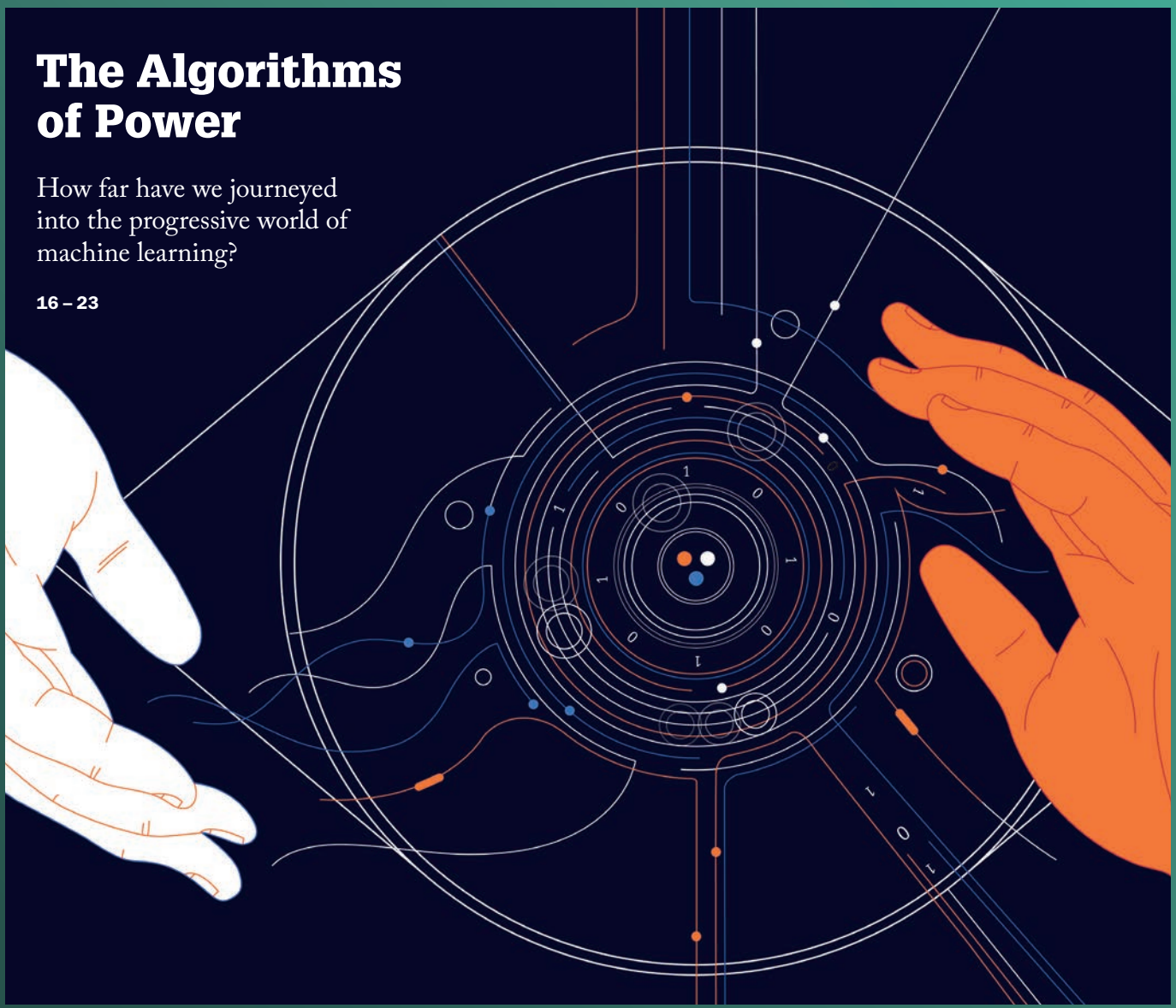
SEPTEMBER / OCTOBER 2022 # 63

the Ophthalmologist™

The Algorithms of Power

How far have we journeyed into the progressive world of machine learning?



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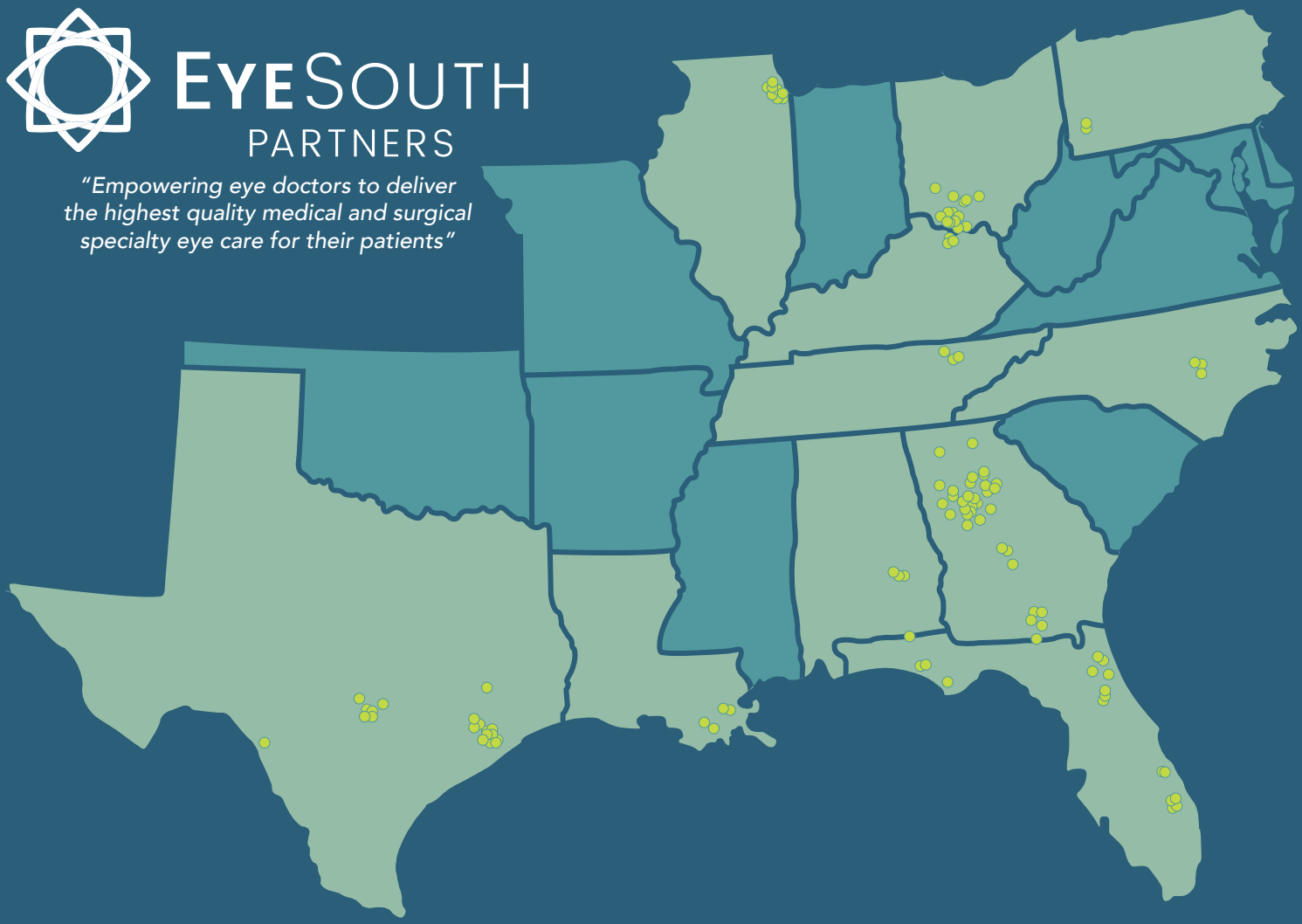

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See It, Say It, Change It

If innovators are looking for far-reaching success, they must include data from all ethnicities

According to the gurus who shared their perspectives in this issue's cover feature (page 16), system bias is a key challenge in the continuous development of AI in ophthalmology. As Michael Chiang, Director of the National Eye Institute at the NIH, describes it: "AI systems are typically trained and validated in fairly narrow populations and specific imaging devices, whereas real-world applications will need to be rigorously validated to ensure they work across broad populations and devices without bias."

The same concern pops up time and time again. When I spoke with Anthony Khawaja, a Moorfields Eye Hospital glaucoma specialist and genomics expert, he was uncomfortable about making progress in medicine that would only benefit people from one ethnic background. "It seems clear that more work needs to be done to replicate prior research for other ethnic groups – and to develop a framework that leaves no group of patients disadvantaged" (1).

Although attempts are being made to deploy research projects in developing countries – for example, Zambian and UK ophthalmologists are using deep learning to screen for diabetic retinopathy (2) – most R&D is conducted in industrialized economies. Even in the most diverse populations, it is not always easy to gather data across different ethnicities, and, as Michael Abràmoff told me previously (3): "There are legitimate concerns about racial and ethnic bias in AI. It is important that autonomous AI is designed and validated in a way that ensures those concerns are addressed, and any inappropriate bias is corrected."

But that's easier said than done when implicit bias is so prominent in society. Even electronic health records (EHR) have been perpetuating racial bias, as discovered by a group using machine learning techniques to analyze data of over 18,000 adult patients in Chicago (4). So, is there hope? The EHR project investigators found that the situation improved after March 1, 2020 – perhaps due to "social pressures [that] may have sensitized providers to racism and increased empathy for the experiences of racially minoritized communities."

Visibility and awareness are key: you cannot change things you don't, can't, or won't see. It is vital that we all shout from the rooftops about inequality – wherever we see it, including the sphere of ophthalmic innovation and research.

Aleksandra Jones
Editor

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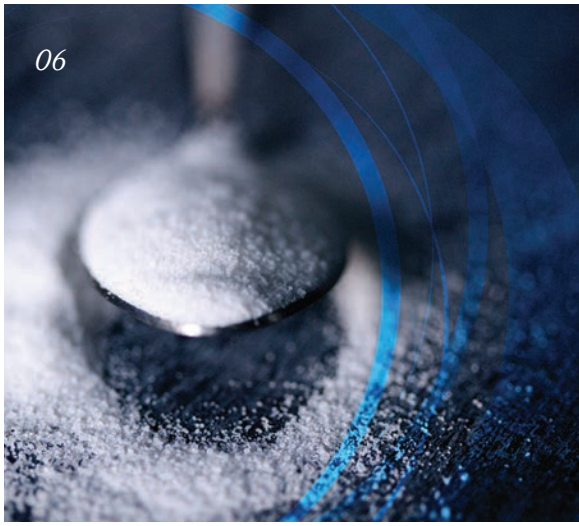
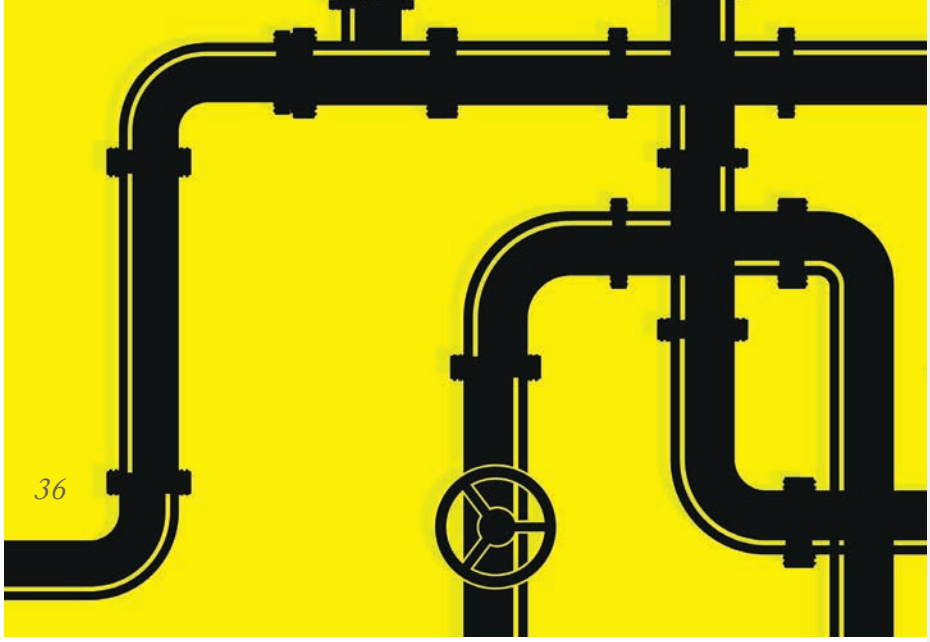
1. *A Jones, "Genomics and Glaucoma," The Ophthalmologist (2019). Available at: https://bit.ly/3SLQoHU.*
2. *V Bellemo et al., "Artificial intelligence using deep learning to screen for referable and vision-threatening diabetic retinopathy in Africa: a clinical validation study," Lancet Digit Health, 1, e35 (2019). PMID: 33323239.*
3. *A Jones, "The Ethics of AI," The Ophthalmologist (2020). Available at: https://bit.ly/3UZT2vu.*
4. *M Sun et al., "Negative patient descriptors: documenting racial bias in the Electronic Health Record," 41, 203 (2022). PMID: 35044842.*

Contents



On The Cover

What is the current state of AI in ophthalmology?



Practice Fundamentals

Profession

Sitting Down With...

the Ophthalmologist

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Upfront

Research
Innovation
Trends

A Spoonful of Sugar

Theranostics could be the efficient way to diagnose and treat retinoblastoma

How great is it to accomplish two things at once? Personally, I try to defeat my multitasking demons by reading while using my exercise bike (assisted by a tablet stand – and preferably with a coffee in hand!). But when it comes to medicine, diagnosis and treatment are normally two separate entities and by no means as easy to juggle as my heart rate zone and the latest ophthalmology literature. Recently, however, the dichotomy of diagnosis and therapy is beginning to disappear thanks to theranostic technologies. If you think that "theranostic" sounds suspiciously like a mix of "therapy" and "diagnostics," then you have earned your spoonful of sugar.

Researchers from the Second Affiliated Hospital of Chongqing Medical University in Chongqing, China, are using theranostics as a potential retinoblastoma treatment. They designed a nanoparticle drawn to the negative charge of cholesterol that accumulates in cancerous tissue; can be detected using ultrasound, photoacoustic, and magnetic resonance imaging techniques for diagnostic purposes; and also produces heat to kill cancer cells when targeted by activation of photothermal and photodynamic processes with a 808 nm laser (1). The nanoparticle itself is a folate and magnetic cationic nanoliposome that encapsulates two active components, indocyanine green and perfluorohexane. In the lab, it targeted cancer cells with just over 95 percent cell uptake rate and, when used in mice, achieved almost complete tumor regression. The therapy was also deemed to be safe and have no off-target toxicities when tested in mice. This combined approach to therapy not only simplifies the treatment and synthesis processes, but also lowers manufacturing costs.

The results offer promising evidence that these nanoparticles could be used for diagnosis and treatment of retinoblastoma – but, on a wider scale, they're another checkmark in the column of superparamagnetic theranostics as an efficient cancer treatment option in many tissues. Hopefully, this medicine won't require a spoonful of sugar to help it go down in a most delightful way!

See references online.

INFOGRAPHIC

On Thin Eyes...

Researchers probe the relationship between cardiovascular risk factors and inner retinal thickness

Cardiovascular risk factors and inner retinal thickness relationship was analyzed in **8288** patients

Assessed factors included **AGE, LIFESTYLE, BODY COMPOSITION** and **OCT MEASURED RETINAL THICKNESS**

Credit: Image sourced from Unsplash.com

ARVO IN FOCUS

The latest research from ARVO journals Investigative Ophthalmology & Visual Science and Journal of Vision

Bolt from the blue

A study has linked blue light exposure to AMD damage through a protein (ubiquitin-protein ligase E3D, UBE3D) associated with AMD in East Asian populations (1). UBE3D was also associated with DNA damage response in the study, finding that the AMD-associated V379 mutation might be causing oxidative damage, and therefore be a target for therapeutics.

Berberine

Researchers have determined that berberine (BBR), an extract produced by a traditional Chinese plant, has therapeutic activity to combat thyroid-associated ophthalmopathy (TAO) (2). The study found that BBR had positive effects on adipogenesis, inflammation, hyaluronan production, and fibrosis. This builds on recent findings of berberine's effects on mechanisms of inflammation, fibrosis, and lipometabolism, and sets a foundation for the safe and affordable compound to potentially be used to help people with TAO.

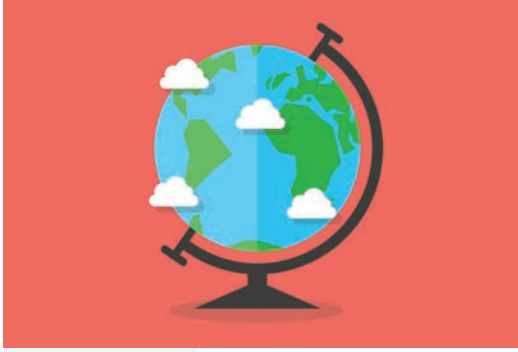
Pupil power

The pathogenesis of central serous chorioretinopathy (CSC) is relatively unclear. What is clear, is that CSC primarily affects middle-aged men under chronic stress, and is thought to arise from choroidal disturbances. To better understand, diagnose, and treat CSC, researchers looked to the autonomic nervous system, a key player in the stress response, to develop a quick and easy link to the condition's pupillary responses and heart rate variability. They found that it was possible to associate CSC with these biological metrics, and that larger pupil dilation during mental tasks could also be a marker of psychophysiological stress (3).

Scaling a pseudo font

Researchers have developed a new pseudo font for measuring visual acuity that has a consistent complexity and a refined degradation under blur (4). The font, PseudoSloan, is based on the optotype font Sloan, uses glyphs that are based on the Latin alphabet on a letter-by-letter basis, and allows for separation of orthography (recognition of a letter) from lexical knowledge (formation of a word).

See references online.



Clarity on Global Disparity

Global healthcare disparity puts children at unnecessary risk of eye loss and death from retinoblastoma

Healthcare disparities are a major issue globally, and now, socioeconomic status has been highlighted as a major risk of childhood death from retinoblastoma (1). Recent data shows that children in low-income countries are 16 times more likely to die from retinoblastoma – the most common eye cancer – in the first three years following diagnosis.

Death from retinoblastoma is rare in high-income countries, but the survival rate drops from 99.5 percent to almost 50 percent in low-income countries. Although essential treatment is available, patients in low-income countries tend to seek clinical help too late – highlighting the importance of increased early retinoblastoma symptom awareness.

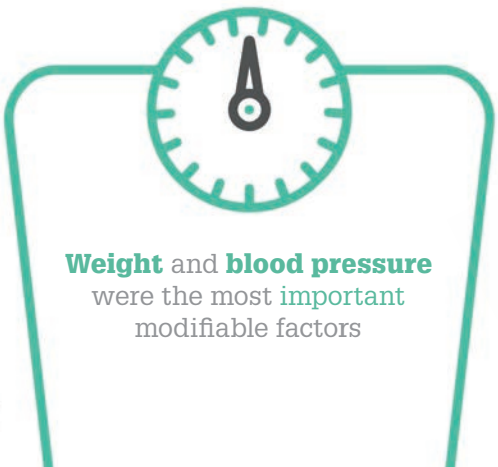
Reference

1. *Global Retinoblastoma Study Group, Lancet Glob Health, 8, E1128 (2022). DOI: 10.1016/S2214-109X(22)00250-9.*

Cardiovascular risk factors explained

12.6 percent

of the variance in the ganglion cell-inner plexiform retinal layer



Weight and **blood pressure** were the most important modifiable factors

BMI's negative association with all inner retinal layers indicates that obesity causes **thinning** of the **inner retina**

Reference

1. *T von Hanno, et al., Invest Ophthalmol Vis Sci (2022). 63, 16 (2022). PMID: 35960516.*

Building Castles in the Eye

Rebuilding "unzipped" retinas starts with identifying how they were originally held together

If you've ever seen a building collapse, you're aware of the damage a lack of structural integrity can cause. Similar principles apply within the eye, where stability is maintained by the connecting cilium linking the outer segment of photoreceptors with the cell body. Connecting cilium structural defects are already associated with retinal degeneration; however, its nanoscale molecular composition, assembly, and function are relatively unknown. University of Geneva researchers have identified a four-protein molecular zipper whose loss removes a protective structural foundation, resulting in photoreceptor death and retinal degeneration (1). Focusing on the RP28 retinitis pigmentosa subtype, associated with recessive mutations in the human FAM161A gene (which produces one of the molecular zipper proteins), they explored when and where defects arise, because knowing how everything collapses may provide new ways to rebuild and strengthen vision.

