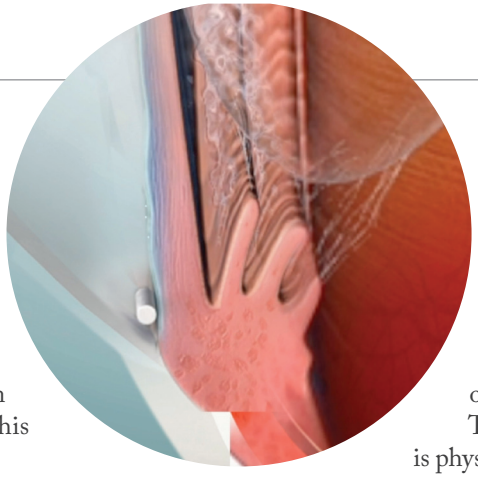
DURYSTA™ is contraindicated in patients with: active or suspected ocular or periocular infections; corneal endothelial cell dystrophy (e.g., Fuchs' Dystrophy); prior corneal transplantation or endothelial cell transplants (e.g., Descemet's Stripping Automated Endothelial Keratoplasty [DSAEK]); absent or ruptured posterior lens capsule, due to the risk of implant migration into the posterior segment; hypersensitivity to bimatoprost or to any other components of the product.

WARNINGS AND PRECAUTIONS

The presence of DURYSTA™ implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of DURYSTA™ should be limited to a single implant per eye without retreatment. Caution should be used when prescribing DURYSTA™ in patients with limited corneal endothelial cell reserve.

DURYSTA™ should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3) or anatomical obstruction (e.g., scarring) that may prohibit settling in the inferior angle.

Macular edema, including cystoid macular edema, has been reported during treatment with ophthalmic bimatoprost, including DURYSTA™ intracameral implant. DURYSTA™ should be used with caution in



Glaucoma is a leading cause of irreversible vision loss, affecting 70 million people globally. This chronic, progressive disease is characterized by elevated IOP – a major risk factor for glaucomatous visual field loss. While eye drop medications are the standard first-line treatment to lower IOP, adherence is an important factor and for some patients this may be challenging (2).

DURYSTA™ (bimatoprost intracameral implant) is the first and only FDA-approved biodegradable, intracameral implant indicated for the reduction of IOP in patients with OAG or OHT. DURYSTA™ comprises a sterile implant containing 10 mcg of prostaglandin analog preloaded into a single-use applicator that should only be administered once per eye without re-treatment. The applicator contains prostaglandin analog, bimatoprost, which is believed to lower IOP in humans by increasing aqueous humor outflow through both the trabecular meshwork and uveoscleral outflow pathways. DURYSTA™ is administered directly into the anterior chamber of the eye, via a pre-loaded 28-gauge needle, where it delivers bimatoprost 24/7 for several months. The implant – measuring approximately 1 mm in length – is made of a preservative-free polymer matrix, designed to slowly degrade over time into lactic and glycolic acid. The benefit for physicians? DURYSTA™ is physician administered, bypassing the ocular surface for direct delivery to diseased tissues (1). The availability of DURYSTA™ marks a major milestone for IOP lowering in glaucoma. For more information, visit durystahcp.com.

References

1. *DURYSTA™ [Prescribing Information]. Irvine, CA: Allergan, Inc. (2020).*
2. *B Gomes et al., "Assessment of eye drop instillation technique in glaucoma patients", Arq Bras Oftalmol, 80, 238 (2017). PMID: 28954024*

aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Prostaglandin analogs, including DURYSTA™, have been reported to cause intraocular inflammation. DURYSTA™ should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Ophthalmic bimatoprost, including DURYSTA™ intracameral implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. While treatment with DURYSTA™ can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Intraocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering DURYSTA™, and patients should be monitored following the administration.

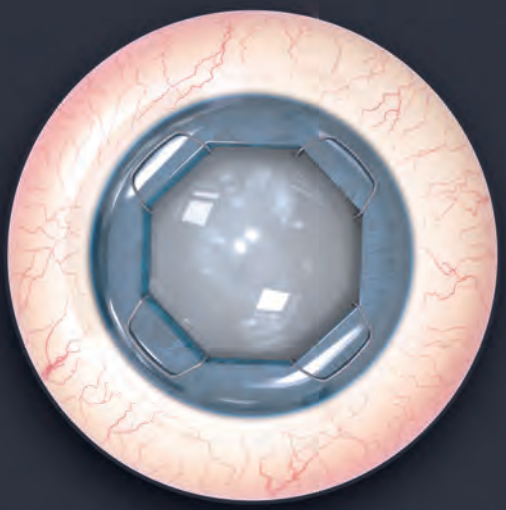
ADVERSE REACTIONS

In controlled studies, the most common ocular adverse reaction reported by 27% of patients was conjunctival hyperemia. Other common adverse reactions reported in 5%-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, iritis, and headache.

For full Prescribing Information for DURYSTA™, please click here.

DIAMATRIX

X1 IRIS SPECULUM



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Blood Ties

Hematology researchers are embarking on the world's first collaborative natural history study on congenital plasminogen deficiency – and ophthalmologists have a critical role to play

By Amy Shapiro

Congenital plasminogen deficiency (C-PLGD) is an ultra-rare genetic disorder characterized by the development of fibrinous pseudomembranes on mucous membranes throughout the body (1). While patients can develop lesions on the skin, respiratory tract, central nervous system, oropharynx and gingiva, middle ear, and renal collecting system, one of the most common presentations of the disease – affecting approximately 80 percent of patients – is ligneous conjunctivitis (LC). When left untreated, LC can result in visual impairment or blindness (2). Presentation of visual symptoms typically results in ophthalmologists being the first clinicians to evaluate and potentially diagnose patients at symptom onset (see Figure 1).

As the disease's prevalence is currently estimated at 1-2 per one million in the general population, C-PLGD is often misdiagnosed. This is due to both its rarity and the fact that symptoms are often ascribed to other, more common entities. There exist important knowledge gaps in C-PLGD, with little known of its true incidence, triggers, disease course based upon established severity categories, and overall impact. Quantifiable information about disease management, the need for surveillance of other potentially affected areas, the burden of disease, and patient experience is limited. Clinicians currently rely on anecdotal information, personal experience, and a limited number of case studies to develop patient care plans. No currently licensed specific and efficacious therapy is available to treat C-PLGD, compounding knowledge gaps and contributing to less than optimal outcomes.

