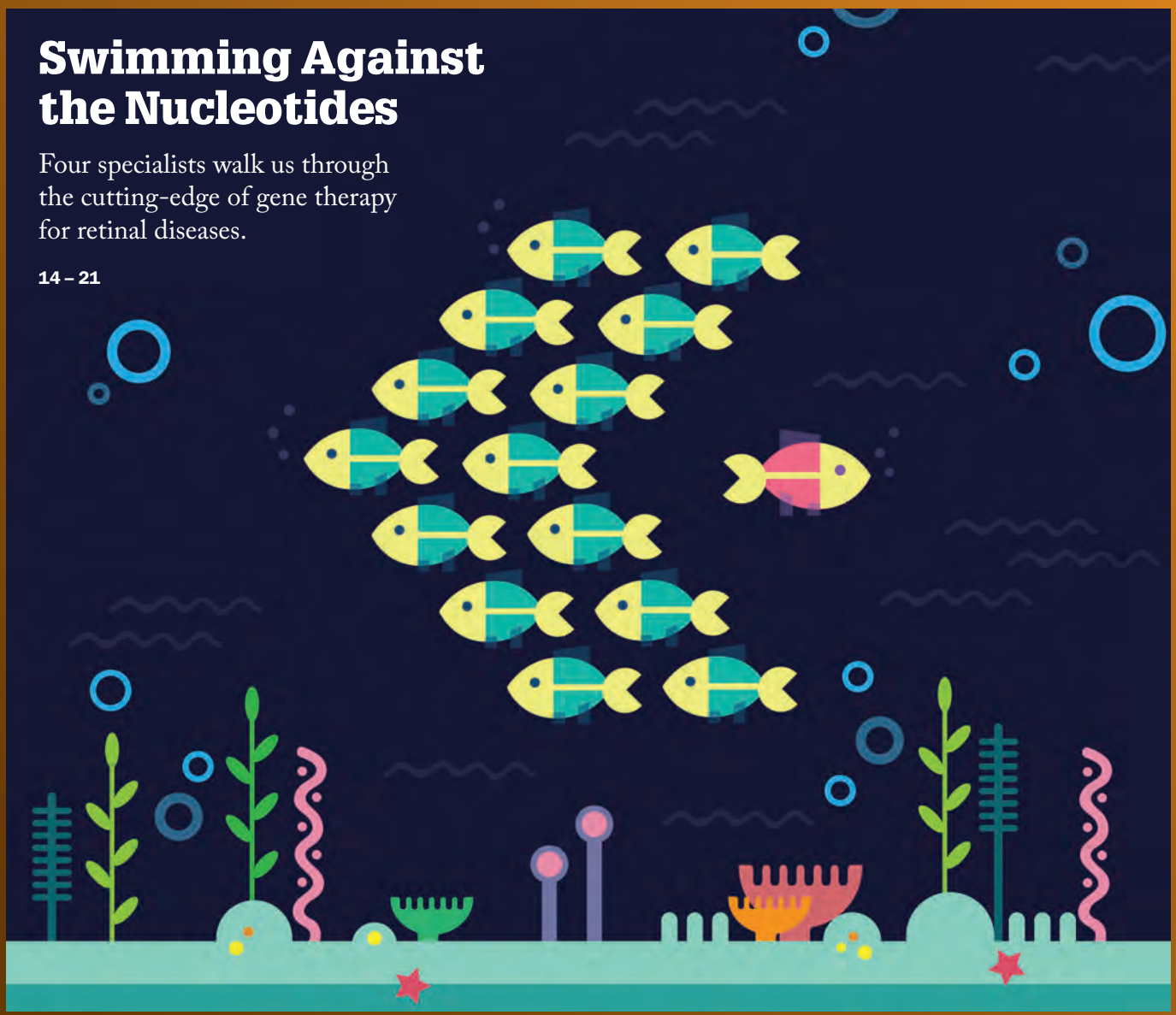
MARCH 2019 # 31

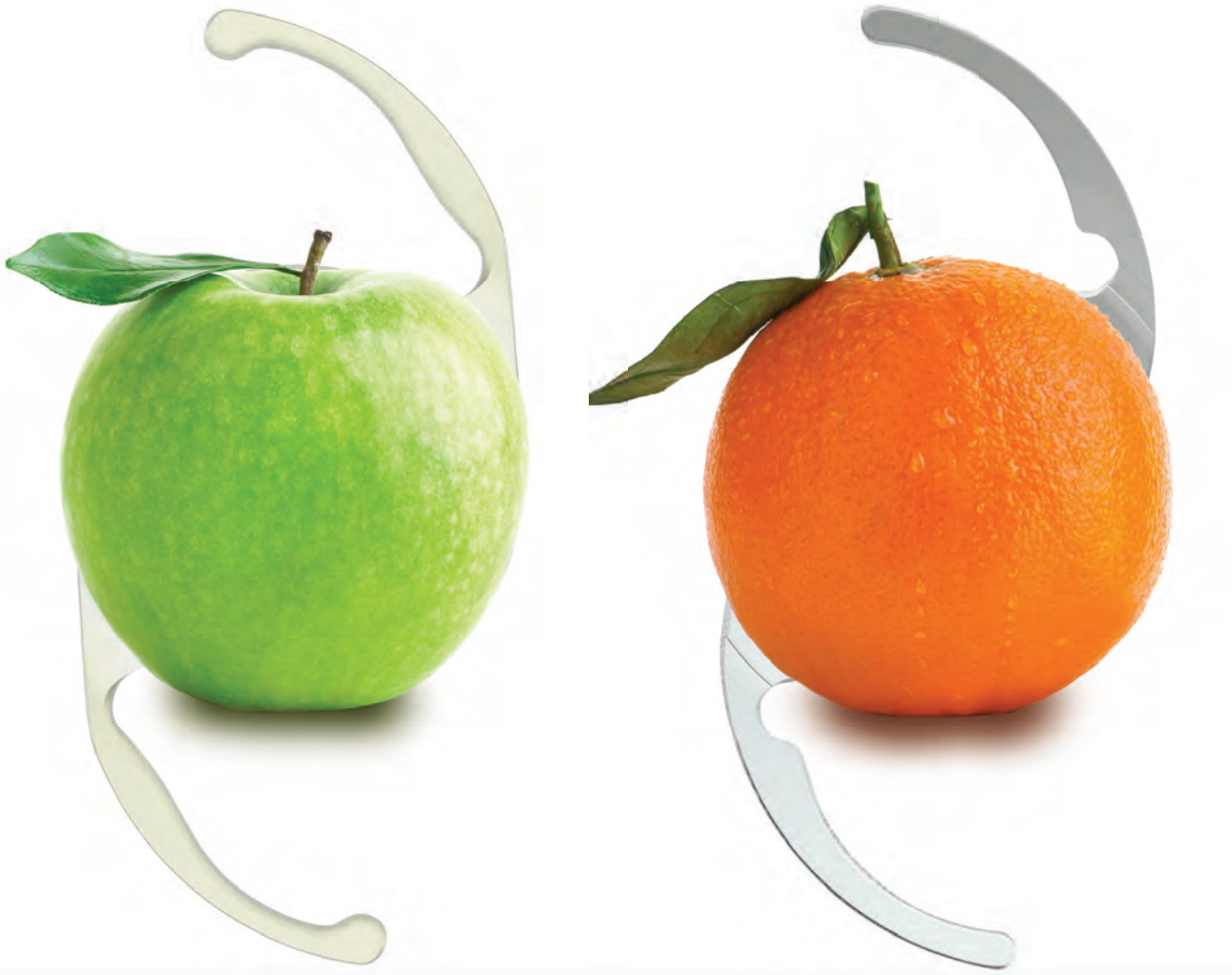
the Ophthalmologist™

Swimming Against the Nucleotides

Four specialists walk us through the cutting-edge of gene therapy for retinal diseases.