Lead researchers, Virginie Hamel and Paul Guichard, are no strangers to analyzing biological architecture. "Our laboratory specializes in structural cell biology. Particularly interesting to us is the centriole, a microtubule-based organelle found at the core of mitotic division as well as cilium formation," explains Hamel. "We were intrigued that all identified scaffold components are localized to the connecting cilium within photoreceptors, with mutations within these proteins resulting in photoreceptor degeneration. This led us to hypothesize that a similar inner scaffold structure could be present in photoreceptor cells."

Retinal tissue expansion microscopy was key, providing a new and easy method of high-resolution imaging. This allowed protein localization observation at nanoscale resolution, using only a simple wide-field microscope. This powerful tool may complement gene therapy approaches, for example, by enabling monitoring of the impact of adding back inner scaffold components. Expansion microscopy may make rescuing defects within the connecting cilium a possibility through gene therapy approaches to restore the molecular zipper, ensure microtubule structural integrity, and prevent photoreceptor death.

Hamel and her team will continue to lead the charge, focusing on the FAM161A protein. "One area of our future research will be the continued dedication to understanding retinal degeneration. We plan to explore FAM161A gene therapy as a therapeutic tool for RP28." She continues, "We still have key steps to achieve, but we want to contribute to this effort using expansion microscopy. Concurrently, we also aim to explore and better understand the retina's molecular composition and organization using ultrastructure expansion microscopy."

See reference online.

Light Up Your Life

New research shines a light on why poor-quality lighting may affect mood

Light has often been correlated with mood. For many, shorter winter days and increased time spent indoors with harsh artificial lighting leads to feelings of depression, indicating that both the quantity and quality of light we're exposed to can impact how we think and feel. But how and why does the light we take in affect our frame of mind?

To answer this, Brown University researchers looked to the neural pathway connecting intrinsically photosensitive retinal ganglion cells to the prefrontal cortex of the brain, involved in cognitive processing and mood regulation (1). They found that light suppressed prefrontal cortex activity in proportion to light intensity, and that those light-evoked responses resembled those seen in the intrinsically photosensitive retinal ganglion cells.

This suggests a functional link between light exposure and prefrontal cortex mediated cognitive and emotional responses. It seems light really can brighten your outlook – in more ways than one!

See reference online.

IMAGE OF THE MONTH

Around the World

This issue's image shows a world map in the form of a fundus fluorescein angiography.
Credit: Jonathan Brett, courtesy of the Wellcome Collection.

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

QUOTE OF THE MONTH

"Biosimilars are a promising option that might expand access to retinal therapies – reducing costs and improving real-world treatment outcomes as a result."

Anat Loewenstein – Director of the Department of Ophthalmology, Tel Aviv Medical Center, Tel Aviv, Israel

Smoke Zero

Stopping smoking early in life has many benefits, including helping to manage glaucoma

Smoking has had a rollercoaster century in scientific research, from a declaration of safety in the early 20th century to its downward trajectory after proof that it can cause lung cancer and contribute to many other health conditions. We know that smoking increases the risk and progression of glaucoma, but does stopping have any effect? Research from the Hamilton Glaucoma Center at the University of California San Diego, USA, goes some way toward answering this question, with data showing that former heavy smokers who had quit at least 25 years previously had a risk of visual field progression similar to that of people who had never smoked (1).

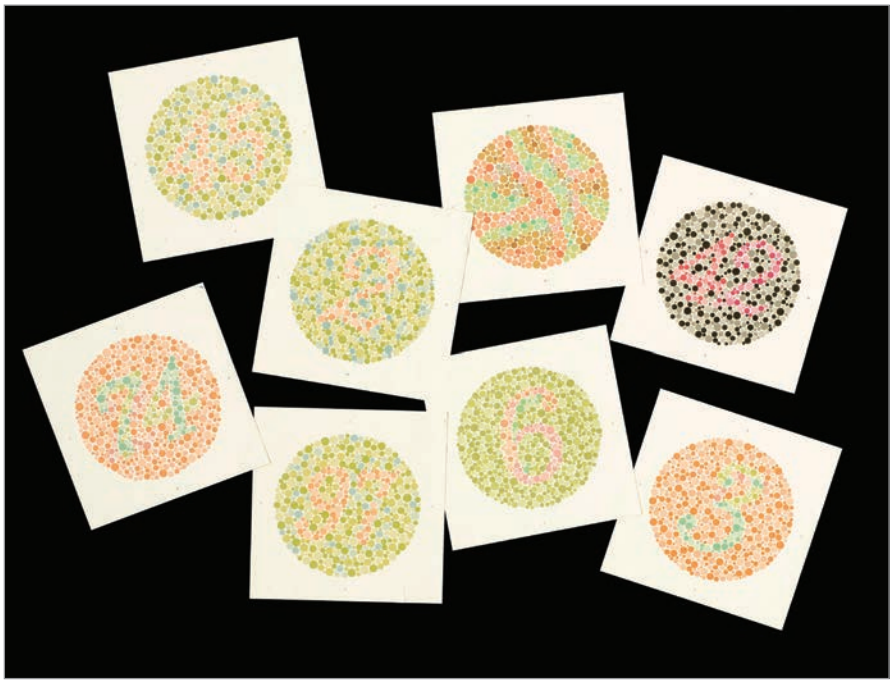
It's apparent that disease progression correlates with smoking intensity, and that quitting not only improves outcomes, but can turn back the clock of visual field progression risk to that of someone who has never touched a cigarette. The pile of research suggesting that not smoking or giving it up early in life can reduce the risk of losing vision continues to grow…

Reference

1. *G Mahmoudinezhad et al., J Glaucoma, [Online ahead of print] (2022). PMID: 35939832.*

The Color Code

Celebrating the life and work of ophthalmologist Shinobu Ishihara – creator of the Ishihara Color Test



Credit: Eight Ishihara charts for testing colour blindness, Europe, 1917–1959. Science Museum, London. Attribution 4.0 International (CC BY 4.0)

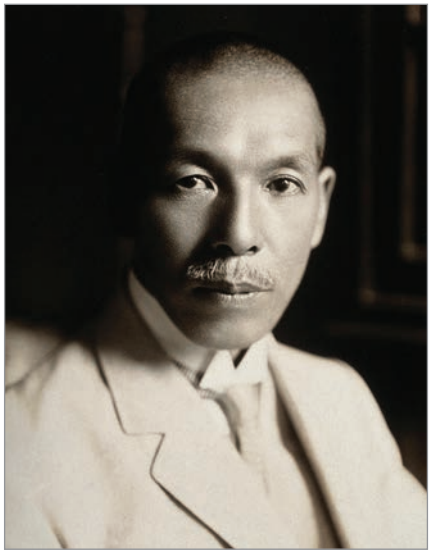
Color blindness is relatively common, affecting around one in 12 men and one in 200 women. Although it is generally not a cause for health concern, the inability to see certain colors can affect occupational pursuits. That's where the star of this article comes in: Shinobu Ishihara, an ophthalmologist who developed the Ishihara color test in 1916 to identify color blindness in military personnel. Ishihara was born on September 25, 1879, in Tokyo, Japan. He graduated from the Imperial University of Tokyo in 1905 on a military scholarship and became a military physician until he completed his doctorate in ophthalmology in 1916. He then became full professor and Chief of the University Eye Clinic at Imperial University of Tokyo in 1922 and took on the role of Dean from 1927 until his retirement in 1940.

The test uses a series of plates – customarily 14, 24, or 38 – with closely packed colored dots of varying sizes forming a round depiction of a disguised number or character. The number of correct answers translates to a score that quantifies the severity of color blindness.

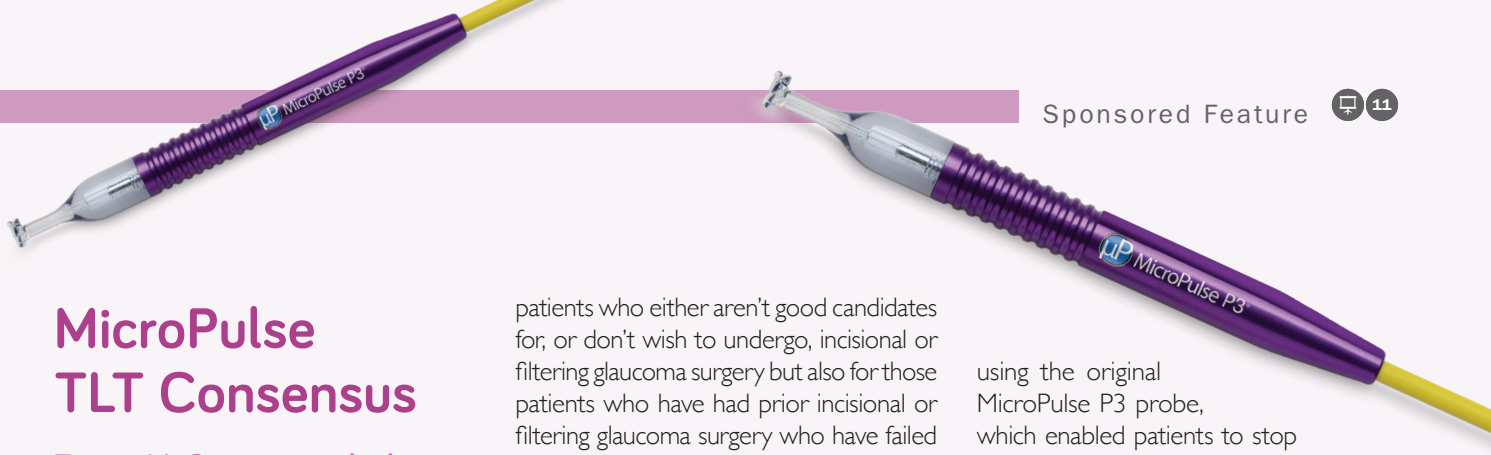
The original plates were all hand-painted in watercolor by Ishihara; the images depicted were of hiragana characters and later moved on to katakana (both Japanese phonetic lettering systems). When the plates were produced for international distribution, they moved to Arabic numerals. One of the issues with this test is that its success is very dependent on the quality of the colors on the plate, which can be affected by sunlight, wear and tear, and inconsistencies in the printing process. Although these issues haven't gone away, the advent of a digital society and strong international printing capabilities have reduced the challenges faced in the early to mid-20th century.

The test is also limited to detecting red-green color blindness, but that hasn't obstructed its popularity or usefulness. Even now, over a century after Ishihara painted his first plates, it is a quick and easy first test to detect defects in color vision that can be confirmed using more robust methods. It is also one of the most remarkable ways for people to understand how differently others may see the world.

The test is a fine legacy for an eye care professional, but it is far from Ishihara's only impact on the medical community. He was so beloved by those he taught over the years that, upon his retirement, his students built him a cottage near the hot springs of the Izu Peninsula, west of Tokyo. There, he lived a modest life and worked as a doctor to the local community until his death on January 3, 1963.



Credit: Portrait of Shinobu Ishihara. Wellcome Collection. Attribution 4.0 International (CC BY 4.0)



MicroPulse TLT Consensus

Tomas M. Grippo reveals the findings from the International MicroPulse Transscleral Laser Therapy (TLT) Consensus Panel

Tomas M. Grippo, MD, Director and Founder, Grippo Glaucoma & Cataract Center, Buenos Aires, Argentina, serves as co-chair of the International MicroPulse TLT Consensus Panel, and has plenty of experience using MicroPulse Transscleral Laser Therapy (TLT). Here, we ask him about his experience using the therapy in the treatment of glaucoma and about the findings of the international consensus panel of 10 glaucoma experts, who discussed best practices for MicroPulse TLT.

Firstly, what is MicroPulse TLT?

MicroPulse TLT is a unique and non-incisional surgical option to manage glaucoma patients. It's a titratable procedure that can be repeated without limiting the use of other therapies.

So how does this differ from conventional continuous-wave transscleral cyclophotocoagulation?

There is greater thermal control and lower temperature targets, which both contribute to a lower risk of complications compared with transscleral continuous-wave cyclophotocoagulation (CW-TSCPC).

Who are the ideal patients for MicroPulse TLT?

Due to its favorable safety profile, it can be considered as a therapeutic option in any part of the glaucoma treatment algorithm after medications and trabeculoplasty have failed to control the disease. It's ideal for patients who either aren't good candidates for, or don't wish to undergo, incisional or filtering glaucoma surgery but also for those patients who have had prior incisional or filtering glaucoma surgery who have failed to successfully control IOP. It's also an option for patients on maximum tolerated medical therapy, including acetazolamide, in order to stop the acetozolamide.

And what treatment parameters does the panel recommend for the procedure?

As a starting point, when using the Cyclo G6 laser and revised MicroPulse P3 delivery device, the panel recommends 2500 mW of power with a 31.3 percent duty cycle, with four or five sweeps for 20 seconds in each hemisphere.

When a more aggressive treatment is desired, the panel recommends an escalation of approximately 25 percent in energy delivery, which can be achieved by either increasing the power, slowing the sweep velocity, or increasing total treatment time.

Can you share a few treatment/technique pearls of wisdom?

Firstly, it's always important to use a transparent and optically neutral coupling agent, like lidocaine gel, for more effective power transmission. Also, place the footplate of the revised MicroPulse P3 Probe with its bunny ears at the limbus, or err slightly posterior of the limbus if it is not clearly defined. Finally, gently compress the conjunctiva for an optimal laser transmission during the sweeps, and exclude the positions at 3 and 9 o'clock.

What are the expected outcomes?

The literature shows a pressure reduction of between 30 and 50 percent using the original MicroPulse P3 probe, which enabled patients to stop oral acetazolamide. At the 2022 AGS meeting, Leticia Checo and colleagues presented a study using the revised probe, which showed – using settings near the consensus-recommended settings – an average pressure reduction of 44 percent achieved at the 12-month follow-up. The consensus panel agrees that when using the recommended starting settings with the revised probe, an expected pressure reduction would be closer to between 25 and 35 percent.

Can these patients be retreated?

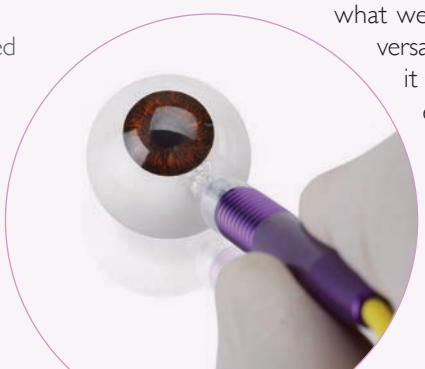
Absolutely. The possibility to retreat is one of the benefits of this procedure. In the literature, two to three retreatments have been reported in several series.

Should physicians be concerned about potential side effects?

Most articles in the literature conclude that MicroPulse TLT is safe and effective. But, as with every glaucoma procedure, there are potential side effects. Now that we have a better understanding of dosimetry, surgical technique, patient selection, and can use the revised probe for a more posterior and stable treatment, many of these side effects can be minimized or prevented altogether.

Finally, what does the future of MicroPulse TLT look like to you?

The MicroPulse TLT technique - and our understanding of it – have evolved significantly since it was first used in 2015. We are just scratching the surface of what we can achieve with this versatile treatment. I consider it an indispensable and extremely valuable tool when taking care of my glaucoma patients.



In My View

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

Bridging the App

The smartphone software that makes IOL selection clearer than ever

By Gurpal Virdi, Founder of EyeLabs AI and ophthalmology resident at the University of Missouri, and Matt Hirabayashi, Founder of eyeflymd.com and ophthalmology resident at the University of Missouri, USA

Smartphone technology is on the rise across all medical disciplines – and ophthalmology is already benefiting from improved screening, surgical planning, outcome tracking, and education, and one of the latest areas of ophthalmology to benefit from smartphone tech is IOL selection. If you've ever felt overwhelmed by the sheer number of IOLs on the market, you may have wished there was "an app for that." Well, now there is: our "IOL Reference" is an app available for iOS-based phones and tablets (sorry, Android users – you'll have to wait, for now) or as a website directory at IOLReference.com.

The app assists in operative planning by allowing surgeons to search according to their needs and specifications through a database of currently marketed and FDA-approved IOLs; finding the perfect fit is as easy as filtering the search parameters on your weekly online shop. It also provides a resource for residents and students to learn about the entire spectrum of current lens options. One great advantage of having the technology available as an app is that it immediately becomes accessible for anyone across the globe, and anyone familiar with smartphone apps will be comfortable with the set of options provided.

The database contains almost 10,000 individually cataloged lenses and is updated daily to include newly FDA-approved IOLs, changes to current lenses, and corrections submitted by users or company representatives. A good relationship with industry has allowed our team to stay up to date and ahead of new lens options to make the app as accurate as possible.

The app allows surgeons to input multiple parameters, such as power, toricity, material, manufacturer, cartridge, injection, among others, to view a final selection of appropriate IOLs. It can also be used to quickly search by model number, manufacturer or lens platform to rapidly find information on lenses in one area.

Our next step for the app is to make it accessible on Android devices, which will open access and ease of use even further. For Android and web-based users, the directory (as well as updates, app news, and a feedback form) is available at IOLReference.com. We have immediate plans to expand functionality to include an outcome tracking feature that will provide detailed data on refractive outcomes, surgically induced astigmatism, and personalized A-constants. Further updates will include a biometry transcription feature for error-free access to online IOL calculations that may not be available on in-office machines. This update would allow more surgeons to have practical access to the newer IOL calculations integrated with machine learning algorithms and the most recent methods for accurate predictions. We believe these features will make the app fit better within a clinic flow, as it avoids manual entry of any parameters, and tracking can be as easy as scanning the desired input with a smartphone.

"The database contains almost 10,000 individually cataloged lenses."

In our view, we've produced something valuable for the whole community – but we're always keen to receive feedback. Let us know what you think!

A Burden Shared

Are community-based services the support needed to bolster a struggling NHS?

By Imran Rahman, Consultant Ophthalmologist and CEO of Community Health and Eyecare Ltd., UK

The UK's National Health Service (NHS) is currently facing record high waiting lists of more than six million patients, many of whom are awaiting cataract surgery – and the backlog is only expected to increase between now and 2024. Although the COVID-19 pandemic was clearly a significant contributor to the situation (1), more than four million people were already waiting for treatment before the pandemic began. A step-change beyond post-lockdown resumption of procedures is needed to support the NHS in managing these unprecedented waiting lists (2) – and, despite the government's 2021 announcement of a £36 billion funding increase over a three-year period, the NHS continues to face intense pressure (2), making it clear that funding alone is not enough. Instead, I propose adopting a shared-care partnership model to allow community-based healthcare services to provide some relief.

The backlogs are having a significant impact on patient outcomes – and not just when it comes to elective surgery. In UK emergency departments, the expectation is that at least 95 percent of patients should be seen within four hours, yet every day of 2021, more than a thousand patients across the country waited for at least 12 hours. And with research showing that, for every 82 patients spending six to eight hours in the ER, one will come to avoidable harm, these delays are having long-lasting detrimental impacts on many patients (3). Eye care is no exception. In particular, it is vital that cataract surgery patients receive quick and efficient care. The NHS guidelines recommend waiting no longer than 18 weeks before treatment, but the average wait time for cataract surgery in 2021 was nine months (4), a delay that can significantly affect patients' quality of life. More concerningly, research suggests that delay in treatment can cause further eyesight issues and increase the risk of complications. In 2021, up to 22 patients lost their vision each month while on the surgery waiting list (5), which highlights the fact that delivering efficient, timely, high-quality care is essential to achieving better outcomes for patients.

Community ophthalmology providers

As waiting lists continue to grow, it is becoming increasingly clear that the NHS cannot be left to cope with this crisis alone. Instead, community-based services can step in to ease the pressures by offering elective care in local settings. Specialist providers of community ophthalmology, such as Community Health and Eyecare Ltd (CHEC), provide key eye care treatments and services in local communities. Through these offerings, CHEC supports the NHS in treating over half a million patients waiting for eyecare services.

"In UK emergency departments, the expectation is that at least 95 percent of patients should be seen within four hours, yet every day of 2021, more than a thousand patients across the country waited for at least 12 hours."

The effectiveness of a shared-care partnership model cannot be understated. It has been suggested that community-based healthcare has been key to the fast and efficient recovery of the healthcare systems in both Denmark and the Netherlands (2), and adopting a similar model in the UK could be instrumental to clearing the NHS backlogs. Community-based care offers a wide range of services and already provides support for around 100 million patient contacts each year (6). However, despite the important role these treatment centers play, there is often a lack of recognition – and, as a result, funding – relative to the need for their services. One of the fundamental elements to facilitate increased awareness of community-based services and ensure that these services support

the NHS to their maximum potential is to highlight the importance of the NHS Patient Choice Framework, which allows patients to select their provider when referred for treatment.