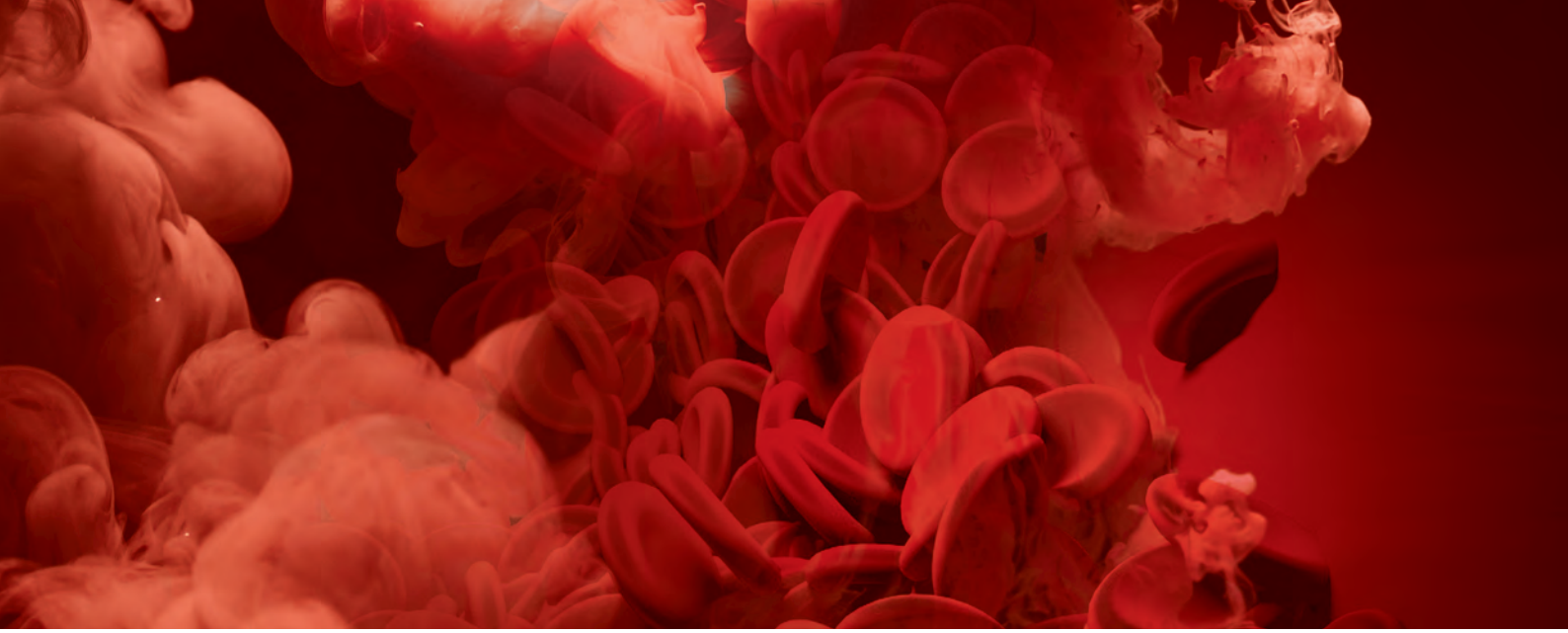
Teams at the Indiana Hemophilia and Thrombosis Center (IHTC), the Fondazione Angelo Bianchi Bonomi, IRCCS Ca'Granda Ospedale Maggiore Policlinico of Milan (IRCCS), and the University of Milan (UNIMI) are working to address these needs through the first-ever collaborative natural history study of C-PLGD, titled "Hypoplasminogenemia: An International RetroSpecTive and PrOspective CohorRt StudY," also known as "HISTORY." The results of this research effort could have important implications for ophthalmologists in the years ahead.

Current coagulation disorder data collection

There are currently two main repositories for data from patients with rare coagulation disorders, led by the American Thrombosis and Hemostasis Network (ATHN) and the European Network of Rare Bleeding Disorders (EN-RBD). While these organizations have made great strides in collecting data, a few issues have limited its applicability.

Neither program specifically addresses C-PLGD. The ATHN, in conjunction with the Centers for Disease Control, has accumulated a data repository with more than 80,000 participants, but it is a US-based program, making data regarding treatment and outcomes of included populations less applicable to patients living in other countries with different medical resources and populations.

The EN-RBD created the Rare Bleeding Disorders Database in 2004 to organize clinical, genetic, and treatment data surrounding rare bleeding disorders



beyond classical hemophilia A and B. Early data from the study was collected from 592 patients based in 11 European countries. This data allowed for the development of a new classification system for the severity of bleeding symptoms associated with these disorders. Since its inception, the database (later renamed the Prospective Rare Bleeding Disorders Database (PRO-RBDD)) has expanded to include prospective data collection from patients at 62 centers throughout the world. The goal of the expanded study is to support more accurate assessments of the prevalence of specific rare bleeding disorders, in addition to gaining new insight into symptoms, disease burden, and clinical management. While results have the potential to provide important information related to all rare bleeding disorders, the study does not include C-PLGD.

Making HISTORY

The HISTORY project is the first international study aiming to assess and define the natural history of C-PLGD, define severity categories, and identify triggers of disease manifestations. Coordinated by IHTC and IRCCS/UNIMI, it is an extension of PRO-RBDD that will take place over the course of four years – participants provide one year of retrospective data at baseline, followed by three years of prospective data. Upon enrollment, subjects are evaluated at an in-person visit at a study center to collect retrospective data, perform a physical examination, and obtain biological samples. Participants then have follow-up data collection conducted via telephone every six months until the end of the study, when they are seen in person. If subjects experience a clinical event suspected to be due or related to pseudomembrane development, or another medical event such as pregnancy, they will be seen in person for evaluation and sample collection.

Researchers will collect data from approximately 500 participants, including up to 100 C-PLGD patients and their first-degree family members. The study will evaluate a number of elements, including participants' overall health, age at diagnosis, reason for original C-PLGD screening, phenotypes, and genotypes. Participants with confirmed C-PLGD diagnoses will be classified as asymptomatic, intermittently symptomatic, or continuously symptomatic and their data will be considered in relation to gender, environmental influences, genetic information, and other laboratory measures.