FOR ROTATIONAL STABILITY, THERE'S NO COMPARISON[1,2]



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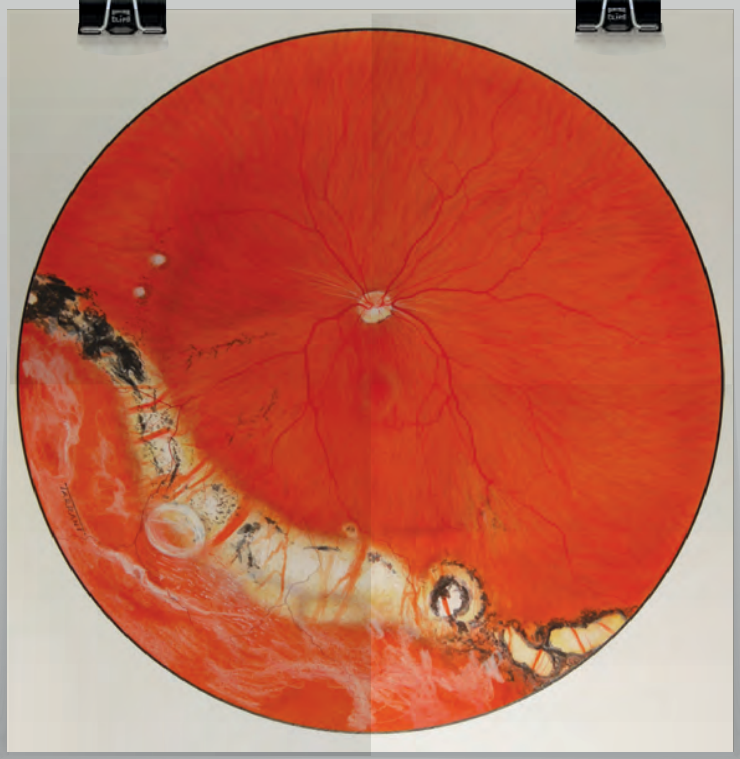

The Worm's Eye View

This month's image shows blood vessels radiating from the optic nerve head. Below is an area of elevation and pallor resulting from surgery. The author of the 1976 painting is Terry Tarrant, one of the best-known ophthalmic medical illustrators, who spent many years working at the Institute of Ophthalmology and then Moorfields Eye Hospital in London, UK.

Credit: Terry Tarrant, courtesy of UCL Digital Collections

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On The Cover

We asked four gene therapy researchers to talk about their current projects, challenges and hopes for the future of genetic treatments for retinal diseases.

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Reference: 1. Data on file. Chromatic aberration of the TECNIS® Symfony IOL. Johnson & Johnson Surgical Vision, Inc. Santa Ana, CA.

Genetic Versus Economic

Our newfound ability to harness the power of gene therapy is facing an age-old challenge: financial constraints

Over the last few months, I've been asking gene therapy researchers about the biggest obstacles ahead. The most common answer I received: funding. The image in general is not bleak: most researchers are able to work with commercial partners to receive the support they need, but there are areas of gene therapy that are particularly difficult to commercialize.

Mariya Moosajee, Associate Professor and Honorary Consultant at the University College London's Institute of Ophthalmology, told me about a patient whose case was recently featured in a BBC documentary on the history of Moorfields Eye Hospital. Four-year-old Vicky has a genetic mutation in the RDH12 gene, which causes one form of Leber Congenital Amaurosis – and she is losing her vision every single day. I have a four-year-old son, so I can perfectly understand how desperate Vicky's mother is to save her child's eyesight.

Moosajee is working hard to develop a treatment for patients like Vicky. On my recent visit to the institute, I got a chance to see the zebrafish her team is using to model the condition – it's cutting-edge work. But, as Moosajee points out, there may only be a hundred patients in the world with the same mutation who may be eligible for treatment – after all, there are at least 20 forms of LCA, each caused by a defect in a different gene. The cost of preclinical and clinical work, and then further development of the therapy per subset of patients would be astronomical. Developing therapies for young children adds another potential complication to the list: disease history studies performed on adults may result in standardized outcome measures that aren't so standard for children. To combat the problem, researchers need to pour even more time and – you've guessed it – money into their endeavor.