Local treatments, convenient solutions

Alongside their ability to provide systemic support, community-based services offer a number of benefits for patients. For one, adopting a shared-care partnership model can ensure that patients seamlessly access the right treatment as quickly as possible. Shared-care models, such as the partnership between CHEC and the NHS, offer patients integrated services, enabling them to access the most appropriate practitioner for their care. Additionally, community-based services provide end-to-end care. In fact, 99 percent of CHEC's post-cataract surgery patients receive treatment in their community setting, ensuring consistency of care at every stage of their treatment.

At CHEC, we are always looking for innovative ways to offer the best possible service. The recently launched patient booking app is one of our key initiatives to support the NHS in tackling waiting lists through improved efficiency. The app allows patients on-the-go access to appointment booking, ensuring that they can be seen as efficiently as possible. The app determines how urgent an appointment is, allowing patients to book the most appropriate slot for their needs and minimizing cancellations or missed appointments. With patient experience at the heart of all we do, the app's ultimate goal is to ensure that services are as accessible and efficient as possible.

Our answer to a recent survey finding that 31 percent of adults found it hard to access healthcare during the pandemic is the Home to Hospital service, another initiative aimed at tailoring healthcare patients' needs (7). This free service offers patients transportation to and from their eye care surgery and appointments with local drivers who have undertaken training to support patients before and after their appointments. The Home to Hospital service also underpins broader efforts to address healthcare inequalities. A recent study highlighted that people from certain ethnic minority groups were more likely to report poor experiences at their doctors' offices (8). By offering transport to appointments alongside other initiatives, such as translation services, we can help ensure that everyone receives the same excellent healthcare experience.

"The backlogs are having a significant impact on patient outcomes – and not just when it comes to elective surgery. In UK emergency departments, the expectation is that at least 95 percent of patients should be seen within four hours, yet every day of 2021, more than a thousand patients across the country waited for at least 12 hours."

Addressing NHS backlogs will take a considerable amount of time and a concerted effort. I believe that accessible, bespoke community-based care is essential to delivering better outcomes for patients, making the NHS run smoothly, and supporting healthcare professionals. To that end, patient-oriented services such as easy-to-use booking apps and transportation services are vital to ensuring that patients receive the service that is right for them.

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Embracing Tissue Models

How can tissue engineering improve our knowledge of the eye?

By Hannah C. Lamont,, candidate at the EPSRC-SFI Centre for Doctoral Training in Engineered Tissues for Discovery, Industry and Medicine, University of Birmingham, UK

No tissue model is perfect. From animal to cell, every way that we try to recreate the inner workings of our body comes with pros and cons – and our lab's particular disease model does not escape this inevitability! There is a clear disconnect between models of disease and the translation of research to human benefit – with many treatments that are tested in the lab or in animals ultimately not making it through the pipeline.

My work at the University of Birmingham, UK, centers on developing models of the trabecular meshwork (TM) and Schlemm's canal (SC) to investigate the pathology of glaucoma (1) – yet it is a field of research that has used many traditional models of disease with no breakthroughs in the knowledge of how the TM becomes diseased. This is a good example of the disconnect between models and translation – and is a prime example of why we may need to rethink how we model diseases and adapt with the progressive breakthroughs in biotechnology to enhance the proportion of research that actually goes from bench to bedside.

In drug discovery, 2D cell systems and animal disease models are not effective predictors of human efficacy. Can animal models fully represent aspects of human diseases? Often, the answer is no – leading to a poor understanding in disease pathogenesis and no new mechanisms of action for drug targeting. Drug development failure rates exceed drug success rate, with a majority of drug candidates failing clinical trials – far from ideal for company budgets, patients, healthcare providers, and potential innovation in the field.

The use of animal models has become an ethical "gray area." We don't use animal models because they are fully reliable, we use animal models because they are the most reliable thing we have.

In my view, we need to move on from both 2D cell models that lack the physiological complexity of a 3D tissue, and from animal models that don't recreate the specific physiology of human biology; tissue engineering is now at a point where the combination of biomaterials, human cells, and 3D cell modeling should give us the best of both worlds in the lab.

The current in vitro models often lack the complexity of actual tissue, using single cell types in isolation and on 2D surfaces – therefore not recreating the complex interactions between different cell types and the surrounding microenvironment. It's becoming increasingly apparent from research that, when cells are placed in 3D culture, they adopt a level of genetic expression and complex cellular communication closer to cells in a living tissue environment, compared with 2D culture – this step forward will be a significant factor in the development of biomimetic TM models, and those for any tissue.

What's clear is that any model we create must be fit for purpose. If the tissue has a function that is drastically affected by fluid flow or involves a specific intersection of tissue components, then these factors should be taken into account with the cellular model, when possible and practical.

The current field of in vitro models to mimic the TM and the SC endothelia is still within its infancy, so it's important to try and focus in on the important aspects of the tissue that will give the most beneficial answers to research questions – whilst also understanding the limitations of a lab grown biomimetic tissue. A feature of the tissue that many groups will be striving to facilitate in vitro is the constant fluid flow that occurs within the eye. This aspect is difficult to integrate, with most in vitro models being static, but it is clearly a factor that significantly affects cell function given the dramatic tissue variability seen in the TM based on cell location.

Potentially an even bigger challenge will be ensuring that newer models have clear testable outputs that can translate to high-throughput research. And that requires highly reproducible models that are cost effective and scalable.

By improving the quality of human in vitro models through tissue engineering techniques, such as 3D cell culture, bioprinting, and the use of human stem cells, we can more easily bridge the gap between bench and bedside – increasing the translational potential of research to the benefit of more effective pharmaceutical development. Not only will we reduce our reliance upon animal models, we'll also improve the success rate of drug discovery and development process.

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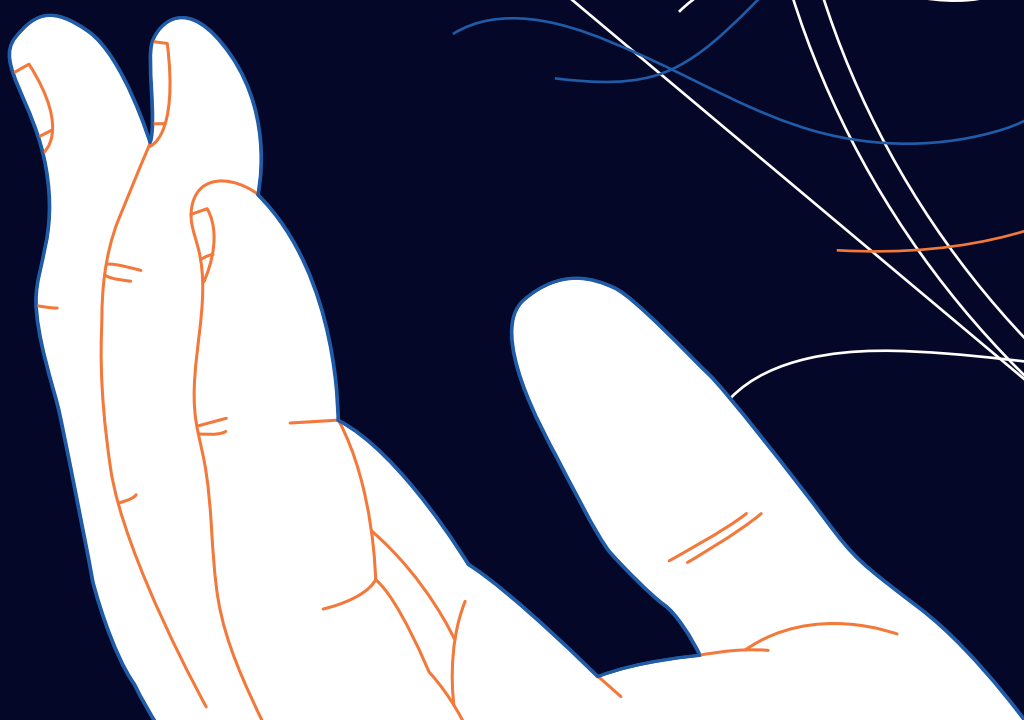
THE ALGORITHMS OF POWER

Five gurus of ophthalmic AI – Linda Zangwill, Michael F. Chiang, Damien Gatinel, Paisan Ruamviboonsuk, and Michael D. Abràmoff – consider where and how the technology can help deliver the highest quality eye care

Perspectives gathered by Andrzej Grzybowski, edited by Aleksandra Jones

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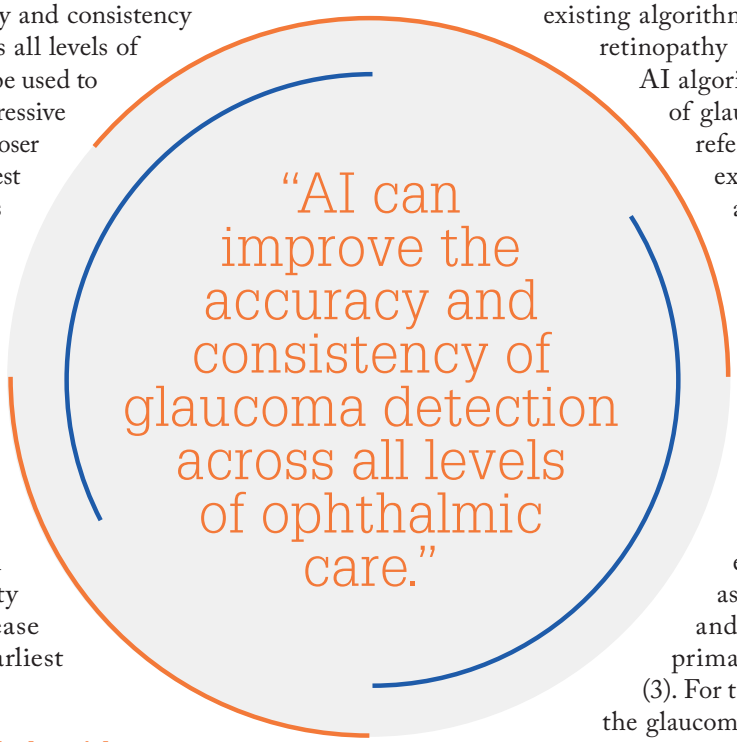
AI AND GLAUCOMA

Linda Zangwill, Professor of Ophthalmology in Residence, Richard K. Lansche and Tatiana A. Lansche Endowed Chair, Co-Director of Clinical Research, Hamilton Glaucoma Center Director, Data Coordinating Center, Shiley Eye Institute, UC San Diego, California, USA

Why should AI be used in glaucoma? What are the benefits of AI in this field?

There are numerous benefits to using AI to assist in clinical decision making for glaucoma detection and management. AI can improve the accuracy and consistency of glaucoma detection across all levels of ophthalmic care. It can also be used to detect individuals with progressive glaucoma who are in need of closer follow-up and conversely suggest that a patient's glaucoma is stable and requires less frequent follow-up. In addition, by providing information on the probability of glaucoma, the clinician can integrate this information into their patient management decisions. Moreover, AI can help to screen high-risk individuals for glaucoma in primary care and community settings, so that the disease can be diagnosed in its earliest treatable stages.



Do we know which AI algorithms are better: those based on OCT or those developed on fundus images?

AI algorithms for glaucoma detection based on OCT and fundus images both have high diagnostic accuracy (1, 2). Both are useful as they can be valuable in different settings. OCT is the standard of care for the clinical management of glaucoma in most ophthalmology clinics. However, in many communities, particularly in underserved areas, fundus photography is much more likely to be available than OCT imaging. Moreover, glaucoma detection using fundus photography can be integrated with screening for other eye diseases such as diabetic retinopathy and macular degeneration more easily in primary care settings. It is therefore important to develop accurate AI algorithms for both OCT and fundus photography.

Might AI-based glaucoma detection algorithms be used in glaucoma screening in the future?

I believe that AI-based glaucoma detection algorithms will be used for targeted glaucoma screening of high-risk individuals in primary care and/or community settings. Glaucoma screening will likely be integrated with existing algorithms for detection of diabetic retinopathy and other eye diseases. As AI algorithms provide a probability of glaucoma, the cut-off used to refer for follow-up ophthalmic examination can be set to a high specificity needed for screening tests. It should be noted that the US Preventive Services Task Force on Screening for Primary Open Angle Glaucoma recently concluded in the general population of asymptomatic adults 40 years and older "the current evidence is insufficient to assess the balance of benefits and harms of screening for primary open-angle glaucoma" (3). For these reasons, integration of the glaucoma screening with other eye diseases, and targeted screening to high-risk populations should be considered.

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RETINOPATHY OF PREMATURITY PERSPECTIVE

Michael F. Chiang, Director, National Eye Institute, National Institutes of Health, Bethesda, Maryland, USA

Why was there a need for a new retinopathy of prematurity (ROP) classification?

Interestingly, the early studies on ROP, then called retrolental fibroplasia, were conducted by Thaddeus S. Szewczyk, an American ophthalmologist of Polish origin, who is mostly forgotten today. He was the first to indicate a relationship between the development of ROP and high exposure to oxygen in an incubator or by withdrawing oxygen too rapidly. What has changed in understanding of the ROP pathophysiology in recent 50 years?

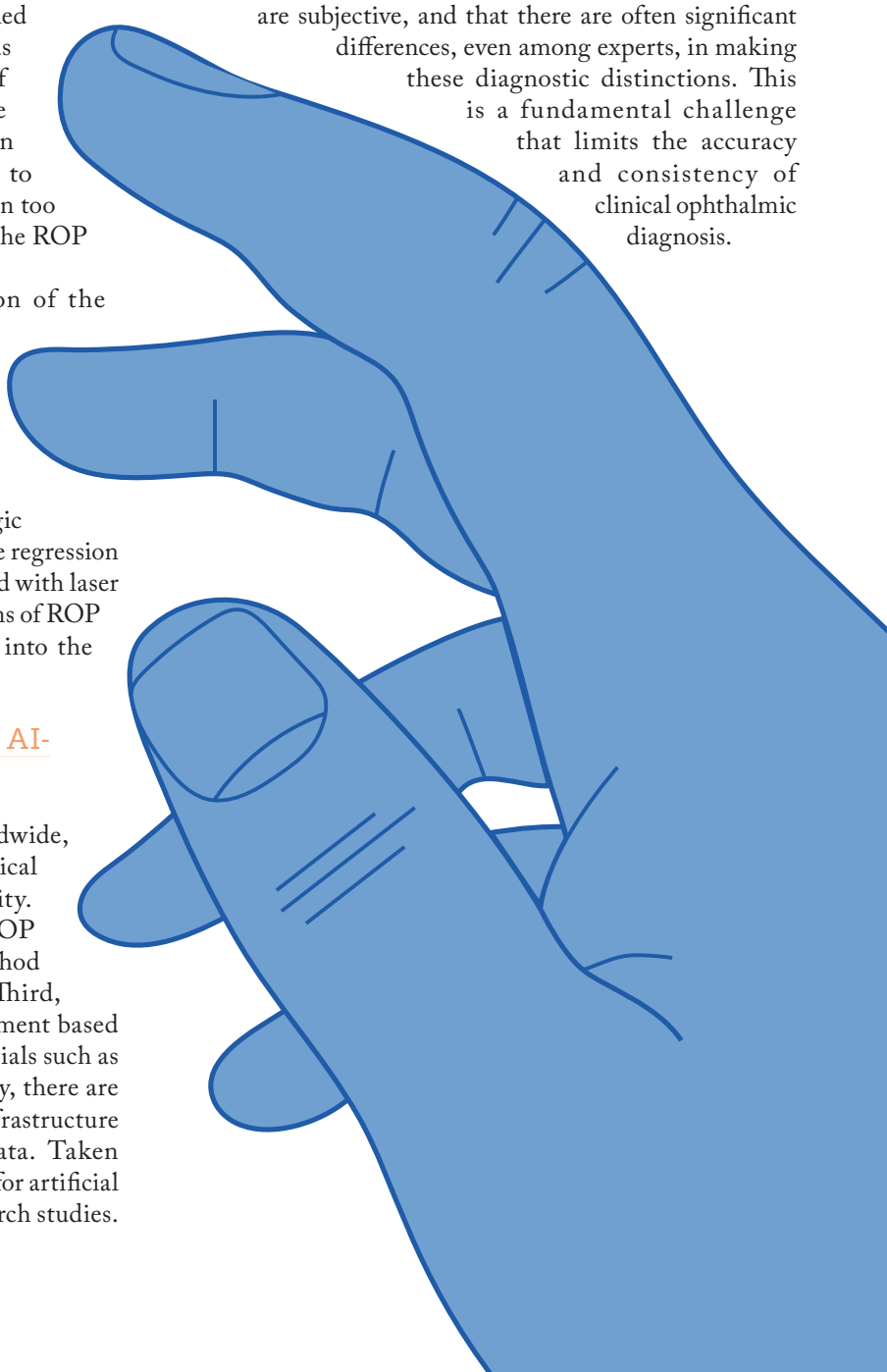
We've recently published the third version of the international ROP classification system because a number of new challenges since the previous in 2005 have arisen: (i) concerns about subjectivity in critical elements of ROP disease classification such as plus disease and zone, (ii) innovations in ophthalmic imaging and artificial intelligence, (iii) novel pharmacologic therapies (such as anti-VEGF agents) with unique regression and reactivation features post-treatment compared with laser photocoagulation, and (iv) recognition that patterns of ROP in some regions of the world did not neatly fit into the previous classification system.

Why is ROP such a promising area for AI-based medical devices?

First, there are unmet needs in ROP care worldwide, such as workforce challenges, subjectivity of clinical diagnosis, and significant medical legal liability. Second, there is an existing international ROP classification system so there is a standard method of clinical diagnosis that is used worldwide. Third, there is a standard approach to clinical management based on decades of multicenter collaborative clinical trials such as CRYO-ROP, ETROP, and BEAT-ROP. Finally, there are pediatric retinal imaging devices coupled with infrastructure to capture clinical diagnosis and outcome data. Taken together, these factors create a good environment for artificial intelligence implementation and evaluation research studies.

What do we know about problems related to differences between graders?

Classically, we diagnose ophthalmic diseases by examining morphology of the eye. These clinical observations are typically qualitative, and we often convert those morphological observations into structured classifications (for example, "stage 1" or "plus disease" in ROP, "neovascularization elsewhere" in diabetic retinopathy, and similar). We and many others have shown that these clinical diagnoses and classifications are subjective, and that there are often significant differences, even among experts, in making these diagnostic distinctions. This is a fundamental challenge that limits the accuracy and consistency of clinical ophthalmic diagnosis.



What are the major challenges to the future development of AI?

LINDA ZANGWILL

Development of AI algorithms to detect glaucoma is now relatively straightforward if one has appropriate datasets and computational resources. One of the major challenges to the implementation of AI in clinical settings is to ensure that the algorithm is generalizable to the targeted populations and not biased due to limitations of the training set. Evaluating the generalizability of the results requires extensive testing of the AI algorithm on external datasets from diverse populations. Another challenge is determining how to integrate the AI system and results into clinical practice. Where and how should the AI algorithm results be placed in the electronic health record or PACS system that the clinician uses in their routine management of glaucoma patients? What type of summary information and/or visualization of the AI results should be provided? It is essential to determine how the AI results can be provided in a way that is easy and fast to use so that it provides added value and does not slow down the busy clinical workflow. One can develop the best AI algorithm, but if clinicians are not willing or able to use it, it will not improve clinical care. Other challenges for the development and implementation of AI include how best to open the black box to provide information on what the algorithm used to make its decision, as well as medical, legal, ethical, and privacy issues.

MICHAEL F. CHIANG

I will articulate a few challenges: first, we are losing many opportunities to utilize ophthalmic image data for developing AI systems because those data are locked in proprietary standards and inaccessible to researchers and clinicians. Second, we need to improve the culture of data sharing, standards for data representation, and methods for establishing ground truth to take full advantage of building large, AI-ready datasets for knowledge discovery. Third, AI systems are best at addressing discrete questions (such as "Is there plus disease in this retinal image from a baby undergoing ROP screening?"), whereas real-world scenarios require addressing numerous questions in parallel. Fourth, AI systems are typically trained and validated in fairly narrow populations and specific imaging devices, whereas real-world applications will need to be rigorously validated to ensure they work across broad populations and devices without bias.

DAMIEN GATINEL

The limits of AI development mainly concern data collection because the common point of any project is to use a large volume of quality data. It is common that even when a large data set has been compiled, it is necessary to reduce its size drastically.

We can also foresee certain ethical problems insofar as we sometimes do not know by what mechanism(s) certain results are obtained in terms of classification or prediction.