C-PLGD-related lesions will be observed based on site, frequency, and duration in addition to the type(s) and duration of treatments. The study will evaluate laboratory parameters, information surrounding the management of surgical procedures, obstetric data, and any treatment complications.

One key aspect of this study will be the collection of data from asymptomatic first-degree family members of C-PLGD patients. This data will make a significant contribution to C-PLGD literature, as asymptomatic affected patients may not be tested for the disease and heterozygous individuals are not routinely assessed or followed. Data from affected asymptomatic participants in the study may hold valuable information regarding the triggers of disease manifestations. In addition, data from heterozygous family members will provide insight into the relationship between minimal plasminogen activity levels and the natural history of C-PLGD.

Implications of C-PLGD research in ophthalmology

Researchers hope to employ data and samples collected to address knowledge gaps in the clinical care of C-PLGD, ultimately establishing a superior standard of care. Given that LC is a common first presenting symptom of C-PLGD, the data have the potential to provide significant support to ophthalmologists and other

clinical eye healthcare providers who currently have very limited information and guidance for care of these patients. For example, if patients experience LC, there is currently no data available to assess the likelihood that they will develop lesions in other systems – including ones that could be life-threatening – what surveillance methods should be utilized and when, how frequently each person should be monitored, or how long they should receive treatment.

While an ophthalmologist may be able to provide some symptom relief for LC, they may not be able to predict what other specialists the patient will need to see. The HISTORY study could support the development of consistent and effective standards of care for patients with C-PLGD, including those who present with LC. Currently, there is no approved therapy for C-PLGD so medications are prescribed off-label, providing inconsistent and less than optimal outcomes. The HISTORY project aims to collect data in a way that allows for the development and confirmation of disease severity categories, more accurate prediction of the disease's course, effective identification of specific surveillance needs in subpopulations and the creation of treatment algorithms, more comprehensive recommendations, and best practices to guide disease management.

The HISTORY project also has the potential to help form the foundation for future clinical research through the development of a biorepository and the use of advanced coagulation testing. Researchers can potentially use information collected during the study to evaluate the use of locally performed tests as diagnostic tools.

The development of a disease-specific screening test would allow for assistance in diagnosis and prediction of disease course, facilitating earlier intervention and establishment of a more accurate prevalence rate. Currently, the diagnosis of C-PLGD is confirmed through analysis of blood plasminogen activity and antigen levels. These tests are not universally available and may not be standardized. Mutation analysis provides further confirmation but also is not always available.

Figure 1. Illustration of ligneous conjunctivitis.

Clinical research in ultra-rare diseases, as exemplified by C-PLGD, is challenged by both patient identification, phenotypic heterogeneity, and ultimately recruitment. The small populations of affected individuals involved in trials make generalizing data difficult. The data collected and analyzed during this study may assist in identifying patients for future clinical trial eligibility. While there are currently no approved specific and efficacious treatments available, researchers are exploring the use of a plasminogen concentrate derived and isolated from the blood of healthy donors to treat C-PLGD. The investigational therapy is currently under review by the FDA. Plasminogen is a key zymogen that plays a fundamental role as the precursor of plasmin, the main enzyme involved in the lysis of blood clots and clearance of fibrin; thus, plasminogen plays a central role in maintenance of mucous membranes, wound healing, cell migration, tissue remodeling, angiogenesis, and embryogenesis.

One of the most important goals of the HISTORY project is to increase awareness of C-PLGD among ophthalmologists and other medical specialists who may play a central role in patient care. Providing ophthalmologists with new levels of quantifiable information and insight into C-PLGD has the potential to improve time to diagnosis and the ability to advance patients to appropriate care.

For more information about the HISTORY project, visit the study website (plgdeficiency.com) or ClinicalTrials.gov, (clinicaltrials.gov/ct2/show/NCT037974).

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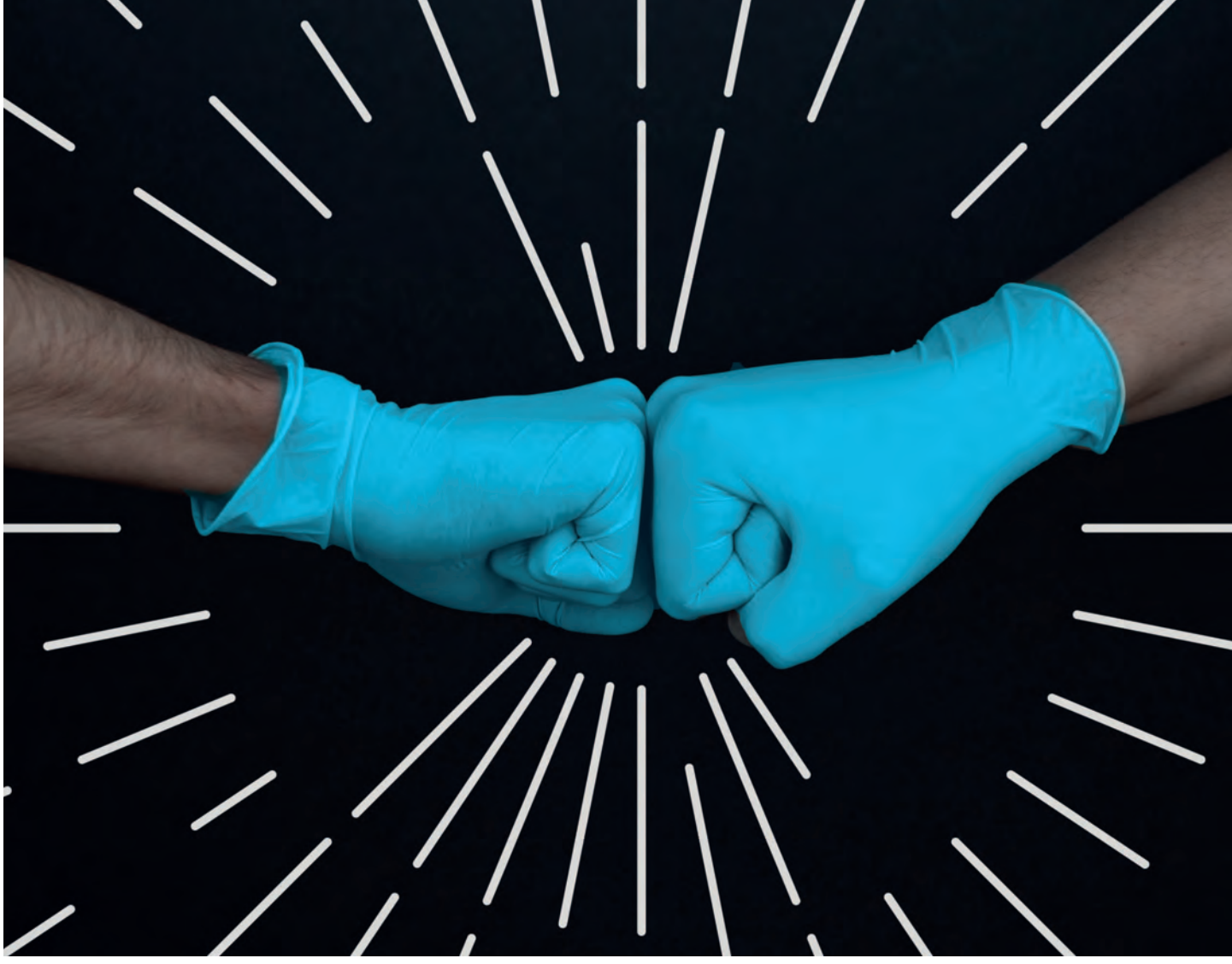

Nurses First

In honor of World Diabetes Day, we speak to the practitioners prioritizing nurse-led intravitreal dexamethasone implant services in the fight against DME

Allied healthcare professionals and nurse practitioners doing invasive procedures are not novel. Nurse practitioners have been performing invasive procedures in other specialities almost two decades before the first publication of intravitreal anti-VEGF drug delivery by nurse practitioners (1). But with a shortage of doctors and an ageing population, the need to find creative means of delivering intravitreal pharmacotherapy has become more pressing. Plymouth Eye Hospital, UK, decided to tackle the problem after an audit of their own consultant-led services revealed a significant delay in the delivery of injection from the time a clinical decision was made. The study identified an inadequate number of injectors and limited capacity as reasons why. The constraint in capacity was addressed by moving the service from the theater to the cleanroom in the outpatients setting. Two senior nurse practitioners experienced in intravitreal anti-VEGF injection were trained to deliver the intravitreal dexamethasone implant service.

Between February 2017 and October 2019, the two nurse practitioners administered 1,006 injections, and reported no cases of endophthalmitis or other visually significant complications, such as retinal detachment, vitreous haemorrhage, hypotony or iatrogenic cataract. A patient satisfaction survey was overwhelmingly positive, with the majority advocating for the continuation of the nurse-led service. The paper made the case for experienced nurses who already provide anti-VEGF injections to inject the intravitreal dexamethasone implant (Ozurdex), streamlining the service and reducing waiting time for patients.

Alison Triggol – one of those nurse practitioners – holds the position of macular lead nurse at the Royal Eye Hospital, Plymouth. In honor of World Diabetes Day 2020 "Diabetes: Nurses Make the Difference," we spoke with Ali about her experience administering the implant – and asked for her opinions on the evolving role of nurses in ophthalmology and DME treatment.

Macular clinics in lockdown

How has your practice been affected by the pandemic?

Myself and another colleague – another full-time injector – have been trying to keep the macular clinics going; it's very important that our patients don't lose their sight. We've been busy offering a one-stop clinic throughout lockdown but it is only in the last month or so that we've struggled to cope with numbers as people start to come out of isolation.

Are you anticipating another delay after this lockdown?

We noticed a change as soon as the government made the announcement. We're not reducing our clinic hours but we're already seeing patients not turn up for their appointments out of worry, particularly in the South West of the city where infection rates are worse now than they were in the first lockdown. The average age of a patient here is about 70 or 80 years old (not to mention three or four over 100) which makes them a lot more vulnerable. We're also seeing more COVID-19 patients admitted to hospital, but we have our own entrance and are taking all the necessary safety measures such as social distancing and adequate PPE.

Can you tell us more about the nurse-led trial?

We had to apply to the governor's board to make the case for doing the project at all. We told them it would free up theaters for more pressing cases and made the argument that it's cheaper for a nurse practitioner to perform injections in the outpatient department rather than taking up the theater time getting a consultant to do it. Even when they can, they typically only do one or two cases per session. This means significantly longer wait times for patients who may spend five hours waiting for a single injection. We actually had patients fill out a satisfaction questionnaire at the end of the trial and the majority said they were amazed at how quickly they were seen because as nurses, we could just fit them between other injection appointments. The satisfaction rates went from 58 percent with a consultant to 96 percent with nurses.

Why do you think that is?

As nurse practitioners, we're so proficient at giving injections, the patient often feels less pain than they would in theatre – and that's with us only using topical anaesthetic. It's also incredibly quick, taking the same amount of time as we would for an anti-VEGF injection.

Some doctors have reservations about nurses taking on this kind of work. Did you have any reservations yourself beforehand?

Ozurdex requires a completely different technique to anti-VEGF, so it was important to get the right training. I was taught by one of the consultants, Konstantinos Papadedes, who took me through the ins and outs of what could go wrong – deflating the eye, causing a slow leak. I was initially a bit scared but after a lot of practice, you get a feel for it. We've had no complications so far.

"I've given talks to nurses throughout the country about implementing these practices and I tell them: be positive and don't be frightened of taking on new roles."

One of the key takeaways from the paper is the benefit of nurse-led services. Was your experience positive overall?

Definitely. We have gone from doing two or three sessions a week to 15 or 16 sessions – it's constant. Our aim is to offer a one-stop clinic for injections but we have so many patients in our catchment area, we can't possibly provide it for everybody. Nurse-led clinics like ours frees up doctors to do more theater sessions, which is undoubtedly a good thing.

How do you think the role of nurses in ophthalmology is going to change?

It is becoming obvious that we're going to have to take more responsibility – and not just because of COVID-19. There is a general increase in numbers of patients presenting to ophthalmology departments, in part because the equipment we use is so advanced we can now see things we couldn't before, which generates more work for us, and the fact that people are living longer which means we are treating them for longer too. Morbidity rates are also increasing. The only issue is getting the nurses. We're having difficulty with that at the moment. The majority of nurse practitioners are 45-plus and all on the verge of retiring. We need new blood coming in but there is a reluctance – a squeamishness – amongst nurses to do ophthalmology, so unless we can recruit more, we're going to have a big problem in the years to come.