PAISAN RUAMVIBOONSUK

I think we can take advantages of multimodal images in ophthalmology to develop AI models that are more efficient in screening or detecting diseases or detecting disease progression. There are countless AI models for different kinds of tasks today; however, the major challenges for me rest on how useful these models are in reducing the risk of blindness; how useful they are to be deployed in the real-world. Many AI models work well in internal validation but fall short in real-world deployment. The other challenges would rest on the "prediction" of treatment outcome and disease progression. The models for these tasks now have accuracy around 70 percent, we look forward to better predictions in the future.

MICHAEL D. ABRÀMOFF

Theoretical challenges that I see: in healthcare, training data will always be sparse, so how can we build AIs that use limited amounts of training data and how do we use proxies under deep learning conditions? Under what conditions can an AI be changed "somewhat" without requiring full (and often expensive) validation? We have to be able to figure out how we expand reimbursement for AIs that meet some but not all of the criteria above, and how we deal with the information loss that comes with repeated examination of existing datasets, such as an expensive validation dataset. Practical challenges that I predict include, but are not limited to: the need for better education and adoption of highly validated AI systems that are integrated into clinical workflows and sustainably reimbursed. AI in healthcare needs to focus on solutions that offer the greatest benefit to patients. How do we regulate vernacular AIs that are safe and effective in certain subpopulations but not others? While there may be AI technologies that sound exciting, if they aren't positively impacting patient outcomes, they won't bring any real benefit to healthcare and could slow the adoption of the solutions having a positive impact. Of course, all of this is dependent on having access to appropriately diverse and reliable data sets with which to train new AI systems.

ANTERIOR SEGMENT AND ARTIFICIAL INTELLIGENCE

Damien Gatinel, Head of the Anterior Segment and Refractive Surgery Department, Rothschild Foundation Hospital, Paris, France

What are the differences between supervised and unsupervised learning in AI? Is the second option safe enough since we do not understand how the algorithm works?

In both cases, the prerequisite is identical; have a large amount of good quality data. In the case of supervised learning, we use labeled data, and we train an algorithm to classify data as inputs in the most efficient way or make predictions. In the pathology of the anterior segment, screening for keratoconus is an obvious application. To develop an effective algorithm, one must have training data from distinct groups (keratoconus versus normal cornea). Whatever the type of algorithm used (logistic regression, decision trees, neural networks), it will use input data for which its origin it is clearly indicated. In the case of supervised learning, the approach is significantly different; the problem is usually to uncover hidden and unknown relationships present within a disparate dataset or to search for unknown patterns. It is less a question of predicting than discovering links between certain data that allow them to be grouped together, making it possible to classify large volumes of data. The algorithms allow to reduce the dimensionality of the data entered in the system and estimate the distance in a smaller residual space between the data that one seeks to group. We used this process to evaluate the possibility of automatically classifying large volumes of topographic examinations, which can be of great interest for quickly finding specific categories (eyes operated on for refractive surgery, keratoconus, and similar). In any case, it is important to clear up confusion; if the algorithms are built according to a well-identified approach, the variables used to establish the groupings are not always easily identifiable. It is always necessary to be careful and have methods to limit the risk of overfitting and ensure that the system one develops remains generalizable.

> "In the pathology of the anterior segment, screening for keratoconus is an obvious application."

The development of the PEARL-DGS Formula – the AI-based IOL calculation formula – is an important achievement. What are its parameters and how can it be used and tested today by practitioners?

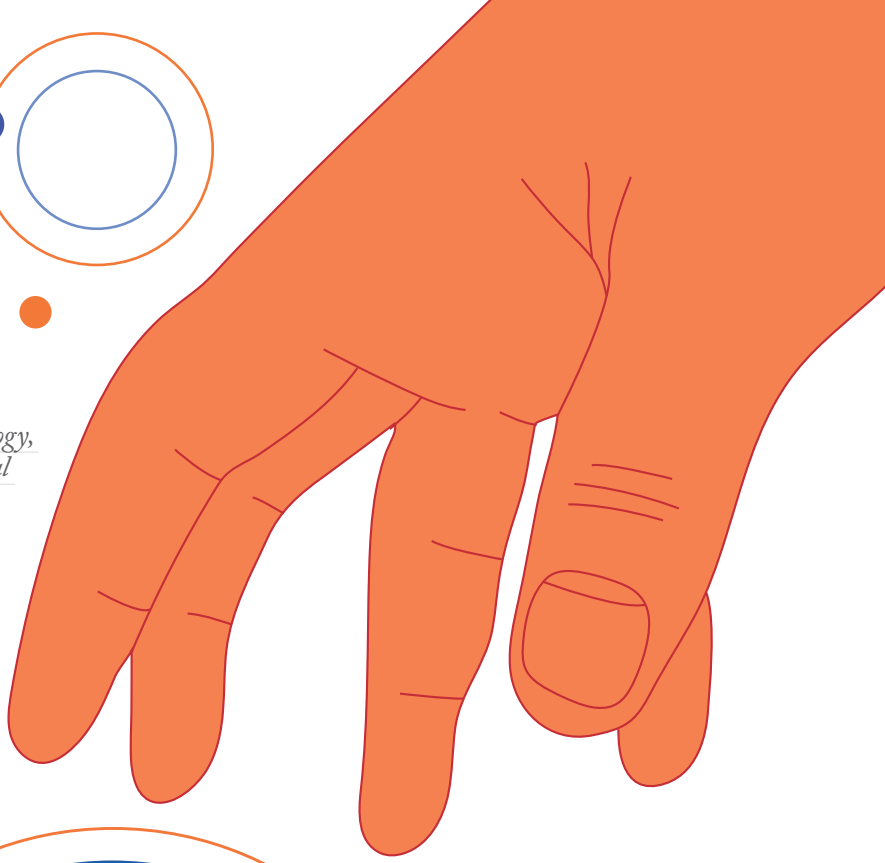
The PEARL-DGS formula is based on an optical model using thick lens formulas, AI algorithms for the prediction of the anatomical position of the implant, and the curvature of the face posterior surface of the cornea (when this surface is not measured). The methods used correspond to supervised learning, made possible by obtaining a large set of quality data from pseudophakic eyes containing preoperative biometric data and the refractive result obtained. It also uses an axial length value per approximate or exact segment sum if the biometer provides this value. It makes it possible to consider a history of corneal refractive surgery and the results obtained for the first eye surgery to improve the precision of the power calculation. All the steps used to calculate the implant's power have been published and the code was deposited in an online directory. The formula is available under the following link: www.iolsolver.com.

What will be the next AI-based applications in the anterior segment?

Anterior segment pathologies are a wide range of areas where one can consider using AI. The calculation of the implant's power is of course already part of the landscape, but we are working on using neural networks and high-resolution OCT images of the anterior segment to establish an objective diagnosis of lens opacity. For a more objective distinction between proven cataracts (visually significant opacities) and non-dysfunctional lenses in terms of transparency. The same process has also been used to characterize the presence of corneal stromal edema. In both cases, it is possible to obtain an enriched image where the probability of lens opacity or corneal edema is shown for each pixel. Other interesting applications include improving the adaptation of contact lenses on irregular or reshaped corneas by quickly predicting the parameters of the lens, better predicting the size of phakic implants from biometric and refractive data. It is also possible to envisage diagnostic aid devices based on image banks of the anterior segment using conventional image recognition methods. Finally, we were interested in predicting subjective refraction from the objective measurement of the wavefront and high-degree optical aberrations. These are just examples, but the limits are those of your imagination!

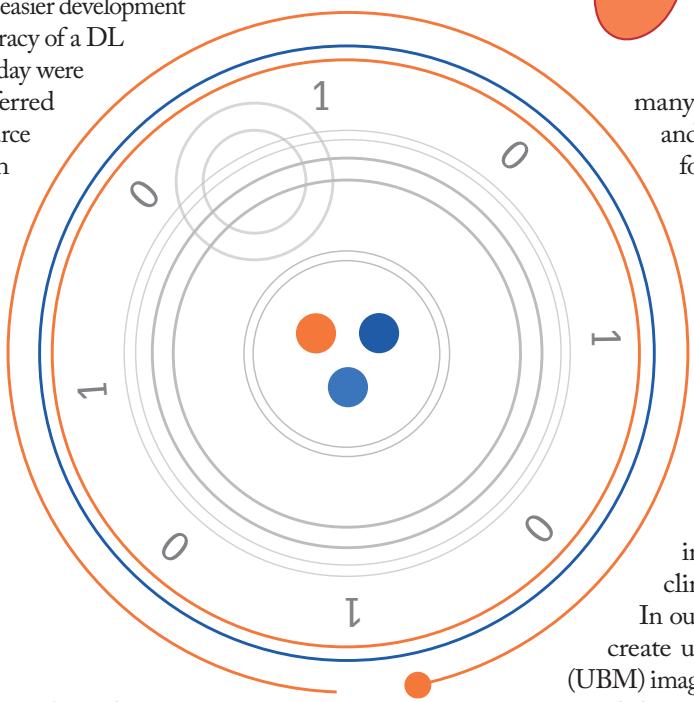
ON TRANSFER LEARNING, GANS, AND MORE

Paisan Ruamviboonsuk, Clinical Professor of Ophthalmology, College of Medicine, Rangsit University, Assistant Hospital Director for Centers of Medical ExcellenceCenter of Excellence for Vitreous and Retinal Disease, Rajavithi Hospital, Bangkok, Thailand



What is transfer learning and why do you think it can bring benefits to healthcare and ophthalmology?

Transfer learning (TL) is a type of deep learning model made use of other, already available, deep learning (DL) models or other datasets. TL may be used for the easier development of a DL model or to improve the accuracy of a DL model. For example, many models today were developed from information transferred from ImageNet, which is an open-source model available on the internet. In ophthalmology, information from OCT datasets, for example, can be transferred to corresponded datasets of color fundus images (CFI) to develop a DL model for making analysis on CFI, which may provide better accuracy than traditional DL developed from only data from CFI. This is because the model learns more from both CFI and OCT datasets. The benefits would include more AI models developed, with better performance.



What are the limitations of traditional AI models?

Traditional AI models may require a very large dataset developed to achieve high enough performance. In addition, there are lots of data available today from multimodal imaging in ophthalmology, but traditional AI may be able to make use of only one type of data at a time.

What are GANs and how can they help ophthalmologists?

GANs is a DL model developed to create new images from existing images, and therefore, GANs is a TL model in nature. There are many uses of GANs in movie and advertisement industries, for example when creating an image of a zebra from an image of a horse. In medicine, GANs is used to create images of a modality that may be less commonly used, such as MRI, from images of a modality that may be more commonly used, such as a CAT scan. The new images may be used in AI research or to guide clinicians in clinical studies. In our study, we used GANs to create ultrasound biomicroscopy (UBM) images of anterior segment from corresponded anterior segment OCT images to detect plateau iris. In another study, researchers used GANs to create fundus images to unlock the black box of DL. The researchers in this study developed a DL model to detect where nerve fiber layer or optic disc neuroretinal rim was thinning in fundus images of glaucomatous eyes. They used GANs to create a fundus image in which that thin area had normal thickness and another image in which that area was extremely thin. These new images highlighted where in fundus images the DL model used for making diagnosis of glaucoma and ophthalmologists could use these images created by GANs to judge if the model pointed out the correct areas.

AI: AUTONOMOUS OR ASSISTIVE

Michael D. Abràmoff, The Robert C. Watzke, Professor of Ophthalmology, Professor of Electrical and Computer Engineering, and Biomedical Engineering, Department of Ophthalmology and Visual Sciences, University of Iowa Hospital and Clinics, Iowa, USA

What is the difference between autonomous and assistive AI medical devices?

The term "assistive" is for AI systems where the clinician makes the ultimate medical decision, and the clinician (the user) is liable for the AI performance, while the term "autonomous" is reserved for those systems where the AI makes the ultimate medical decision, and it is the AI creator who carries the liability for the AI performance, not the user (1). If someone claims autonomy for an AI, the next question should be whether the liability lies with the user (1).

Who should be responsible for a potential mistake made by AI medical device?

Along with my colleagues, we previously proposed that creators of autonomous AI systems assume liability for harm caused by the diagnostic output of the device when used properly and on label (2). The article states that this is essential for adoption: it may be inappropriate for clinicians using an autonomous AI to make a clinical decision they are not comfortable making themselves, to nevertheless have full medical liability for harm caused by that autonomous AI. This view was recently endorsed by the American Medical Association in its 2019 AI Policy. Such a paradigm for responsibility is more complex for assistive AI, where medical liability may fall only on the provider using it, because they are ultimately responsible for the medical decision, or on a combination of both, where even the relative balance of liability of the AI user and the AI creator come into play (3).

What are the major concerns regarding AI and how can they be addressed?

All stakeholders in the healthcare system have valid concerns about AI that need to be addressed. Stakeholders include patients, patient organizations, physicians and other providers, bioethicists, medicolegal experts, regulators such as US FDA and US FTC and Joint Commission, and payers such as CMS (Medicare and Medicaid) and private payers. Is there patient or population benefit, such as outcome improvement, from the use of the AI? I have called AI that is technologically cool but offers no patient benefit "glamour AI." Does it increase health disparities, or otherwise negatively affect some populations? Is there racial, ethnic or other bias in the safety or efficacy of the AI? Who is liable if something goes wrong? What happens with a patient's data when AI is used, and how is patient data used in development and usage?

There may be other, not yet anticipated concerns out there. The only way to address these known and unknown concerns is with an ethical framework for AI, which starts with the basic millennia-old bioethical principles such as Autonomy, Justice, Beneficence and Non-maleficence, and Responsibility. By measuring how much a given AI system meets each of these bioethical principles, AI creators can build systems that address all concerns in a provable (falsifiable) manner; this is called metrics for ethics. I and others have published extensively on these subjects, including an ethical framework for AI that has itself been used to create regulatory consideration for AI with US FDA, and reimbursement considerations for US CMS and other payers, and these have all been applied successfully, leading to regulatory approval and reimbursement for autonomous AI in the US (1, 2, 3).

From the ethical framework, the following can be derived: AI technology also needs to be validated through a preregistered, peer reviewed clinical trial that is conducted in the intended clinical setting, with outcomes that meet or exceed all superiority endpoints. For example, IDx-DR exceeded all superiority endpoints at 87 percent sensitivity, 91 percent specificity, with a valid diagnostic result for 96 percent of subjects, and was proven to have no racial and ethnic bias all of which exceeds human specialist performance. These outcomes led to FDA clearance and helped establish trust with all industry stakeholders facilitating the adoption of autonomous AI into the Standards of Care for diabetes, reimbursement through CPT code 92229, and widespread system adoption. The ultimate goal of AI advancement is to improve patient outcomes by increasing access, lowing costs, and improving the quality of care that is available to the people who need it most.

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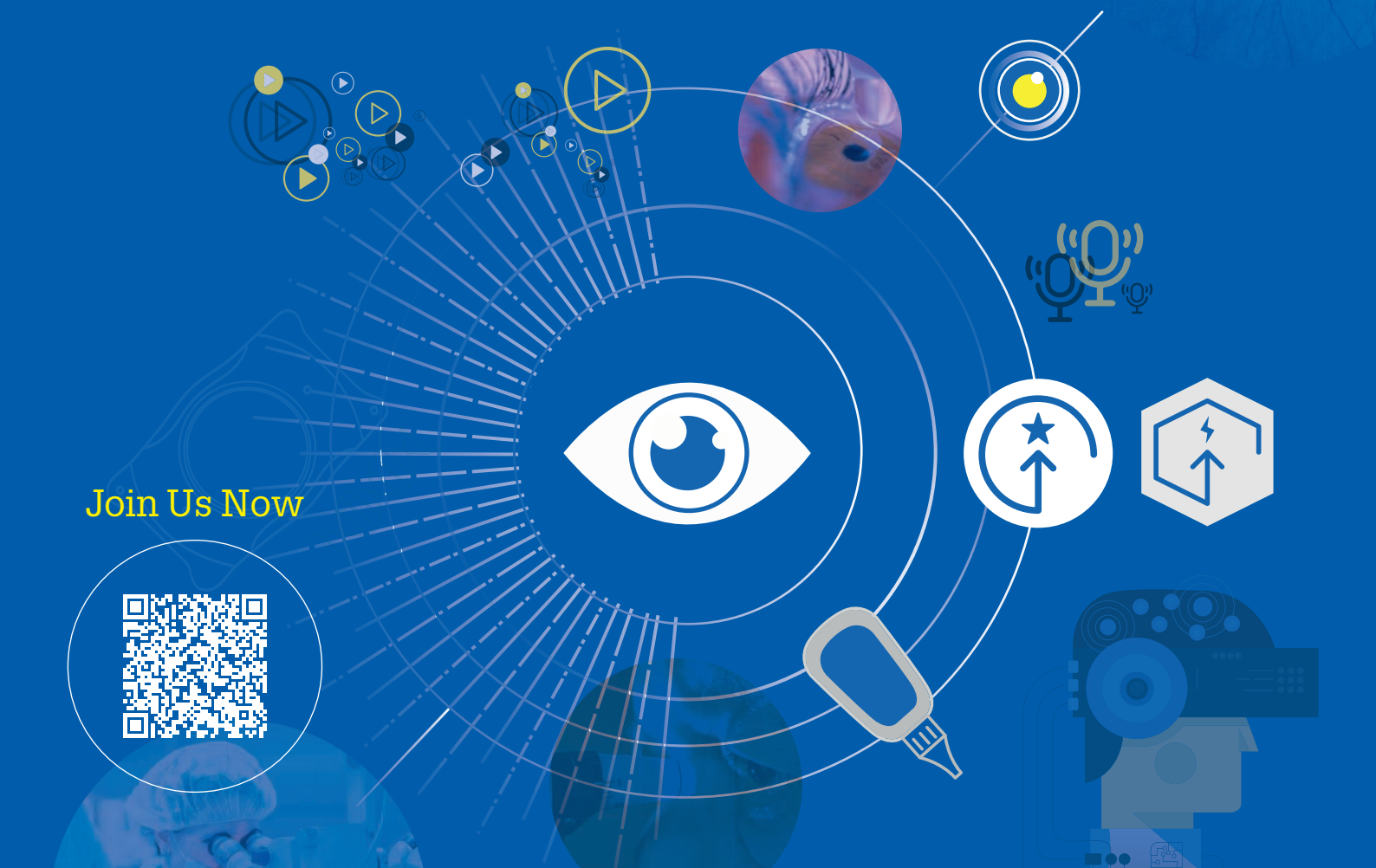

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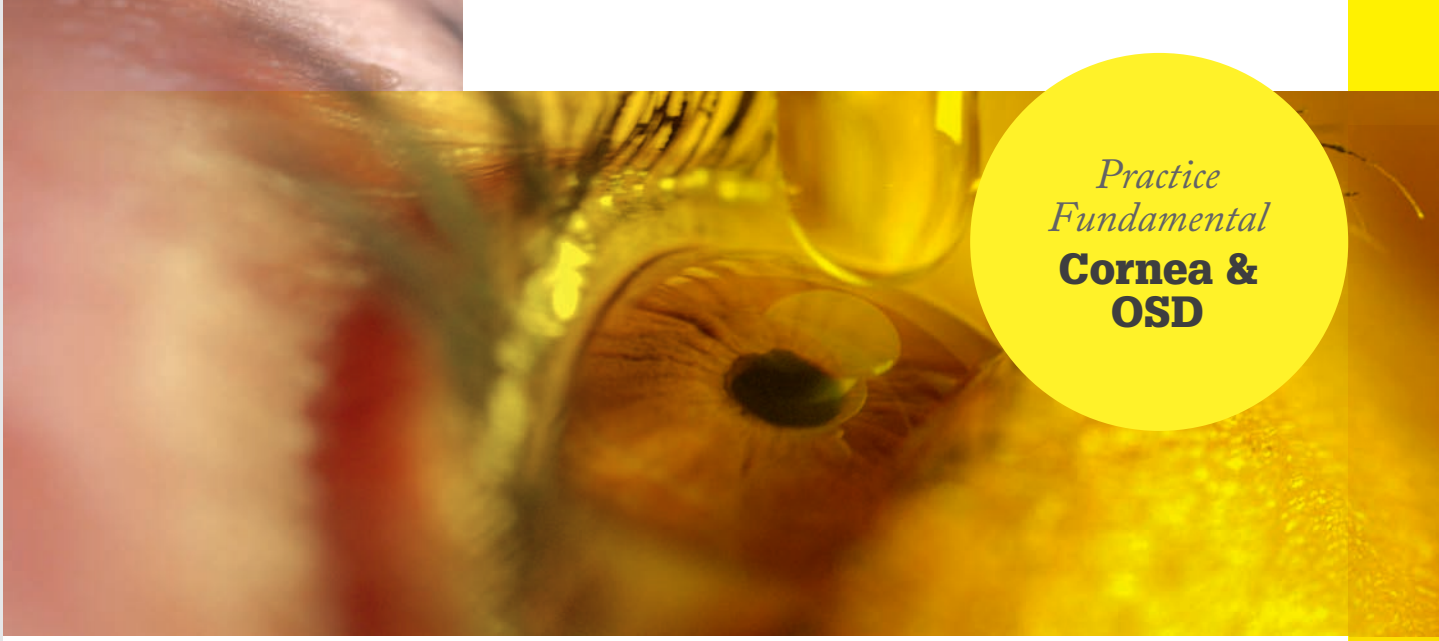

Carbon cornea. Carbon-infused materials may no longer be immediately associated with the frames of high-performance sports cars and bike frames – at least in ophthalmology. Researchers have incorporated carbon nanostructures, formed of single-walled carbon nanotubes and graphene, into the corneal stroma to improve the physical properties of the tissue (1). This may serve as an effective alternative to improve structural properties of the corneal tissue in keratoconus, and paves the way for future nanotechnology applications to be used for ocular tissue reinforcement.

ROCK the boat. Dogs with primary corneal endothelial degeneration (PCED) are able to both get their condition treated and form the next step in testing for future trials in human participants. The topical drug that allows for this is ripasudil, and it was well tolerated and had a therapeutic benefit in 62 percent of these dogs (2). Unfortunately, 38 percent of dogs had their condition progress, but the authors note that this was still slower than for historical controls. Ripasudil is a Rho-associated kinase (ROCK) inhibitor that is currently used in Japan for the treatment of ocular hypertension and glaucoma. ROCK inhibitors have been used in lab tissue models to promote corneal endothelial cell proliferation and adhesion, and are promising for PECD and Fuchs' endothelial corneal dystrophy (FECD) treatment.

Graft evasion. Graft versus host disease is an unhappy consequence in between 30 to 70 percent of patients who have an allogeneic hematopoietic stem cell transplantation (allo-HSCT) – in simpler words, stem cell transplantation that isn't from the patient in question. A team of ophthalmic researchers from Brazil have set out to describe the manifestations associated with graft vs host disease, from a recently opened ocular graft versus host disease unit in the University of Campinas (UNICAMP) Clinical Hospital, Brazil (3). The most common complications were cataract and infections, severe dry eye disease and meibomian gland dysfunction – although the manifestations varied and the disease is challenging to control and avoid. The data generated in this study highlights the need to monitor patients closely, and adds to the clinical data on graft versus host disease.

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IN OTHER NEWS

***Deprivation minus detriment.** A retrospective cohort study shows that androgen deprivation therapy in prostate cancer patients does not alter the rate of dry eye disease – in a Taiwanese cohort (4).*

***Keratoplasty disparity.** Female Medicare beneficiaries are less likely to receive endothelial keratoplasty (EK) and penetrating keratoplasty (PK), and non-white patients are less likely to receive EK, but more likely to receive PK compared with white patients (5). This study featured participants over 65 with Fuchs'.*

***Fountain of youth.** A study into limbal epithelial stem cell sheet donors shows that younger donors have a better regenerative potential. Tissues taken from people under 65 had better stem cell-like properties and increased growth rates.*

Cracking the Cornea Conundrum

Arnaud Lacoste talks about a cell therapy with the potential to change the treatment of corneal endothelial dystrophies

Advanced cell therapies are starting to make their presence felt on the therapeutic landscape across multiple indications. But how could such treatments benefit corneal surgeons and their patients? We spoke to Aurion Biotech's Chief Scientific Officer, Arnaud Lacoste, to find out.


Arnaud Lacoste

Tell us about your unusual background…

Even though I now work in the biomedical sciences sector, my childhood dream was to be an oceanographer, which led to me studying oceanography all the way to my PhD. I think it is an amazing area of research, but the real impact you have is limited by the fact that you have to navigate policymakers and, as a result, the political landscape. Oceanographers tend to spend a lot of time doing research that could greatly benefit our lives, but too often it does not turn into impactful policies. And that's why I moved to biomedical research, with the hope of translating that work directly into improving people's lives. My work at Novartis enabled me to do just that and provided me the opportunity to work on some fascinating projects, such as the one where we sent mice to the International Space Station so we could explore the effects of zero gravity environments on vision and the optic nerve.

My oceanography background has served me well in my current career. I had to look at biology at extremely large scales – an entire ocean or even the planet – and that forces me to see the bigger picture and then take big problems and break them down into small components that could eventually lead to a solution.

How did you first get involved with cell therapies?

It was through an academic lab at the Rockefeller University in New York, US, between 2006 and 2008 – a time when the stem cell community was creating human embryonic stem cells with the hope of developing cell therapies to address many of the worst diseases affecting people. We were one of the first labs, together with colleagues from Japan and from Harvard, to create induced pluripotent stem cells, which opened one of the doors for the creation of cell therapies. Later, when I joined Novartis, the idea was to start similar platforms there, and create an approach to medicine that used not just pharmaceuticals and classic biologics, but also cell and gene therapies.

What led you to pursue the corneal endothelial cell therapy you're working on with Aurion Biotech?

When I was working at Novartis, I learned of the pioneering work of Shigeru Kinoshita, in Japan, using corneal cell therapy to treat corneal endothelial dystrophies. His ground-breaking research confirmed that vision could go from being seriously impaired to fully restored, not only demonstrating the concept in animal models, but also pushing these advancements all the way to patients. When I was introduced to Aurion Biotech, naturally I was intrigued: I recognized the opportunity to build a cell therapy program and an organization that could have a

significant impact on patients affected by corneal blindness.

What's the story behind Aurion Biotech?

Several years ago, we were able to acquire the rights to Kinoshita's technology. In a short period of time, Aurion Biotech has assembled a talented team with deep experience in a variety of areas that include ophthalmology, cell and gene therapies, regulatory, clinical, and commercial development. This experience extends to our new president and chief medical officer, Dr. Michael Goldstein, and our medical advisory board led by Dr. Edward J. Holland – a leading cornea specialist in the field.

Why is a new approach needed – and what makes your technology unique?

Currently, when a patient has corneal endothelial dystrophy, there is not much that can be done in the early stages of the disease. Patients have to wait for the disease to progress – for the cornea's endothelium monolayer to deteriorate, and for the cornea to thicken and become opaque enough, such that the patient becomes eligible for corneal transplantation (typically, either DMEK or DSAEK). Although these procedures restore vision and generally work quite well, they have a few drawbacks. After surgery, patients are required to stay in bed, face up, for up to three days, which may be extremely uncomfortable, or even physically impossible for some people. Corneal transplants may fail over time, requiring a second procedure. In some cases, patients require a regraft to ensure the graft is properly attached to the cornea. Every corneal transplant requires a corresponding donor cornea, yet a study published in JAMA Ophthalmology cites that for every 70 diseased eyes, there is only one donor cornea available (1). Finally, DMEK surgeries are complex to perform: in the US there are approximately 1,200 corneal specialists, and we at Aurion estimate that only 200-300 of them routinely perform DMEK procedures.

Our cell therapy holds the promise of addressing several of these challenges. Right now, we can produce corneal endothelial cells in the lab, enabling us to treat at least 100 eyes from one donor, which can significantly increase the "supply" of treatment options for patients. We hope to be able to get into the thousands with technological improvements and continued innovation in our labs. This will have exciting implications, especially for patients in developing countries who currently can't readily access cornea tissue.

Next, our KOLs believe that this cell therapy procedure is less complex than DSAEK or DMEK. After removing the diseased endothelium, the surgeon injects a solution of corneal endothelial cells grown in a lab from donated corneas, along with a rho kinase inhibitor. The injected cells reform the endothelial monolayer within the cornea. Post-op recovery is faster, with the patient only required to lie face down for three hours. Within weeks, patients can progress from impaired vision to improved vision. It's very rare in medicine that you can take a patient from a very bad state to such an improvement with a single procedure; very often physicians can only slow down the progression of a disease. Being able to support the development of this cell therapy is one of the most incredible experiences of my career.

When will the therapy be available? Do you foresee any challenges?

This year, Aurion Biotech submitted an NDA to the Japan PMDA. It is our hope that regulatory approval for market launch in Japan will occur sometime in 2023. In the US, we are in the process of preparing to submit an IND to the FDA in order to initiate clinical trials. We are in a good place, however, because, unlike many other biomedical science programs, we're approaching the regulatory process with the benefit of having clinical experience with patients. To date, including our work in Japan and in OUS studies in El Salvador, we've treated more than 100 patients. We are eager to bring this technology to patients throughout the world.

How do you see the cell therapy field evolving?

Cell therapies have been around for a long time, if we consider that blood transfusions were the first cell therapy. By the beginning of the 2000s, scientists had gotten much better at cultivating cells to turn into cell therapies, but very little has made its way to patients even now, in 2022. I think that is beginning to change. There are some amazing initiatives that are beginning to change the treatment landscape, such as Kymriah®, which we delivered at Novartis for treating leukemia, and the promising clinical results from Semma Therapeutics' cell therapy for treating diabetes. It is a rising tide; cell therapies are starting to have an impact on patient outcomes.

At Aurion Biotech, we continue to look into conditions that affect the cornea, as it's a natural space for us: we have a great platform here and great relationships within the ophthalmic community. We hope to apply the principles and technology that we have outlined with this project to other corneal diseases, and – in time – perhaps even other diseases of the eye, such as the treatment of retinal degeneration and glaucoma.

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Cornea: Challenges and Achievements

What have been the biggest ophthalmology breakthroughs over the last two decades according to our Power List 2022 cornea experts?

Eduardo C. Alfonso
Chairman and Director, Bascom Palmer Eye Institute, Miami, Florida, USA

Eduardo C. Alfonso

In terms of patient care, the implementation of the electronic health record (EHR) in the early 2000s was a huge breakthrough. Primarily used at its inception to gather and share accurate patient information, we now use EHRs to advance research studies, including large-scale studies that require extensive computing power. In 2018, for example, Bascom Palmer launched its first study using the American Academy of Ophthalmology's IRIS Registry database, which compared real-world patient surgical data with the Tube versus Trabeculectomy (TVT) Study, to determine whether the TVT results could be replicated (1). Since then, more leading-edge studies using the IRIS "big data" repository and other analytic tools, such as artificial intelligence and genetic testing, are trying to solve the underlying mysteries of eye disease.

The development of anti-VEGF therapies for neovascular and exudative eye diseases was another huge breakthrough in ophthalmology. The treatment of these diseases with intravitreal Avastin therapy has prevented blindness worldwide and saved billions of dollars in healthcare expenses. The continuous advancement of optical coherence tomography (OCT) will also guide the diagnosis of eye diseases at earlier stages before irreversible loss of vision takes place.

For Bascom Palmer, the COVID-19 pandemic posed perhaps the biggest challenge that the Institute has faced in six decades – and changed the everyday practice of ophthalmology. In March 2020, the rapid spread of SARS-CoV-2 forced a shutdown in non-emergency

"The pandemic allowed us to critically examine our processes and develop new ideas, instruments, and protocols that will serve patients, education, and research."

clinical visits as a public health measure. However, within a few short weeks, our physicians began to offer telehealth consultations and assessments, followed by "hybrid" visits to maximize patient safety and minimize in-person clinical services. Although the pandemic also affected our research program, forcing a temporary halt to clinical trials and some projects, our scientists and clinicians still made significant contributions to timely COVID-19 studies regarding the impact of the virus on optical tissues. I mention our experience during the pandemic to illustrate our resilience and ability to adapt to changing conditions. The pandemic allowed us to critically examine our processes and develop new ideas, instruments, and protocols that will serve patients, education, and research – now and in the future. Virtual care will also increase patient access and use technology to improve outcomes; this is why virtual education is an important component of our residency education program.

Stephanie Watson

Stephanie Watson
Professor and Head, Corneal Research Group, The University of Sydney, Save Sight Institute; Co-Deputy Director, Industry, Innovation and Commercialisation, Sydney Nano; Head, Corneal Unit, Sydney Eye Hospital; Chair, Australian Vision Research (formerly Ophthalmic Research Institute of Australia); Chair, Advocacy and Outreach Committee, Association for Research in Vision and Ophthalmology, Sydney, Australia

The evolution of corneal transplantation has been a significant breakthrough. The ingenuity of the techniques developed has revolutionized surgery and improved patient outcomes. Patients with blinding corneal disease have had their vision restored quickly, avoiding complications.

When I was a corneal fellow at Moorfields Eye Hospital, London, UK, penetrating keratoplasty was the most commonly performed graft for patients with Fuchs corneal dystrophy. Following the surgery, time was then spent on managing the sutures and patient complications such as astigmatism and abscesses. On my return to the Sydney Eye Hospital in Australia, where I am now Head of the Corneal Unit at the Prince of Wales Hospital, endothelial transplantation was emerging. Initial techniques involved using scissors to remove a section of the host posterior stroma and endothelium and inserting the graft as a "taco." Unfolding the "taco" and placing it in position was quite a challenge. With the emergence of Descemet's stripping techniques and "pull" then "push" insertion of the graft without the need for folding, the procedure improved and patients benefited from faster and more successful visual rehabilitation, avoiding adverse events from sutures.

Just when Descemet's stripping endothelial keratoplasty had evolved to a technique that most corneal surgeons were comfortable with, Descemet's membrane endothelial keratoplasty (DMEK) was developed. Initially a tricky technique with a steep learning curve, DMEK is now part of routine practice for a corneal surgeon and can deliver rapid visual rehabilitation. The journey in corneal transplantation is continuing, with novel treatments, such as cell-based therapies, under development.

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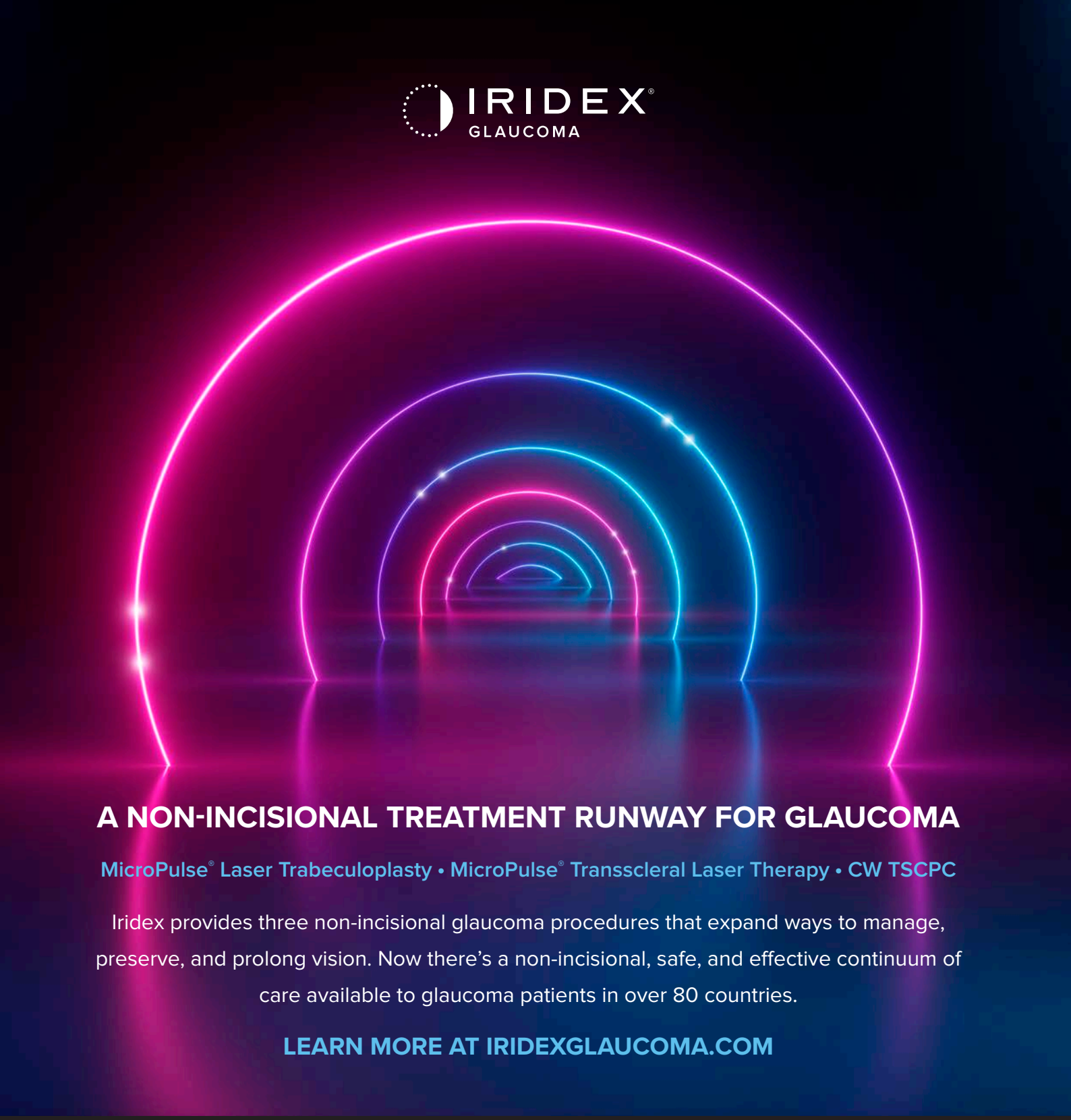

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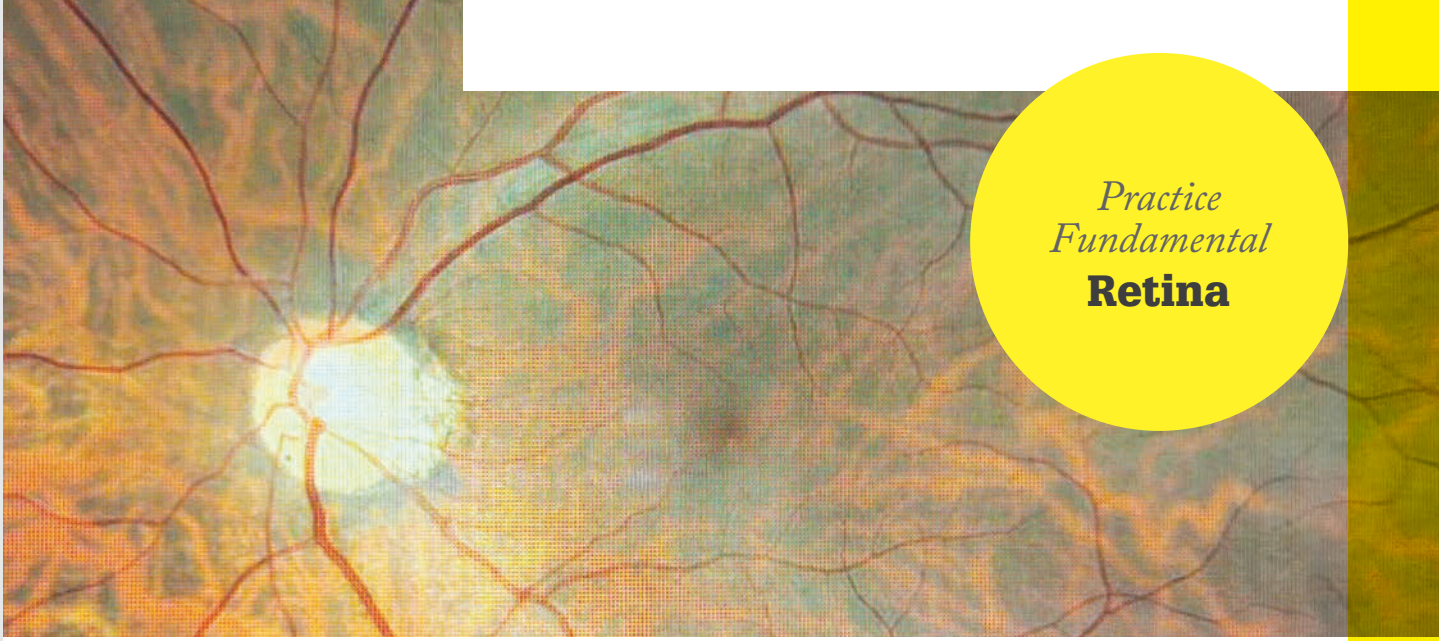


Band together. There is a historical precedent for controversy when characterizing the bands of the retina, and the origin of band 2. Researchers have found supporting evidence that band 2 of the retina partially overlaps with the ellipsoid, due to photoreceptor inner segment length, and as suggested by prior quantitative measurements, the inner ellipsoid must also be inner to band 2 (1). The association band 2b with rods and 2a with cones, which the researchers suggested, would explain certain findings that rods and cones form part of band 2. The images were taken using the latest technical advancements in visible light OCT, and the results provide extra relevance to the interpretation of clinical NIR OCT. In future, these anatomical analyses may contribute and inform the understanding of certain retinal diseases.