Do you have any advice for practices looking to adopt your model?

Get a consultant who believes and trust in nurse practitioners. I've given talks to nurses throughout the country about implementing these practices and I tell them: be positive and don't be frightened of taking on new roles. Training takes times – it took me two months, and that was before COVID-19– but once you refine your injection skills, patients can be out in and out in 15 minutes. Everybody benefits.

How does ophthalmology compare to other specialties you've worked in?

They say the eyes are the windows of the soul, and it is true. We find that we often diagnose other non-ophthalmic problems when we see our patients – whether they're going to have a stroke, if they have problems with their cholesterol, if they are at risk of diabetes. It is very beneficial being able to prevent further diseases this way. In ophthalmology, you tend to get to know your patients, and they get to know you as well, because they come back month after month for treatment, which is something I love.

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What's on Our (DR) Radar?

Exploring the real-world impact of artificial intelligence in diabetic retinopathy screening

By Andrzej Grzybowski and Piotr Brona

Diabetes is becoming a global epidemic; the number of people affected worldwide has risen from 108 million in 1980 to an estimated 463 million in 2019, with an estimated 700 million by 2045 (1). Diabetic retinopathy (DR) and its sight-threatening effects are expected to sharply rise along with the increasing population of diabetics. DR is already one of the leading causes of blindness in the working age group. Establishing robust DR screening programs, as achieved during the last two decades in the UK, has been shown to be effective in tackling this growing issue (2); however, the current model of DR screening is prohibitively expensive for all but a few highly developed countries.

Annual screening for every diabetic, performed by an ophthalmologist, is very expensive and inefficient. It is becoming increasingly clear that not everyone requires yearly screening. Some patients could be safely screened every 2–3 years, for example, presenting a significant cost-saving opportunity. One initiative to target this issue is Retina Risk – an algorithm for stratifying individual risk of developing sight-threatening DR, developed by a team led by Einar Stefansson, Professor at the Department of Ophthalmology at the National Hospital Reykjavik, University of Iceland. Using several inputs, including HbA1c level, Retina Risk is able to calculate if patients are likely to progress to vision threatening DR within the next six months or 1–3 years, then recommending an appropriate follow-up time based on the risk. The majority of diabetic patients do not have DR and, even if they do, only a fraction of them require treatment. Targeting this relatively small – although in absolute numbers very significant – group of patients is the main aim of screening.

The population of diabetics is steadily rising, but the number of ophthalmologists needed to treat them cannot rise fast enough to meet the demand. On average, low-income countries have fewer than four ophthalmologists per 1 million inhabitants; even in high-income countries the number is 76 (3). And so, even in high-income countries, thorough screening programs based on examinations by ophthalmologists are simply not feasible.

Where does AI come in?

AI may help us solve some of these issues, but it should not be mistaken for a cure-all solution. There are many deep-learning algorithms for screening of DR based on fundus images available today – and there are more on the horizon. (4) However, to be effective on a larger scale, these need to be used in pre-ophthalmological, community-based screening settings.

To reach a wider population that is not already being surveilled by ophthalmologists, AI DR screening solutions should be centered around primary care or diabetes clinics. With modern automatic fundus cameras, minimal training is required to allow staff, such as nurses, to take good quality fundus images in the majority of cases. And though it is clear that more staff would be required to capture retinal images overall, the personnel could also provide health education and advice.

We know that screening for sight-threatening DR using fundus images is not a flawless solution; some cases of isolated diabetic macular edema could be missed. We could of course train graders to take and classify OCT images, but fundus image-based screening remains the cheaper and still effective option. This reality was highlighted by the trial that led to the FDA clearance of IDx-DR – an AI based DR screening solution. Effectiveness of the AI system, basing only on two fundus images per eye, was compared with a professional grading center with access to not only stereo widefield retinal photographs, but also OCT. The software identified more than mild DR with 87.2 percent sensitivity and 90.7 percent specificity. 84 percent of center-involved DME cases were identified by the system. Inevitably, some cases will be missed, but human-based grading is also not infallible.

"The current model of DR screening is prohibitively expensive for all but a few highly developed countries."

AI used for DR screening in the real world

Up to now, only the UK and Singapore have introduced comprehensive DR screening programs, mostly because of the considerable associated costs (2,4). In Poland, where we practice, the population of diabetics is around 3 million; from a screening point of view that's 12 million images that must be analyzed. The upshot? Introducing comprehensive DR screening in Poland was not feasible. But introducing AI into this space has completely changed the mindset of the country's DR specialists – the impossible has suddenly become realistic.

During 2018–2019, we conducted pilot studies in Poznań, Poland, starting with a single diabetes clinic with a population of 600 patients. We used pre-ophthalmic screening, working with diabetologists to screen at-risk patients; we wanted to screen as many diabetic patients as possible in the amount of time we had available to make the pilot program as effective as possible (5). Patients in the care of diabetic clinics are also likely to present more advanced stages of diabetes and, as a result, a higher likelihood of DR. In the future, general practitioners/family physician practices could be used to conduct the initial phase of the screening. After the first 600 cases, we then screened a further 1,000 patients. Afterwards, with lessons learned and teething problems largely resolved, we began a large-scale project, co-funded by the European Union, to screen over 40,000 diabetics in 30 diabetic clinics in the Polish region of Wielkopolska over three years. The project is still ongoing (6).

Our overall goal is to present large-scale data that would convince policy makers (in Poland: the Ministry of Health and the National Health Fund) that introducing a large-scale DR screening program in the future will be beneficial to the country's healthcare system and that it should be considered a priority.

Wielkopolska has a population of 3.6 million people (around 10 percent of the country's population) and a successful DR screening program in the region would be a good indication of positive screening outcomes across Poland.