Prosthesis progress. Retinal prostheses are becoming increasingly sophisticated, technologically advanced, and most importantly, closer to being a medical reality. One important factor for the success and safety of these prostheses is the electrode to retina (ER) distance. But how consistent are the measurements of ER between different sites and even different people? Fortunately, it has been established that there is a high level of accuracy in ER measurements across sites and people (2). This means that people with a retinal prosthesis do not have to fear their ophthalmologist going on holiday, or moving across the country, as the assessment appears to be suitable for any trained professional to perform.

Pupil power. The pathogenesis of central serous chorioretinopathy (CSC) is relatively unclear. What is clear, is that CSC primarily affects middle-aged men under chronic stress, and is thought to arise from choroidal disturbances. To better understand, diagnose, and treat CSC, researchers have looked to the autonomic nervous system, a key player in the stress response, to develop a quick and easy link to the condition and pupillary responses and heart rate variability. They found that it was possible to associate CSC with these biological metrics, and that larger pupil dilation during mental tasks could also be a marker of psychophysiological stress (3).

Receptor regeneration. A team across several Philadelphia institutions (led by the University of Pennsylvania School of Veterinary Medicine) is working towards finding therapies for retinal disorders. In a newly published study, the team has demonstrated significant progress toward a therapy that would reintroduce healthy, dish-grown photoreceptor cells to the retina, overcoming serious technical roadblocks in cell mortality and integration (4).

IN OTHER NEWS

Alzheimer's association. *People with Alzheimer's disease have an increased risk of having mild to severe diabetic retinopathy (5). Both conditions share a common risk factor in age, and this data suggests that specific social support and screening could benefit those who are vulnerable.*

Comfort exosome. *Exosomes derived from mesenchymal stem cells (MSCs) reduce the damage caused by diabetic retinopathy (6). This offers a potential cell free method of treating diabetic retinopathy.*

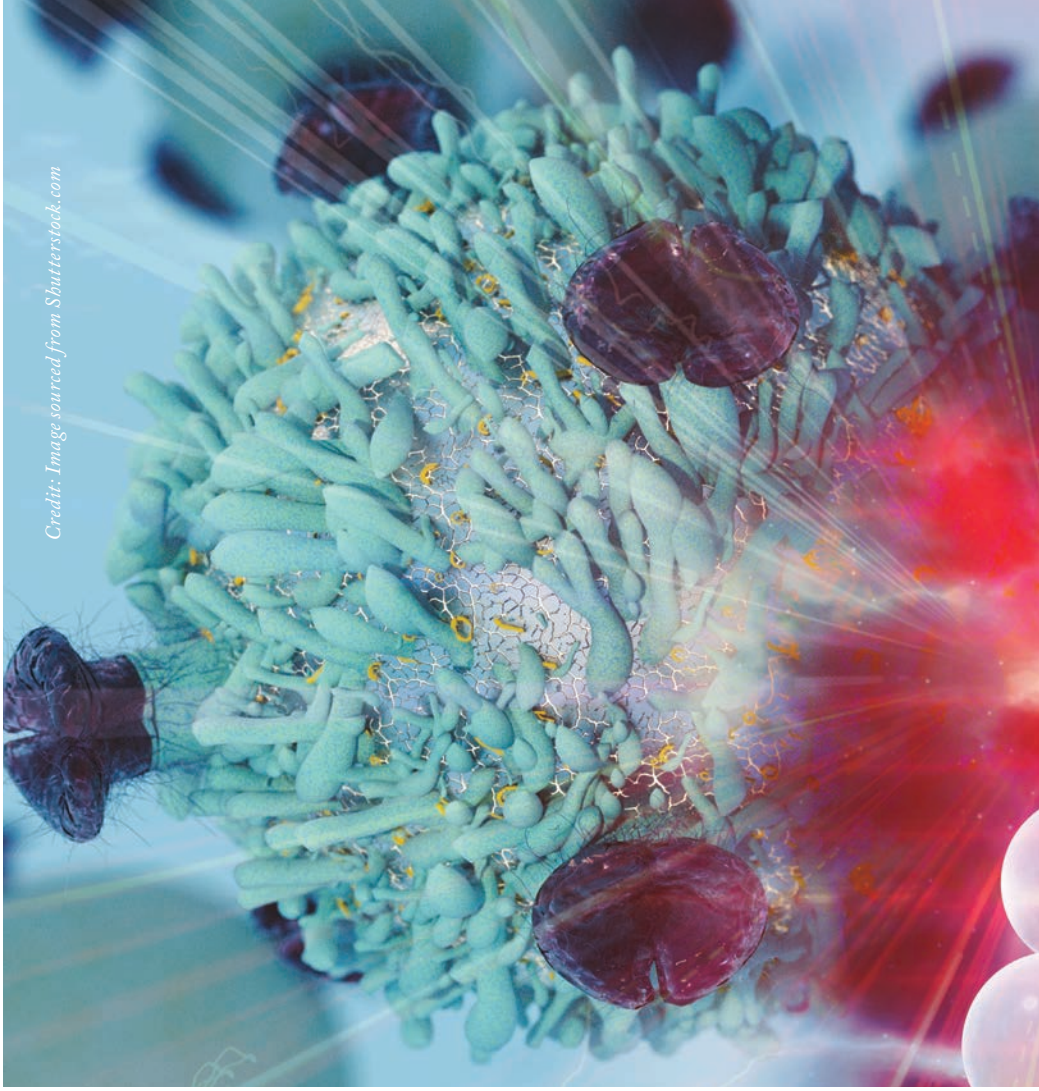
Bolt from the blue. *A study has linked blue light exposure to AMD damage through a protein (ubiquitin–protein ligase E3D (UBE3D)) associated with AMD in East Asian populations (7). UBE3D was also associated with DNA damage response in the study, finding that the AMD associated V379 mutation might be causing oxidative damage, and therefore be a target for therapeutics.*

See references online.

Clearing Stress

A gene therapy to target oxidative stress mechanisms and treat retinal degeneration

By Michael R. Volkert



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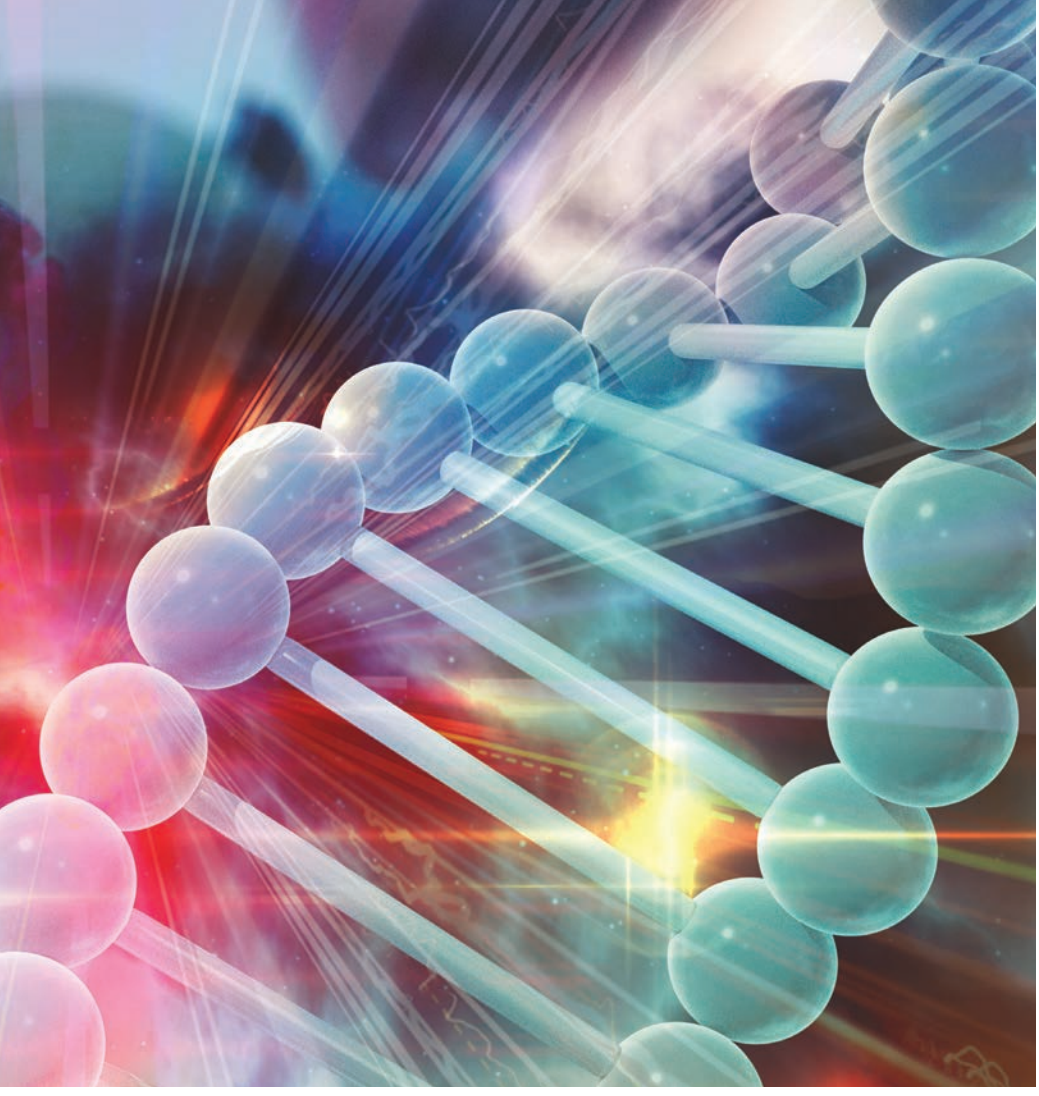
Stress is one of the major players in modern health problems. Those interested in the molecular mechanisms of the retina also know that oxidative stress is a major contributor to photoreceptor cell death in most retinal degenerative diseases. Of course, therapeutics to combat retinal damage are important to saving vision and the ideal targets are degenerative diseases such as retinitis pigmentosa (RP). Genes that protect against oxidative stress are useful targets for gene therapies – potentially allowing the activation of multiple antioxidative pathways in one fell swoop. This is the angle we are taking at the University of Massachusetts Medical School to treat RP by targeting the oxidation resistance 1 (OXR1) gene (1).

We found that elevating OXR1 protein levels increases cellular resistance to oxidative stress regardless of intracellular OXR1 expression levels. More importantly, we showed via electroretinography that subretinal OXR1 injections (with the human gene packaged in a viral vector for delivery) can delay retinal degeneration and photoreceptor loss twice as long as those injected with saline. Histological examination of the retina indicated that rod and cone photoreceptors were still present in transduced regions, but essentially absent elsewhere. The mouse model we used (rd1) has a very aggressive form of retinal degeneration, which suggests that this treatment will be even more effective in other, slower-degenerating mouse models. If slower degeneration correlates with lower levels of oxidative stress in the retina, then it is possible that our therapy will be more effective – with the same positive benefit of OXR1 elevation and a lower level of oxidative stress. We are currently in the process of investigating this further.

Strong as an OXR1

Why examine OXR1? Two studies of retinal degeneration showed that OXR1 levels declined shortly before the onset of degeneration (2, 3), raising the possibility that the decline was related to the onset of degeneration. We decided that, if this hypothesis was correct, increasing OXR1 levels should prevent or delay neurodegeneration. The other feature that makes OXR1 an interesting candidate for gene therapy is that, even in cells that are not impaired in OXR1 expression, increasing OXR1 levels appears to be beneficial.

In our initial experiments, we tested the consequences of overexpressing OXR1 in a photoreceptor-like cell line that is not impaired in OXR1 expression. We made stable cell lines that incorporated an extra copy of OXR1 expressed from a strong promoter. These cells contain about seven times the normal amount of OXR1. This increased their resistance to peroxide-induced oxidative stress resistance such that it took twice the concentration of peroxide to kill 50 percent of the cells as needed to kill 50 percent of vector control cells. These cells also had lower levels of intracellular peroxide and reactive oxygen species than wild type and contained less cleaved caspase at all concentrations of peroxide, indicating lower levels of apoptosis. Combining these results shows that elevating OXR1



protein levels can increase oxidative stress resistance not only when OXR1 expression is impaired, but also when its expression is normal. This suggested that increasing OXR1 levels can be beneficial to cells regardless of their endogenous OXR1 status.

Widespread effects

Oxidative stress also contributes to neuronal cell death in many neurodegenerative diseases (4), and the retinal degeneration studies we performed are essentially a test for the general applicability of OXR1 to neurodegenerative diseases. Interestingly, in the last two years, research has revealed that OXR1 levels also decline shortly before neurodegeneration in several neurological diseases (5, 6). Human patients lacking OXR1 expression have also been identified; they are severely developmentally delayed, have severe neurological defects and, like the OXR1 deletion mutant mouse, develop ataxia.

Similar approach

OXR1 has a similar role to Nrf2, a transcription factor that binds to the antioxidant response element for an antioxidative effect. We have not compared our targeting directly to the Nrf2 gene (NFE2L2), but we are in the process of doing so. There are several features that differentiate OXR1 from Nrf2. Antioxidant genes controlled by Nrf2, including GPX2 and the heme oxygenase genes, also require OXR1 for expression. This suggests some regulatory overlap between these two genes. Because OXR1 functions upstream of multiple transcription factors, several of which are involved in oxidative stress resistance, Nrf2 may be another OXR1-controlled transcription factor. This idea is supported by the observation of Rolland and coworkers that OXR1 binds to Keap1, thereby regulating Nrf2 function (7). The relationship was later shown to be more complicated, with a number of direct and indirect interactions between OXR1 and Keap1 appearing to regulate the gene induction pathway of Nrf2 (8). OXR1 also controls other pathways that contribute to oxidative stress resistance. For example, OXR1 has been shown to control the expression of genes involved in DNA repair, caspase expression, caspase activation pathways, peroxide detoxification, and cell cycle control in response to oxidative stress (9). The recent results showing that OXR1 levels decline shortly before onset of degeneration in multiple examples of neurodegenerative diseases and that mice lacking OXR1 undergo rapid oxidative stress-mediated neurodegeneration, suggests that OXR1 expression levels and neurodegeneration may be closely linked.

Next steps

The immediate next steps are to determine whether the reduction in degeneration seen in the rd1 mouse model of neurodegeneration is also seen in other mouse models of retinal degenerative diseases and whether more slowly progressing retinal degeneration models exhibit better outcomes. The long-range goals are to see whether OXR1 gene therapy can be applied to other neurodegenerative diseases.

Michael R. Volkert is a faculty member in the Department of Microbiology and Physiological Systems, a member of the NeuroNexus Institute, and the Advanced Ocular Therapy Program: all at University of Massachusetts Chan Medical School, Worcester, Massachusetts, USA

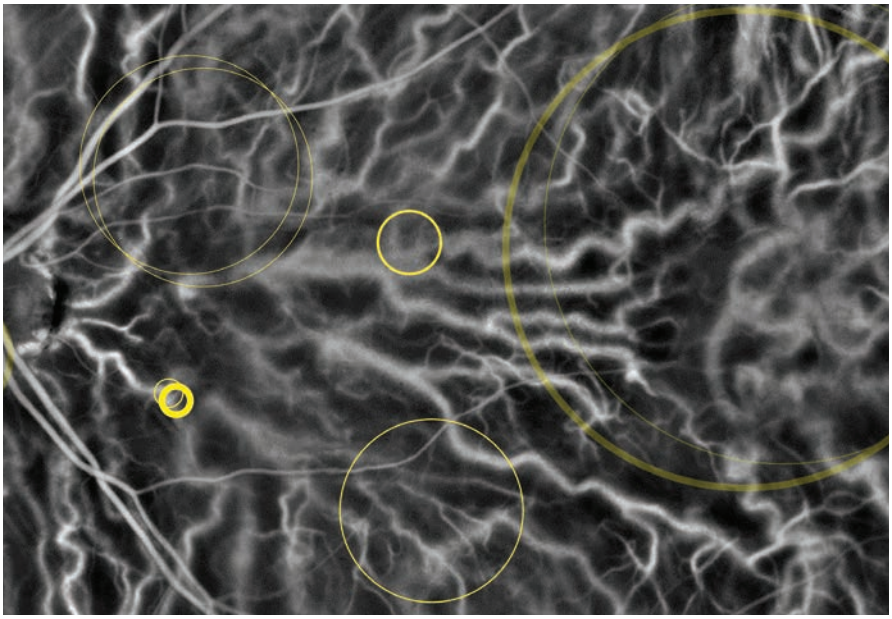
See references online.

Spotting the MOLES

The MOLES acronym simplifies identifying malignancy in melanocytic choroidal tumors

By Bertil Damato

When a tumor is discovered, determining whether it is malignant (and if not, the likelihood of future malignancy) is crucial. However, patients with melanocytic choroidal tumors can present a diagnostic and prognostic challenge. To help, consultant ophthalmologist Bertil Damato devised the MOLES acronym, which highlights the most informative clinical features of a tumor (1) – and here, he shares the process of developing this system and the benefits it could provide.



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In 2018, when I joined the Nuffield Laboratory of Ophthalmology at the University of Oxford, UK, after five enjoyable and productive years at the University of California, San Francisco, USA, I set about tackling the "suspicious nevus problem." Hospital eye clinics across the UK (and, no doubt, elsewhere) are inundated with patients with melanocytic choroidal tumors, very few of which will ever show malignant growth. But I have also seen too many patients with melanoma referred for specialist opinions only after months or years of observation. I knew I had to devise a simple acronym or mnemonic to remind non-experts of the suspicious features of ocular melanoma – collar-stud shape, lipofuscin, large size, documented growth, and retinal detachment.

After a number of weeks of deep thought, I came up with the MOLES acronym. The letters stand for Mushroom shape, Orange pigment, Large size, Enlargement, and Subretinal fluid – and "moles" also happens to be the lay term for "nevi." I knew this acronym would be more useful if it formed the basis of a scoring system so, eventually, I developed a simple system whereby each indicator is scored between 0 and 2 according to whether it is absent or minimal(0), uncertain (1), or definite (2) – and then categorizing tumors as "common nevus," "low-risk nevus," "high-risk nevus," or "probable melanoma," according to whether the sum of these five scores is 0, 1, 2, or more than 2, respectively.

MOLES should help non-experts estimate the likelihood of malignancy in melanocytic choroidal tumors to expedite the treatment of patients with melanoma and avoid excessive surveillance of patients with nevi. I am confident that the MOLES acronym and scoring system will empower ophthalmologists to manage their patients more efficiently, saving time and money for patients and healthcare services while avoiding delays in the diagnosis of melanoma so that opportunities for preventing metastasis, loss of vision, or enucleation are enhanced.

Unlike the helpful TFSOM-DIM system currently in use, MOLES does not include the internal acoustic reflectivity of the tumor. As a system, it can therefore be used when ultrasonography is not possible, either because the necessary skills and equipment are not available or because the tumor is being assessed remotely (through virtual clinics or when triaging referrals via color photographs, OCT scans, or fundus autofluorescence imaging without seeing the patient in person). TSFOM-DIM and MOLES are therefore complementary, providing different benefits in different environments.

Although MOLES performed well when evaluated by ocular oncologists at Moorfields Eye Hospital in London, UK, it must be assessed in a wide variety of real-world situations not only in the UK, but elsewhere as well. At St. Erik Eye Hospital in Stockholm, Sweden, where I now work, we have begun receiving referrals with a MOLES score. Further, there would seem to be scope for educational programs to improve the detection of orange pigment and subretinal fluid on which MOLES depends. I expect that MOLES will become more useful as fundus imaging improves and more ubiquitous as teleophthalmology becomes more widespread.

Bertil Damato is consultant ophthalmologist at Moorfields Eye Hospital, London, UK.

Reference

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More studies needed. A systematic review assessing the safety and effectiveness of laser refractive surgery to treat anisometropic amblyogenic refractive error in children found that laser refractive surgery appears to decrease anisometropia, and may address amblyogenic refractive error in under 18-year olds (1). Data for both improvement in amblyopia and long-term safety are lacking, and more long-term studies with good design using newer refractive technologies in standardized patient populations are needed to fill this gap.

Looking long-term. Evaluating the long-term results of iris-fixated foldable phakic intraocular lens (pIOL) implementation to manage myopia and astigmatism, researchers found, through a prospective clinical study, that pIOL implantation was a stable, predictable, safe and effective procedure at five, 10, and 15 years of follow up, recommending annual follow-up visits assessing endothelial cell density and anterior chamber depth decrease in order to alert patients to this need in the preoperative evaluation (2).