Per aspera… ad astra

To conduct a project on such a large scale, we purchased fundus imaging equipment and trained specialist nurses to obtain consent, take images, upload them to the cloud, provide education, and care for patients involved in the project. The clinics and the staff responsible for capturing images have received financial compensation. Our aim is to perform around 1,500 exams every month; before the COVID-19 pandemic hit, we were averaging around 800-900 exams monthly. Providing support to so many clinics and trained graders at the same time has naturally proved to be a challenge. In this real-world study, we have had to rely on professionals with varying degrees of computer literacy and willingness to learn. We have had some nurses refuse to take part in the project as they considered this new training to be beyond their capabilities. In those cases, we had to source suitable locally-based personnel, such as trained optometrists outside the clinic.

Images were captured according to a standardized imaging protocol – with one disc- and one fovea-centered 45-degree image per eye – and submitted to an autonomous AI-based DR system (IDx Technologies) for automated image quality evaluation. The system returned results of i) "more than mild" DR not detected, ii) "more than mild" DR detected, or iii) vision-threatening DR detected. Patients with "more than mild" not detected results were given a recommendation to attend another screening in one year's time; all

other results recommended an urgent ophthalmology referral. The images were also reviewed by ophthalmic specialist graders, and, if inconsistencies with the AI algorithm were detected, patients were notified at their next diabetic clinic visit (in the case of a false-positive result) or by phone (if the result was a false-negative).

Notably, the AI system has previously received a class II certification in Europe as well as US FDA authorization and may be used as an autonomous screening device, meaning that the results can be relied upon for a referral decision without review by a clinician.

Our findings

Based on preliminary analysis of data gathered from the first 450 screening episodes, we determined that the IDx-DR system was able to analyze 78 percent of screening episodes, compared with 82 percent in the case of a human grader. Overall, according to a single clinician reference standard, sensitivity was 94 percent and specificity was 95 percent, with positive predictive values of 82 percent and negative predictive values of 99 percent. We found the system easy to implement and use. Automatically saved results were available for analysis within a minute. In the future, we would like to conduct a cost-effectiveness analysis, acquire additional data of patients' DR risk factors, and expand the program beyond the high-risk population. So far, the program has proven to be very successful, with our accuracy results higher than those previously reported in the literature, including the FDA pivotal clinical trial (7-9). Moreover, based on our in-growing database of fundus images, recently we started testing other AI algorithms for DR screening and we are open to collaborate on this subject with teams working on novel ideas.

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Stronger Together

Charles Holmes and Ignacio Tuduri on the Allergan AbbVie vision for the future – post-merger

In May 2020, Allergan merged with Abbvie – the global research-based biopharmaceutical company. We caught up with Charles Holmes, Associate Vice President, Head of Global Marketing, Eyecare at Allergan, who is based in the UK, and Ignacio "Nacho" Tuduri, Vice President, Global Marketing at AbbVie, based in Chicago, Illinois, USA, to ask about the fusion, their experience in the field, addressing unmet needs in ophthalmology, and current and future projects.

Tell me about the recent AbbVie-Allergan merger…

Nacho Tuduri: The merger has given us an opportunity to invest in science in the long term, and look for new solutions in areas where unmet medical needs still exist. It allows us to diversify our business and expand our global skills in many areas: ophthalmology, immunology, hematologic oncology, and neuroscience. Our R&D funding capacity will be increased, and Allergan's heritage in eye care means that we are expecting to be bringing many "firsts" to this market. We're very happy about how the integration has gone – it was a seamless process and a great success.

How are you hoping to address unmet needs in ophthalmology?

Nacho: We have a busy pipeline of transformative solutions for different areas of eye care: glaucoma, retina, dry eye... We are focusing on launching products that actually fulfil existing needs.

Charles Holmes: Indeed! Patient burden in retinal conditions, such as DME, is very significant, with patients having to travel regularly for intravitreal injections. Now, in a pandemic, with social distancing requirements and a number of lockdowns limiting appointments, there is a tremendous number of patients waiting for a limited number of eye care specialists.

If you look at glaucoma, patients are still battling the same challenges of topical medications they encountered 30 years ago, when I entered the ophthalmic industry; people struggle with red eyes, ocular surface issues; they don't want to carry on applying their eye drops.

And that is why our future solutions have to be truly transformative. We're aiming to fix universal issues that ophthalmology patients have faced for decades.

How are you planning to succeed?

Charles: Allergan has been in ophthalmology for around 70 years and has built amazing relationships, earned physicians' trust, and brought many great products to market. AbbVie is a bigger company, with more scientists and more R&D capabilities. We have new assets available in the AbbVie cupboard that could potentially be repurposed for ophthalmology.

Our focus on eye care – preventing vision impairment and blindness – won't change, but we are focusing even more on addressing problems arising from the world's population growing and aging, as well as issues to do with increased screen use, time spent in air-conditioned environments, and less time spent outdoors. These challenges are going to be even more widespread in the post-pandemic reality. And we are not solely focused on the established markets; we include emerging economies in our plans and recognize common themes and specific challenges in different parts of the world.

"We emphasize the value of following uniform processes and the importance of understanding patient safety."

What current or upcoming projects are you working on?

Charles: I'd like to talk about an important social impact program called Keep Sight. We have been working in partnership with the International Agency for the Prevention of Blindness and Sightsavers to prevent sight loss – predominantly from glaucoma – around the world, through training healthcare professionals and sustaining and reinforcing screening systems.

Working with Sightsavers, we have already been able to screen 12,000 people out of a goal of 35,000. Because of COVID-19, it is difficult for patients to visit screening centers, so attaining this number has been a big achievement for Keep Sight. We are also looking at clinic optimization in developing countries; we know that they are overburdened with patients, so we are working with healthcare professionals on creating and implementing systems that will be able to help more people be seen.

How did each of you get into ophthalmology?

Charles: This question takes me back to when I was a young teenager, aged 12 or 13. My grandfather was a diabetic and

suffered from DME. At that time I had no clear idea of what diabetes meant, but I noticed that the biggest issue for my grandfather was its impact on his vision. Later, I worked in a hospital and when I saw patients coming into the ER with eye conditions, it always made me very nervous – I realized how vital vision was.

These feelings were at the back of my mind when I landed a job at Alcon, where I spent 17 years working in the ophthalmic space, and I absolutely fell in love with it. The understanding of how to save people's sight – be it with antibiotics for corneal diseases, IOLs for cataract patients, or surgical solutions for glaucoma – has been a revelation. I then moved to Bayer and spent a further 10 years focusing primarily on retina, and I recently joined Allergan to be able to work on all aspects of ophthalmology. My three jobs in 30 years have all been in ophthalmology, and it has been a labor of love. I am very passionate about what I do.