Power prediction. The anatomical variations in effective lens position (ELP) require compensation from systematic biases in the IOL power formula. These changes in formula could change the actual power of the IOL, and cause nonsystematic modification of predicted IOL power, according to the biometric characteristics of the eyes that were studied (3). The consequences of lens variation mainly concern eyes that are receiving high power IOLs, and the effect on corneal power is minimal.

Lacking confidence. A research team evaluated trainee perception and experience within the national health service and the independent sector in the UK (4). Through the conduction of a cross-sectional questionnaire-based survey study, they demonstrated a reduction in cataract training with many trainees not feeling confident in reaching the required level of competency having not received any training on managing high volume cataract lists and inadequate training on human factors and ergonomics crucial to running a safe and efficient surgical list.

Waste worries. A position article written by the Ophthalmic Instrument Cleaning and Sterilization Task Force critiques topical drug waste within the ophthalmology operating room, explaining how drug waste significantly increases both the costs and carbon footprint of ophthalmic surgery (5). Methods for reducing waste include use of topical drugs in multidose containers on multiple patients until the expiration date, and patients taking home partially used medication for post-operative use. The recommendations made are based on published evidence and policies from multiple agencies and would help combat the waste generated in most ambulatory surgery centers and hospitals performing cataract surgery.

IN OTHER NEWS

Simplifying surgery. *A new surgical technique for fixating the capsular bag to the sclera using a capsular tension segment and flanged iris hook is simple, minimally invasive and time saving (6).*

Molecule malfunction. *Congenital nuclear cataract caused by deficiency of junctional adhesion molecule C is accompanied by defective degradation of nuclei and organelles in lens fiber cells, lens structure disorder and UPR activation (7).*

The model model. *Researchers were able to assay a large number of hit compounds within a short time and at a reasonable cost using a newly developed zebrafish cataract model (8).*

Outdoor outlook. *In a large cohort of Australians between the ages of 45 to 65 years, spending more time outside and the ease of tanning with sun exposure were associated with lower incidence of cataract surgery (9).*

See references online.

Clockwise from left: Cathleen M. McCabe, Damien Gatinel, and H. Burkhard Dick

Cataract and Refractive Revolutions

What do cataract and refractive specialists on the Power List consider to be the biggest breakthroughs in ophthalmology?

Cathleen M. McCabe
Chief Medical Officer, Eye Health America; Medical Director, The Eye Associates; Chair, Refractive Surgery Clinical Committee ASCRS; Co-Chief Medical Editor, Cataract Refractive Surgery Today; Co-Chief Medical Editor, Ophthalmic ASC Magazine; and President, Outpatient Ophthalmic Surgery Society, Bradenton, Florida, USA

The biggest breakthrough that I've seen in my career has been the shift in focus from disease mitigation (by removal of cataracts with cataract surgery) to that of improving the quality of vision and independence from glasses. The evolution of premium IOLs has allowed us to treat presbyopia, providing a range of spectacle-independent vision, as well as maximizing distance vision. We have also seen the development of better diagnostics, intraoperative digital guidance, femtosecond lasers, and advanced IOL calculation formulas. The recent commercialization of the light adjustable lens is taking outcomes to a new level of precision.

The other monumental development has been the advent of MIGS procedures and the opportunity to improve quality of life and image quality by increasing pressure control and independence from the need for topical pressure-lowering medications. Depot medications are another sea change in how we think about the impact of drops on patient compliance and ocular surface toxicity. Additionally, I have seen a dramatic increase in treatment options for dry eye, including medications, meibomian gland treatments, nutraceuticals, and even more in the pipeline. Cenegermin is the first dry eye medication that treats the underlying cause of dry eye with efficacy that lasts much longer than the treatment time.

Having practiced through an era where we've seen a full change from paper charts to electronic medical records, I understand the pain that has been a part of this transformation, the unrealized potential to improve how we communicate with other providers, through an increase in the portability of the record, and the strength of pooled data, such as the IRIS registry. With that pain, however, we've realized benefits beyond data gathering, such as a more legible record and the opportunity – with machine learning – to automate data transcription and outcomes analysis and optimization. I am hopeful that it will bring additional advantages in the future.

Damien Gatinel
Head of the Anterior Segment and Refractive Surgery Department, Rothschild Foundation Hospital, Paris, France

The eruption of the laser in refractive surgery with the excimer and the femtosecond technology 20 years ago has profoundly reshaped the landscape of surgical procedures. It allowed LASIK to become the safest, most versatile, and the most reproducible technique in refractive surgery. I like to remember that lasers were initially predicted in a purely theoretical way by Einstein at the beginning of the 20th century, but we had to wait another 50 years before seeing his brilliant predictions become a practical reality and then penetrate many medicine sectors, with ophthalmology at the forefront.

Though light is ubiquitous in the universe, laser light is not natural but the result of applying theories developed using pure human intelligence and learning. I consider laser light as a symbolic beacon that radiates the intelligence, knowledge, and technical expertise that humankind has been able to develop.

H. Burkhard Dick
Professor and Chairman, Director, Ruhr University Eye Hospital, Germany

Gene analysis and gene therapy are, in my view, breathtaking developments. They will not only lead to new options in treating diseases, but will also enable us to take the next step of preventing diseases from happening at all. I predict that, within 10 years, a quick mouth swab will provide us with an individual risk profile and thus tell us what can be done to stop a potential affliction from ever happening. I think this will far surpass anything we have seen in medicine so far.

In my specific field, the introduction of the femtosecond laser into cataract surgery is a major breakthrough. This technique allows us to operate with unparalleled precision, particularly when it comes to capsulotomy. It is not only an immensely efficient tool for IOL implantation, particularly premium IOL implantation, but, in our clinic, has proven to be extremely helpful in very special and challenging cases, such as pediatric cataracts, intumescent cataracts, and in eyes with comorbidities, such as cornea guttata.

"Lasers were initially predicted in a purely theoretical way by Einstein at the beginning of the 20th century, but we had to wait another 50 years before seeing his brilliant predictions become a practical reality."

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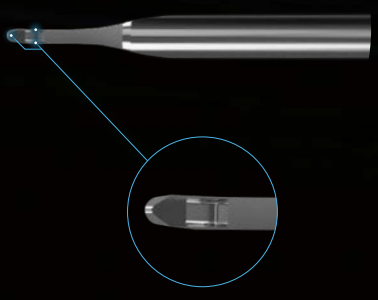
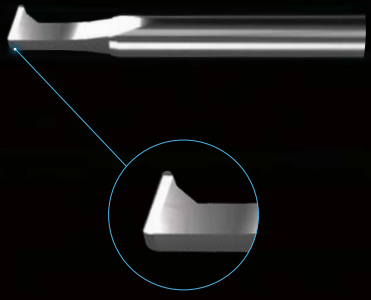
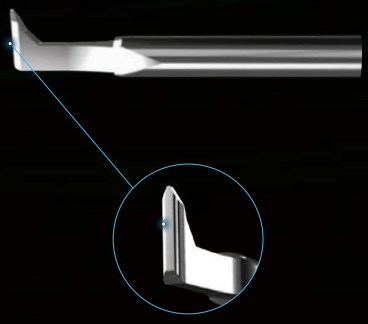


ROUNDED HEEL



TAPERED SIDES & FOOTPLATE



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Address Stress. Looking to investigate the perceived levels of stress of adult primary open-angle glaucoma (POAG) patients and explore the associations with their clinical characteristics, researchers assessed the stress level of 67 POAG patients using a validated questionnaire, the Perceived Stress Scale, and collected relevant additional patient data (1). They found that POAG patients who have worse visual function are more likely to have a higher level of mental stress. This suggests that stress level might be an important consideration for ophthalmologists when treating people with POAG.

Tobacco turmoil. A retrospective cross-sectional study analyzing 106 and 326 eyes from preperimetric and perimetric open angle glaucoma patients respectively to determine the effects of smoking on optic nerve head capillary density measured by optical coherence tomography measured by angiography found that smoking intensity is associated with reduced optic nerve vessel density in glaucoma supporting the value of obtaining an accurate history of smoking, in particular the intensity which may be useful when it comes to screening and monitoring this patient group (2).

Continual contacts. Purdue University researchers introduce a class of smart soft contact lenses that enables continuous 24-hour IOP monitoring, including during sleep (3). Build upon a number of commercial brands of soft commercial contact lenses without altering the intrinsic properties including lens power, biocompatibility, softness, transparency, wettability, oxygen transmissibility and overnight wearability. The research team have shown that the contact lenses are able to fit across a range of human corneal curvatures and thicknesses and are thus able to accurately measure absolute IOP under ambulatory conditions.

Thinking about thinning. A retrospective review of 111 eyes of subjects with open angle glaucoma (OAG) that have undergone optical coherence tomography more than four times during three years of follow up aimed to compare the rate of thinning between retinal nerve giber layer thickness (RNFLT) and Bruch's membrane opening minimum rim width (BMO-MRW) in open angle glaucoma according to glaucoma severity (4). They found that the rate of RNFLT thinning was consistently fastest in the inferotemporal sector however, BMO-MRW displayed a change in the fastest thinning sector from inferotemporal to superotemporal, increasing in severity from early to moderate OAG.

See references online.

IN OTHER NEWS

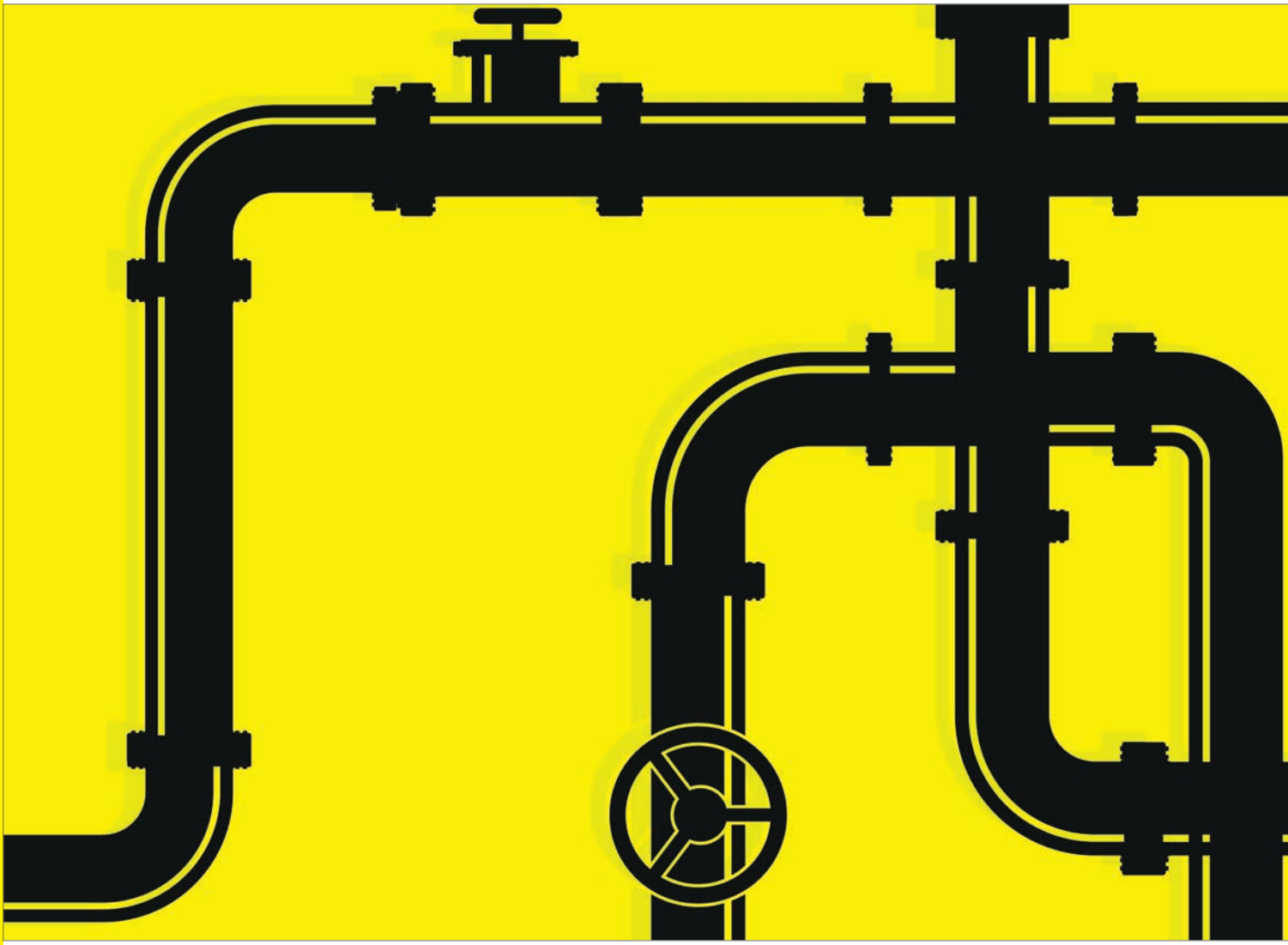
Feasibly feasible. *A trial on early lens extraction surgery compared with medication in PXFG is feasible, with early lens extraction appearing to be an effective treatment for PXFG (6).*

Reimbursement reduction. *US Medicare reimbursement for glaucoma procedures have shown a significant decline between 2000 and 2020, providing insight into changing practice patterns (7).*

Predicting perception. *A high proportion of Hong Kong PACG patients present with higher IOP and more advanced disease than POAG patients (8).*

Refill roadblocks. *Approximately a third of electronically prescribed glaucoma medications are not received by patients within a month of refill request due to systemic barriers (9).*

Effective exercise. *20 minutes of moderate physical exercise increases macular blood flow without significant change to the optic nerve and lowered intraocular pressure in glaucoma and control subjects (10).*

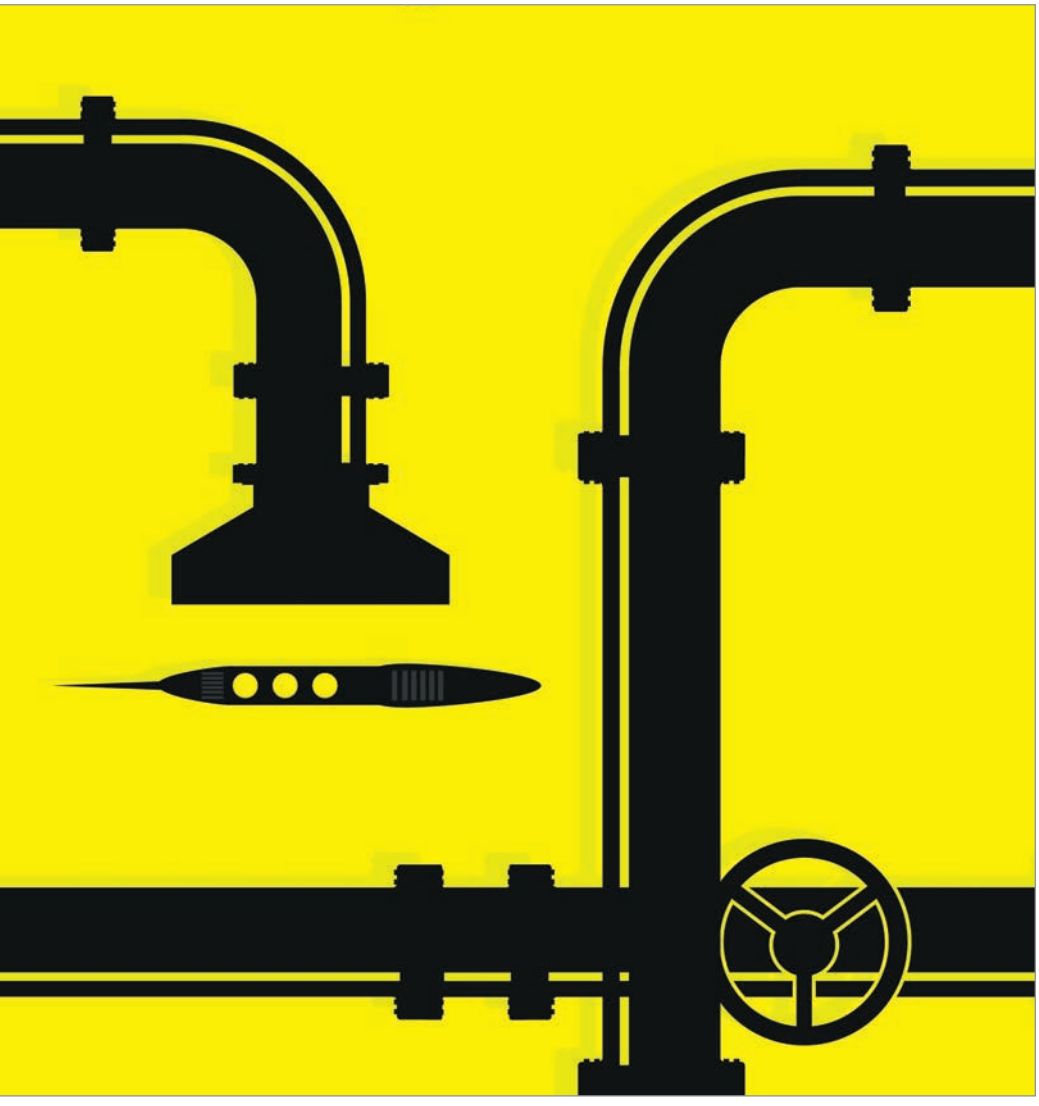


My MIGS of Choice, with Ken Lin

When I was asked about my favorite MIGS device, it was an easy question to answer: Trabectome!

In 2015, I co-authored a paper that reported the safety and efficacy of the Trabectome as a method for reducing IOP in patients after failed glaucoma shunt surgery. During our study, we found patients' IOP – 12 months after surgery – to be markedly reduced from their preoperative values (1), results that have since been corroborated by other studies (2). Additionally, the Trabectome has also been shown to have long-term success in contending with tube shunts, significantly improving visual acuity in the majority of patients, eight years after surgery (3). Although many of these patients continue to require topical medications, the results still indicate the promise of the Trabectome; the alternative would have been the placement of another glaucoma tube shunt or trabeculectomy.

I practice in a busy academic setting and, as such, receive many referrals for uveitic steroid-induced glaucoma. The etiology of rising IOP in the disease is primarily from the trabecular meshwork, and the Trabectome electrosurgical blade has been shown in many electron microscopy images to achieve meshwork ablation and exposure of the backwall of the Schlemm's canal very cleanly and accurately. In addition, uveitic glaucoma patients tend to be younger and the Trabectome averts the need for these patients to undergo more invasive



procedures, such as trabeculectomy and glaucoma drainage implants, which also come with lifetime risks of infection and exposure.

Another thing to take into consideration is patient satisfaction, which – in my experience – is high when performing irrigating goniectomy using the Trabectome. The surgical procedure is quick, taking only a few minutes, with faster vision recovery when compared with the tube shunt. It can be performed as a standalone procedure or in combination with cataract surgery. I personally appreciate being able to do all of my Trabectome cases with only topical anesthesia, which is unlike glaucoma drainage devices that require retrobulbar or sub-Tenon anesthesia. Patients require fewer post-op visits – a crucial benefit and not only in a pandemic.

If you were to draw a Venn diagram of MIGS devices, taking into consideration the factors of ease of use, variety of indications that can be treated, magnitude of post-operative care, hardware needed, and flexibility to be used with or independent of cataract surgery, you would likely find the Trabectome in the center. The device's versatility allows me to provide enduring IOP reductions across the spectrum of glaucoma patients – and that makes it my choice MIGS.

"Another thing to take into consideration is patient satisfaction, which – in my experience – is high when performing irrigating goniectomy using the Trabectome."

Would you like to tell our readers about your favorite tool or device? Email your views to *edit@theophthalmologist.com* or leave a comment below.

Ken Lin is a Associate Clinical Professor, the Director of Medical Education of the Ophthalmology School of Medicine at the University of California, Irvine, USA.

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It's a Drug's Life

The eye finally gets a chapter to itself in the book of drug metabolism

By Geoffrey Potjewyd after interviewing Eva M. del Amo Páez, Adjunct Professor at University of Eastern Finland, Kuopio, Finland.

Ocular diseases are an increasing societal problem, exacerbated by our aging population, environmental factors, and a global epidemic of diabetes. The lack of effective treatments for more than a handful of diseases is a compounding problem. Industry and academia are, of course, both keen to advance ocular drug discovery and development in these therapeutic areas, but do we have the right tools at our disposal?

When developing or administering any therapeutic, we must understand how the drug will be affected by the body – the pharmacokinetics. Pharmacokinetics includes drug absorption, distribution, and elimination. The latter may be via metabolism (by changing the drug) or excretion out of the body. Unfortunately, metabolism of ocular drugs are often assumed from data on what occurs in organs far removed from the eyes.

Indeed, information on drug-metabolizing enzymes within the eye is sparse, and I believe new insights in this field would benefit the current and future development of ocular therapies. And that's why it's a major research theme for my team at the University of Eastern Finland, Kuopio, Finland.

Drug metabolism

In fact, we directly address the lack of information on ocular drug-metabolism in our recent publication (1), where we present a comprehensive ocular pharmacokinetic study that investigates the metabolism and distribution of four drugs in the rabbit eye. Each drug – acetaminophen, brimonidine, cefuroxime axetil, and sunitinib – was selected because it interacts and is broken down by distinct enzymes (sulfotransferase, aldehyde oxidase, esterases, and CYP3A, respectively). The drugs were applied through either intracameral or intravitreal routes, and concentrations of both injected drug and the main metabolite of the drug, were measured in six different ocular tissues to determine the route taken. Pharmacokinetic drug and metabolite profiles were then obtained and analyzed.

Interestingly, extremely low levels of metabolites were detected for all the compounds, except the esterase substrate, which shows that drugs are mostly eliminated from the eye by non-metabolic processes, but via "excretory" action of the ocular flows (i.e. metabolism played a minor role in their ocular pharmacokinetics). In simple terms, our study shows that you cannot reliably predict ocular metabolism from data generated through tests for hepatic metabolism (the data that are generally produced during drug development). Only esterases seem to have a major impact on ocular drug clearance.

Ocular impact

As noted, the main mechanism of ocular drug elimination is not metabolism-related, but ocular flow-related (how well the drug can permeate the ocular membranes and be cleared by aqueous humor and ocular blood flows). Typically, intravitreal small molecular weight drugs, such as the ones we investigated, are cleared from the eye rapidly, so controlled drug delivery systems are essential to prolong their therapeutic action in the eye

GOOD MODEL

In our research, we used a cassette-based dosing methodology, which included the four drugs in the same injection solution. And we used a rabbit model, which has been proven as a good model for ophthalmic intravitreal drugs (3). The combination of these two factors means that we were able to reduce the use of the number of animals according to the principle of 3Rs (reduce, refine, replace), with the added bonus of diminishing variability between studies. In future, when investigating a new intravitreal drug, where preclinical pharmacokinetic studies are compulsory, I would definitely choose the rabbit model for its relevance and accuracy.

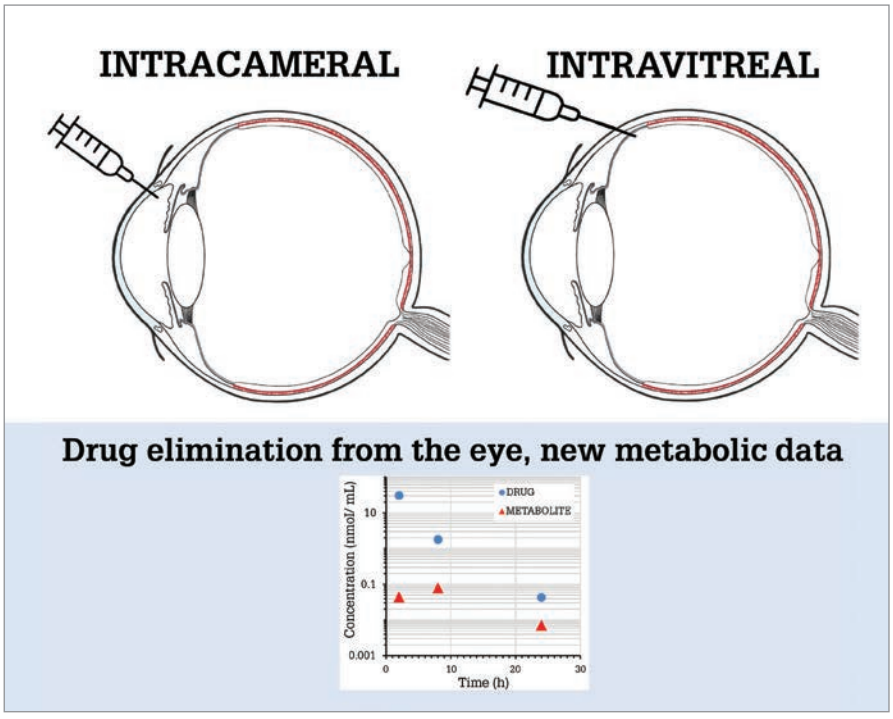

Figure 1. The routes of administration used in the study, and the metabolic data generated

(such as the Ozurdex intravitreal implant containing dexamethasone). For future drug delivery systems, we can expect that pharmacokinetics will not be controlled by drug metabolism. Nevertheless, some very low-level of metabolite formation is expected, and the potential ocular toxicity from the metabolite should be evaluated during drug design and development, especially for these long-acting formulations.

In clinics, antibiotics and antiviral drugs are intravitreally injected to treat endophthalmitis and viral infections (such as cytomegalovirus infections) respectively, while intracameral injections of antibiotics may be given after cataract surgery. Based on our findings, ocular-metabolism will not increase the clearance of these drugs, with the decrease of drug half-life (again, esterase substrates are the exception).

This finding is in line with our previous research, where we observed drug hydrophilicity (chemical affinity to water) to be the key parameter for prolonging duration of ocular residence for intravitreal drugs (2). Hydrophilic drugs permeate less through the blood-ocular barriers and, therefore, have reduced passage into systemic circulation of vascularized tissues. In other words, intravitreal hydrophilic drugs present slower clearance and longer half-lives in the vitreous.

When attempting to select an antibiotic from two with equal potency, we suggest that physicians choose the most hydrophilic one to prolong the effect of the treatment and reduce the number of injections for the patient. Tip: hydrophilicity is easily obtained from web databases, such as drugbank.com, by looking for the one with lowest logD7.4 or logP values.

Diving into the data

Our pharmacokinetic data in six different ocular tissues for four compounds is rich and informative, depicting four clearly different drug behaviors in the eye. The modeling of these drug concentrations in the different compartments should provide a better understanding of the intravitreal and intracameral pharmacokinetic processes specifically for these compounds, and in general on small molecular weight drug distribution and its relationship with physicochemical properties.

The parameters established in our work could also be used for pharmacokinetic simulations to guide the design of new ophthalmic drug delivery systems, informing on the relationships between drug release rates and loading doses of the systems for a specific duration of therapeutic action. They could also feed into simulations for other routes, such as topical, subconjunctival, intravitreal, and intracameral administration to predict drug concentrations in the anterior and posterior segment of the eye. We believe that further modeling on this data will give more insights into the pharmacokinetics and distribution of these drugs.

Another interesting avenue of research would be to develop rabbit-based models of choroidal or retinal neovascularization to investigate the effect of the drug on the disease state while exploring drug pharmacokinetics.

Drug developers: over to you!

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The Beacon of the Blind

My fight for the rights of blind and visually impaired women and girls, inspired by growing up with sight loss in Ghana

By Gertrude Fefoame

Images courtesy of Gertrude Fefoame.

I have been advocating for patients' rights since 1975. The main focus of my work has been improving the quality of life and strengthening the voices of people with disabilities, particularly women and girls. Although one might think that other disadvantaged groups – such as healthy women or other people with disabilities who have experienced discrimination – would be more inclined to appreciate the struggles faced by women with disabilities, and in particular visual impairment, this is not always the case. As a result, I have often found myself advocating within the Organization of the Blind and various women's groups to create spaces and opportunities for visually impaired women and girls and to secure and protect their rights.

My roles and achievements

In 1981, as part of my work with the Ghana Society for the Blind, I helped establish the Ghana Blind Women's Work, which eventually became a full arm of the Ghana Blind Union. I was elected secretary of this initiative and, seeing how useful it was, I transferred that learning and experience into my work with the Africa Union of the Blind. When that organization's first committee focusing on women and girls was established in 1994, I again acted as secretary and, two years later, I became the first female Vice-President of the Union. In that role, I worked assiduously to ensure that women would have a place and voice within the Union.

In 1997, I was appointed Vice-Chair of the World Blind Union's Women's Committee. Even though my tenure as Vice-Chair is long past, I still work as a technical advisor to the World Blind Union, helping to formulate and implement policies and empower women and girls with visual impairment.

"In 1997, I was appointed Vice-Chair of the World Blind Union's Women's Committee."

Currently, I am a member of the UN's Committee on the Rights of Persons with Disabilities (CRPD), fighting for inclusion and increased opportunities for women and girls with disabilities. Before I joined the CRPD, only one of its 18 members was a woman. I also participated in the "Equal UNEqual World" Sightsavers' campaign, which resulted in the election of six women to the CRPD. I continue to be part of the campaign; now that we have reached gender parity on the committee, we are focused on making our work more intersectional.

Last year, I received the World Blind Union Women's Empowerment Award, a great honor that I dedicated to all the blind and partially sighted women and girls working at the grassroots to make change, and to all the women and girls with disabilities who have worked alongside me throughout my career.

So what originally inspired my advocacy work?

The beginnings

I grew up with my grandmother in a community in the south of Ghana, a two-hour drive from the capital, Accra. I first noticed a decline in my eyesight in my early childhood, and by age 10 I could no longer read from the board at school – a problem that led me to seek medical attention. I was given reading glasses, but my eyesight declined so fast that I required new glasses every three months. By the time I was 14, there were no longer any glasses available that would improve my sight, so I struggled through high school.

My family decided it would be best for me to attend the School for the Blind to learn to typewrite and to read and write Braille. I didn't view joining the School as a negative development. I had grown up in that community and had classmates whose parents taught there, which meant that I'd previously encountered blind people and never considered blindness to be anything regrettable. But all this changed in 1975. I was 17 at the time and, one day, three members of my extended family met me at the gates of the school. When asked why I was there, I explained that I'd enrolled at the school, and the way they responded really took me aback. Their words were harsh and cut deep. I could see that they saw me as a brilliant person with many prospects and a bright future, but the loss of my vision also led – in their eyes – to the loss of those qualities. I internalized those sentiments and, by the time I got back to my dormitory, I was in tears. I truly felt like my life was over before it had even begun.

Some time later, I was visited by a young woman from the College of Education who was blind. She told me that she'd just graduated from the Wenchi Methodist Senior High School, an integrated school for visually impaired persons in Ghana. An examiner who came into my secondary school for a day had told her about me and the story made such an impression that she tried to find me – unsuccessfully, until she came across me again by chance and decided to visit me at the School for the Blind.

Seeing her there in her uniform and hearing her talk of how she had enrolled in college, I felt hope. For the first time in a long time, I believed I had a future. That meeting was really meaningful to me because, growing up, I wanted to be a teacher, a journalist, or a lawyer. I had cast those dreams aside as fanciful thinking, but here was someone who was completely blind and yet on her way to success in one of those professions. It reignited my passion and got me to refocus. It also made me realize that, if one person's presence and intervention was so significant to me, maybe I could pass this on to others by mentoring and influencing change. This is what led me to advocacy.

"I first noticed a decline in my eyesight in my early childhood, and by age 10 I could no longer read from the board at school – a problem that led me to seek medical attention."

Women and girls face a double dose of discrimination. Many educated women are not employed and few have the opportunity to access technology. Often, women's input is dismissed or ignored – and there can sometimes even be the risk of abuse. This is what makes empowerment and implementing change so important to me. When we are empowered, we gain self-awareness, assertiveness, and confidence – and we can climb out of the deep holes into which we have been pushed. I know the truth of this, having experienced it myself, and I will continue to work to make sure that every blind and visually impaired woman and girl knows that she has a future.

Gertrude Oforiwa Fefoame is a Community Member, United Nations Committee on the Rights of Persons with Disabilities, Global Advocacy Advisor – Social Inclusion, Sightsavers, Chair - Africa

Impactful Solutions

Sitting Down With… Michael Mrochen, Founder of IROC Science, Serial Entrepreneur: Co-founder of Vivior AG, Allotex Inc, LiveLong Vision, IROC Innocross (Exit) AG, ClearSight Innovation Ltd (Exit), Zug, Switzerland

What first attracted you to ophthalmology?

My training was in physics: optics and lasers, and in 1992, I started working for a company that is now Carl Zeiss Meditec, in the laser development department – it was one of the first companies producing lasers for ophthalmology. The first laser I built was for posterior capsulotomy. In the mid-90s, I began working with Theo Seiler at the Carl Gustav Carus University Hospital of the University of Technology of Dresden, Germany, and I got really attracted to the combination of clinical practice – helping patients – and designing, building, and using new technological innovations. The eye itself fascinates me as an optical instrument. I got hooked and have been working in ophthalmology for more than 25 years.

Who were your role models when you were growing up?

My father was a very creative person. He knew a lot about mechanics, engineering, and how things work, despite not having a formal engineering background. He was always creating new things, which I found very inspiring. The rest of my family were bankers, so my role models were a mixture of creativity and thinking about money!

Have you ever imagined a different career for yourself?

I certainly considered working in different medical disciplines, such as neurology and dermatology, but I realized that the innovation cycle in ophthalmology is quick compared with those in many other fields, and that the working relationships of innovators and ophthalmologists are very close.

When did you know you chose the right path for yourself?

In the mid-1990s, when I worked on laser refractive surgery, and for the first time I was involved in bringing a product from the lab to patients in clinical trials, and then to market – that was that moment. I really felt like I could be involved in creating innovations with global impact. I experienced this again with corneal cross-linking for keratoconus, when we took it from the lab in Dresden to commercial production in 2005, and approvals around the world. Selling my cross-linking business to Avedro finally allowed US approval and global reach. Progressing a project from an initial idea to having an impact on so many patients' outcomes gives me a lot of joy, and is a huge source of motivation for me.

Have you seen first-hand what difference your work has made to patients?

When I worked with Theo Seiler, he made sure I had a chance to interact directly with patients – which is quite unusual for an engineer – and I really appreciated it. I was at a very early stage of my PhD thesis and most of my time was spent building lasers, but I had the opportunity to come to the OR or sit behind the slit lamp, interacting with patients, hearing about their issues and outcomes, and recognizing how certain ophthalmic treatments can be life changing. Then, at the beginning of 2000s, I traveled a lot to different eye centers in South America, the US, Asia, Africa, and Europe, and every one of them had a laser that I had helped to develop. I could see first-hand how many patients were treated using those lasers, and I realized that my work had an impact on millions of people every year.

Corneal cross-linking helps a lot of young people, and seeing that their vision is preserved at an early stage of their life is a huge deal for me, and can feel quite emotional.

How do you find the right balance between professional and personal aspects of your life?

When you're involved in early-stage technologies, they become a huge part of your life, so finding the right balance between career and personal life can be very challenging – and the pendulum can swing a bit too much each way at times. Lately, I have found the concept of personal agility useful. I set myself clear personal and business priorities, which help me make better choices when I have many different things fighting for my time. I wish I had used this concept earlier in my life to make better decisions, but I've had to learn this over the years. I have to choose

"Lately, I have found the concept of personal agility useful. I set myself clear personal and business priorities, which help me make better choices when I have many different things fighting for my time. I wish I had used this concept earlier in my life to make better decisions, but I've had to learn this over the years."

the right things for myself first, as I have learned that if I'm not happy, I'm not going to make other people happy.

And what gets you out of bed in the morning these days?

Coffee! And – of course – the joy of seeing my projects become successful. I have started a couple of new projects that I have big hopes for: I've been working intensely in the field of presbyopia, designing a new solution for Digital Eye Strain with Vivior, and developing a new investment structure for early-stage technology through tokenization of innovation with Overture.

Are there any parts of your work that you dislike?

I have to say: administration. It's a necessary evil, and I appreciate its importance – I just don't like it! Managing it as I go rather than leaving it all for later is the key. I have learned – and sometimes those lessons were hard and expensive – that administrative tasks always catch up with my projects. Finding people who help with this is vital, and I wish I'd figured this out earlier!

How important are interactions with other people to you?

Having a network of people around me who help me answer questions and challenge me has been crucial for my success. I've been involved with some great societies, such as the Refractive Surgery Alliance, the American-European Congress of Ophthalmic Surgery (AECOS), meeting a new generation of specialists. I love seeing their passion, new takes on various topics, and collaboration. I am convinced that we have extremely talented people coming into ophthalmology now, ready to take the field to the next level. Opening pathways for these people and helping them succeed is now the job of my generation, just as the previous generation of experts opened the doors for us. I see it as my future challenge.

Do you have any messages for these younger people following in your footsteps?

If the "old boys" tell you your idea is not going to work, don't let it stop you, but listen carefully and understand their arguments, and use them as challenges to overcome – don't ignore them. When we launched corneal cross-linking, pretty much the whole ophthalmic field was against the idea. We could've stopped, but kept going, using the experts' experience and knowledge to my advantage.

"If the 'old boys' tell you your idea is not going to work, don't let it stop you, but listen carefully and understand their arguments, and use them as challenges to overcome – don't ignore them."

Also, remember that these days you can't do things alone. In the past, it was possible to be a solitary entrepreneur, but the complexity of innovation today means that you need to find people who believe in your idea early on. In that sense it's more difficult than it was 20+ years ago, but there is also much more organized support for young ophthalmologists and those interested in innovation in ophthalmology – it's such an exciting field with huge opportunities.

What impact has the pandemic had on your life and work?

It has been very different from the personal and business perspectives. On a personal level, I enjoyed the time I got to spend with my then girlfriend in lockdowns in our small apartment in Istanbul – and we got married this year. The quiet time we spent together still brings a smile to my face. It was very different on the professional side as my companies struggled a lot. Investor rounds fell apart and customers weren't interested in seeing new products – they just wanted to go back to the way things were. The pandemic has had a huge impact on my two start-ups – their teams and financial results. We are still working hard to overcome the negative effects of the past two years. This experience has made me question whether I'm really spending my time on the right things, and whether I still believe in these projects. The answers have given me the passion to share with those around me. Both companies are now looking much stronger, but it has cost me many sleepless nights. It has taught me the importance of being agile, flexible, adaptive, and brave enough to try new solutions when old ones aren't working anymore. However, it is the team that makes it happen.

Do you have any free time to pursue your interests?

I love skiing and riding motorcycles, and I share these passions with my wife, so we make sure to find time for these activities, but it is usually well planned, not spontaneous. Last year, I spent a week motorcycling in Sardinia with friends. I also enjoy spending time with my grandsons, and my children.

oxervate®
(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

Brief Summary of full Prescribing Information

Consult the full Prescribing Information for complete product information, available at www.oxervate.com/prescribing-information.

INDICATIONS AND USAGE

OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

General Dosing Information

Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

WARNINGS AND PRECAUTIONS

Use with Contact Lens

Contact lenses should be removed before applying OXERVATE because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Eye Discomfort

OXERVATE may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

ADVERSE REACTIONS

Clinical Studies Experience

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

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Lactation

Risk Summary

There are no data on the presence of OXERVATE in human milk, the effects on breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older.

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility

Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD).

In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

Dompé

For the treatment of all stages of neurotrophic keratitis (NK)

NOT JUST ANY SOLUTION

A RESOLUTION

Complete and long-lasting resolution of NK for most patients*[1-4]

- **Up to 72% of patients** achieved complete corneal healing in clinical trials*†[1-3]
- **80% of these patients** remained healed at 1 year (REPARO trial)*[4]

oxervate® (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

* Resolution was evaluated in clinical trials as complete corneal healing, defined as the absence of staining in the lesion area and no persistent staining in the rest of the cornea after 8 weeks of treatment and as <0.5-mm lesion staining at 48-week follow-up.[1-3]

† Key study findings were after 8 weeks of treatment, 6 times daily. REPARO (Study NGF0212): 52 European patients with neurotrophic keratitis (NK) in 1 eye per group; 72% of patients completely healed; vehicle response rate 33.3%. Study NGF0214: 24 US patients with NK in 1 or both eyes per group; 65.2% completely healed; vehicle response rate 16.7%.[2,3]

Important Safety Information

WARNINGS AND PRECAUTIONS

Use with Contact Lens

Contact lenses should be removed before applying OXERVATE because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Eye Discomfort

OXERVATE may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

ADVERSE REACTIONS

In clinical trials, the most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1% to 10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Lactation

The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in pediatric patients 2 years of age and older is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in children.

INDICATION

OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

To report ADVERSE REACTIONS, contact Dompé U.S. Inc. at 1-833-366-7387 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the Brief Summary of full Prescribing Information for OXERVATE on the following page.

References: 1. OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) [US package insert]. Boston, MA; Dompé U.S. Inc.; 2019. **2.** Bonini S, et al. *Ophthalmology*. 2018;125:1332-1343. **3.** Pflugfelder SC, et al. *Ophthalmology*. 2020;127:14-26. **4.** Data on File. Clinical Study Report (NGF0212). Dompé U.S. Inc., 2016.

See more clinical data
OXERVATE.com/hcp

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