Nacho: I am trained physician, specialized in neurology. I spent a few years working in a hospital, including injecting botox, before moving to industry – first on the medical side, and then on the commercial side of the business. My neurology background has really helped me get to grips with ophthalmology quickly. It's been really exciting to see what impact Allergan has made in ophthalmic communities – and it makes me very proud to be part of its endeavors.

What is your leadership style?

Nacho: My motto is: "Surround yourself with experts," and there is certainly no shortage of excellent, highly-skilled specialists working alongside me. I believe leaders have to be very transparent, with communication channels around them wide open. I start from a deep reflection, but keep things real – I believe in a strong connection between strategy and execution.

We want our employees to really enjoy the professional atmosphere – it helps them develop and grow. We need our colleagues to enjoy what they do while working as hard as they do.

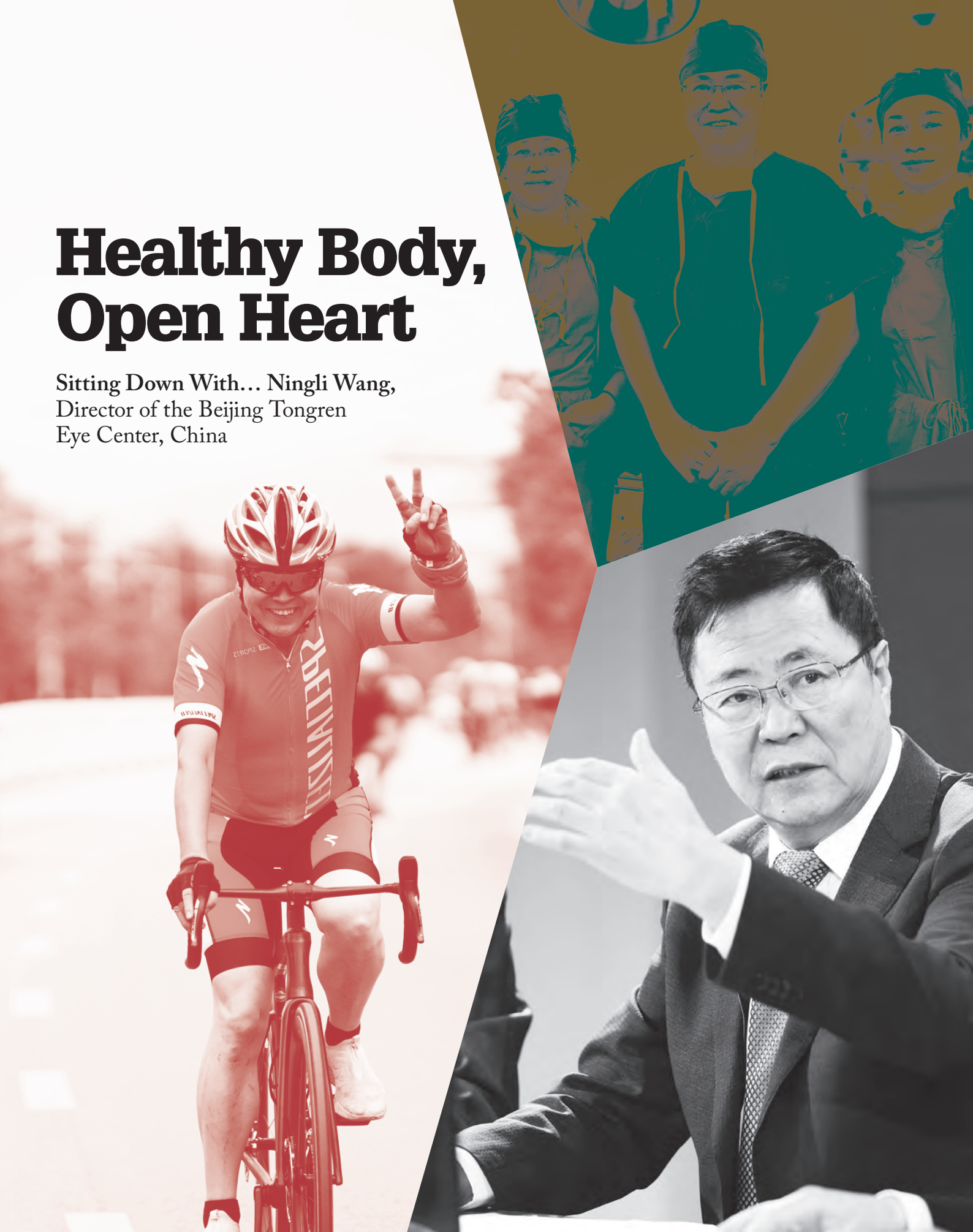
Charles: One common thing that I've noticed coming from legacy Allergan to the newly merged company is patient centricity. For the leadership at Allergan patients have always come first, regardless of anything else – and Nacho absolutely shares this mindset that whatever we do, it has to be right for the patient. In a business like ours, it is crucial. In fact, it is the only way forward.

How can you help physicians deal with post-pandemic backlogs?

Charles: The best thing we can do as a company is to continue to provide products that physicians need for their patients; fortunately, we haven't suffered any shortages, outages or supply chain problems. We are now able to interact one-on-one with our customers, ensuring that we help them keep clinics working efficiently. We will continue to work with healthcare professionals to ensure that patients around the world receive the right treatment for them, saving their vision and livelihoods.

Healthy Body, Open Heart

Sitting Down With… Ningli Wang,
Director of the Beijing Tongren Eye Center, China



What did you want to be growing up?
When I was a child, I wanted to be a scientist. The first book I ever read was "One Hundred Thousand Whys" [a popular Chinese science book]. I was a really curious kid and this book was my first window into understanding the basics of this world. As I grew older, I came to appreciate the beauty of art and was fascinated by the paintings of Salvador Dalí. It was amazing to me that you could present a world almost beyond imagination through the tip of a brush – and so I started dreaming about becoming an artist.

Why did you decide to pursue a career in ophthalmology?
I almost didn't. When it came to my college entrance exams, I actually applied to study art as my first choice and study engineering as my second choice, but was unsuccessful. However, in another way, it actually worked out just fine as I got into medical school – after all, medicine is the perfect blend of science and art.

What route did you take to become Director of the Beijing Tongren Eye Center?
In 2002, Beijing Tongren Hospital issued a job announcement saying they were looking for a Director of their ophthalmology department. Becoming the Director of the ophthalmology department, the largest eye center in north China that has a history of over 120 years, does have its unique appeal. Back then, I was working in the largest eye center in south China, the Zhongshan Ophthalmic Center. With my life, my work, and my family and friends all in Guangzhou, the decision to leave was a hard one to make. However, after thorough consideration, I knew it would be a great platform for me to realize my potential and to see if I would be able to serve not only as a doctor but also as a leader. I decided to apply for the job.

Though the competition was fierce, I managed to get the position. After starting working in Tongren as Director of the ophthalmology department, I led the founding of Beijing Tongren Eye Center. With a decade of effort, under my watch, the center transformed from a clinical center to a center of global influence that pioneers both clinical practice and scientific research. The ophthalmology department of Tongren Hospital is one of its best, with over 200 ophthalmologists. I was then entrusted with an even bigger responsibility – vice-president of the hospital, mainly in charge of scientific research. And in another shift, my social influence, leadership, and management skills were put to use as president of the hospital from 2016 to 2017.

What do you consider to be your greatest success?
With great honor, I have been serving as the head of the National Committee for the Prevention of Blindness. I was one of the co-leaders of a project dedicated to eliminating blinding trachoma in China by 2016. It was a great success, and resulted in the WHO verifying that China had eliminated the condition by 2019. It is incredibly exciting that we managed to do it in a country with a population of 1.4 billion.

How has the glaucoma field changed over the course of your career?
Firstly, there has been a 50 percent decrease in the blinding rate of angle-closure glaucoma. Secondly, the success rate of glaucoma surgery has increased to 90 percent with the introduction of MIGS in congenital glaucoma children. Thirdly, a consensus was issued on artificial intelligence-based fundus screening for glaucoma; we are now carrying out screening in some of the country's most remote areas.

Which piece of research are you most proud of and why?
I would probably say the proposition of the Trans-lamina cribrosa pressure gradient theory, which explained the optic nerve injury in normal tension glaucoma patients and identified low intracranial pressure as a risk factor.

Outside of ophthalmology, what makes you happy?
Cycling. I have cycled around the five famous lakes in China. I hope that someday soon I will be able to participate as a racer in the Tour de France.

Which person outside of the scientific community has been your biggest inspiration?
Leonardo da Vinci. I really admire his free mind. I recently translated Martin Clayton's book, "Leonardo da Vinci: Anatomist," into Chinese.

Can you describe your perfect non-working day?
I'd wake up after a good night's sleep to a shining day in a beautiful place. I'd go cycling with my friends or do some other outdoor activities. At night, I'd read a book or watch one of my favorite movies.

What's changed for you since the start of the pandemic – both professionally and personally?
A few months without clinical work meant I was able to complete a few important projects I had been meaning to do for a while. I now spend more time taking care of my health and have a new hobby: cycling. I lost about 15 pounds and now my biochemical indicators are all back to normal. I don't have a fatty liver anymore!

Finally, what advice would you give to your younger self?
When you fall in love with a girl, don't hesitate to tell her – a second chance may never come.

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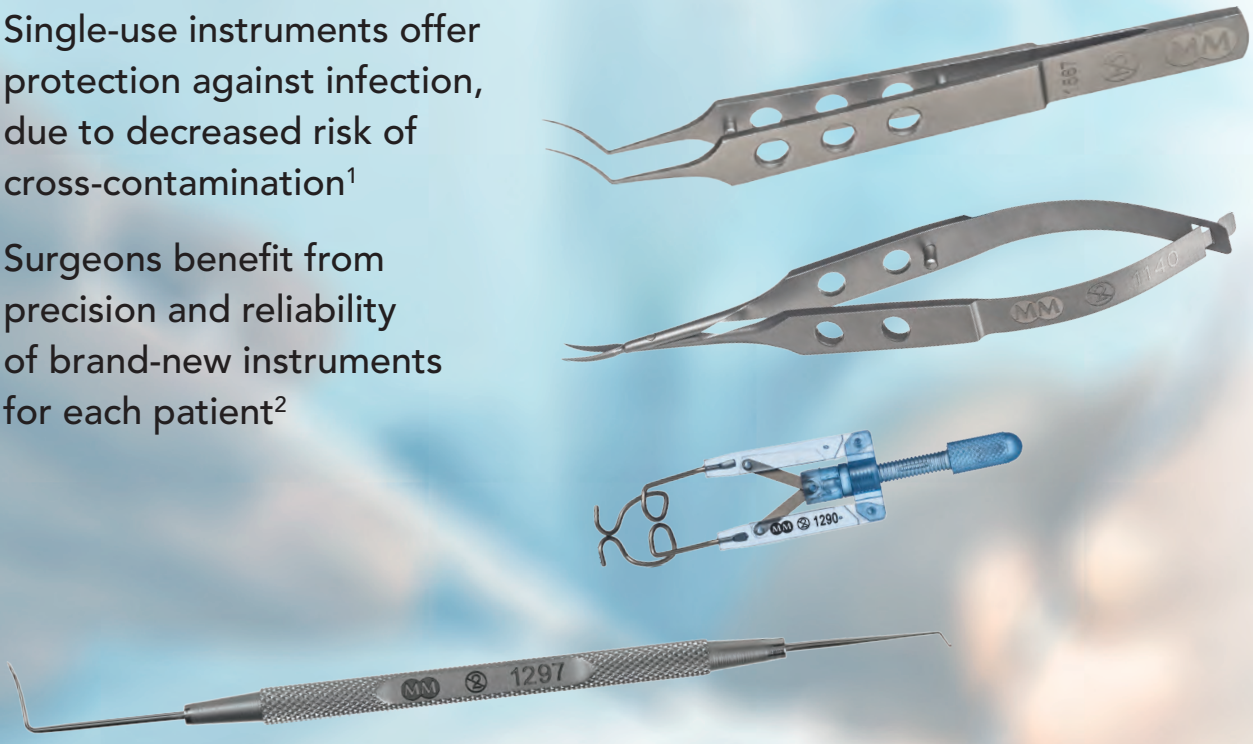

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