While the team at the lab works with new generations of the tiny zebrafish every day, Vicky's sight slowly deteriorates. And though Moosajee is hopeful that she will be able to develop some form of therapy to help patients like Vicky one day, nothing can be certain.

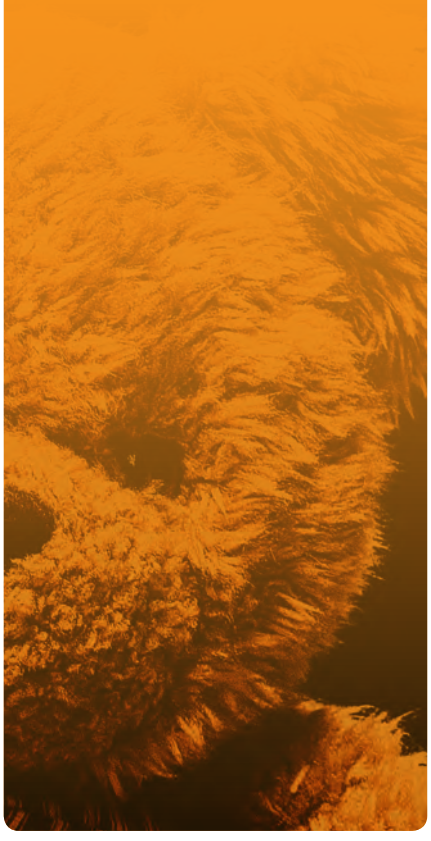
When it comes to funding the research – and any resulting therapies – for patients with inherited retinal disorders, our society must answer an ethically challenging question: what price do we put on a child's eyesight?

Aleksandra Jones
Editor

Upfront

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

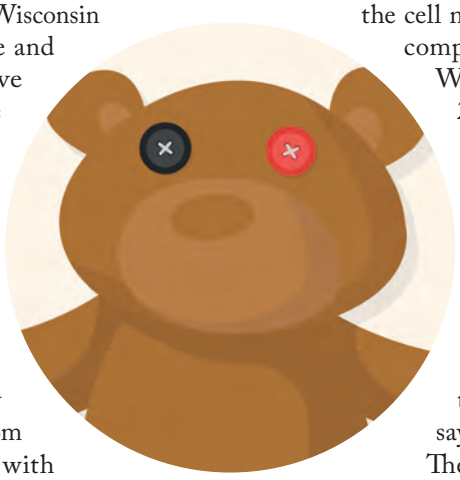
We welcome suggestions on anything that's impactful on ophthalmology; please email edit@theophthalmologist.com



Changing the Channel

A quest to tackle LCA uncovers a novel approach to precision medicine

Leber's Congenital Amaurosis (LCA) affects up to one in every 30,000 children. The result of mutations in as many as 20 genes encoding retina specific proteins, LCA causes severe visual impairment and is incurable. Working towards a solution, researchers at the University of Wisconsin School of Medicine and Public Health have found two possible ways to correct KCNJ13 – the mutant gene behind LCA16 (1).



The group created a "disease-in-a-dish" model from a skin biopsy sample collected from a LCA16 patient with a view to test two possible approaches. Bikash Pattnaik, Associate Professor of Ophthalmology and Visual Sciences and lead author, explains the study: "Unlike traditional approaches, where you compare a mutated cell type with a normal cell, we compared the mutated cell type with iPSC-RPE generated from a normal family member. This comparison takes all common factors between the two individuals into account and only reflects one absolute cause of blindness."

Both cells appeared normal in structure but, explains Pattnaik, "Our study showed that the only difference between the diseased and control cells was a defective potassium ion channel."

"We have previously shown that these channels are crucial for communication between light-sensitive photoreceptor neurons and RPE cells; a defective channel will thus not permit detection of light by the retina."

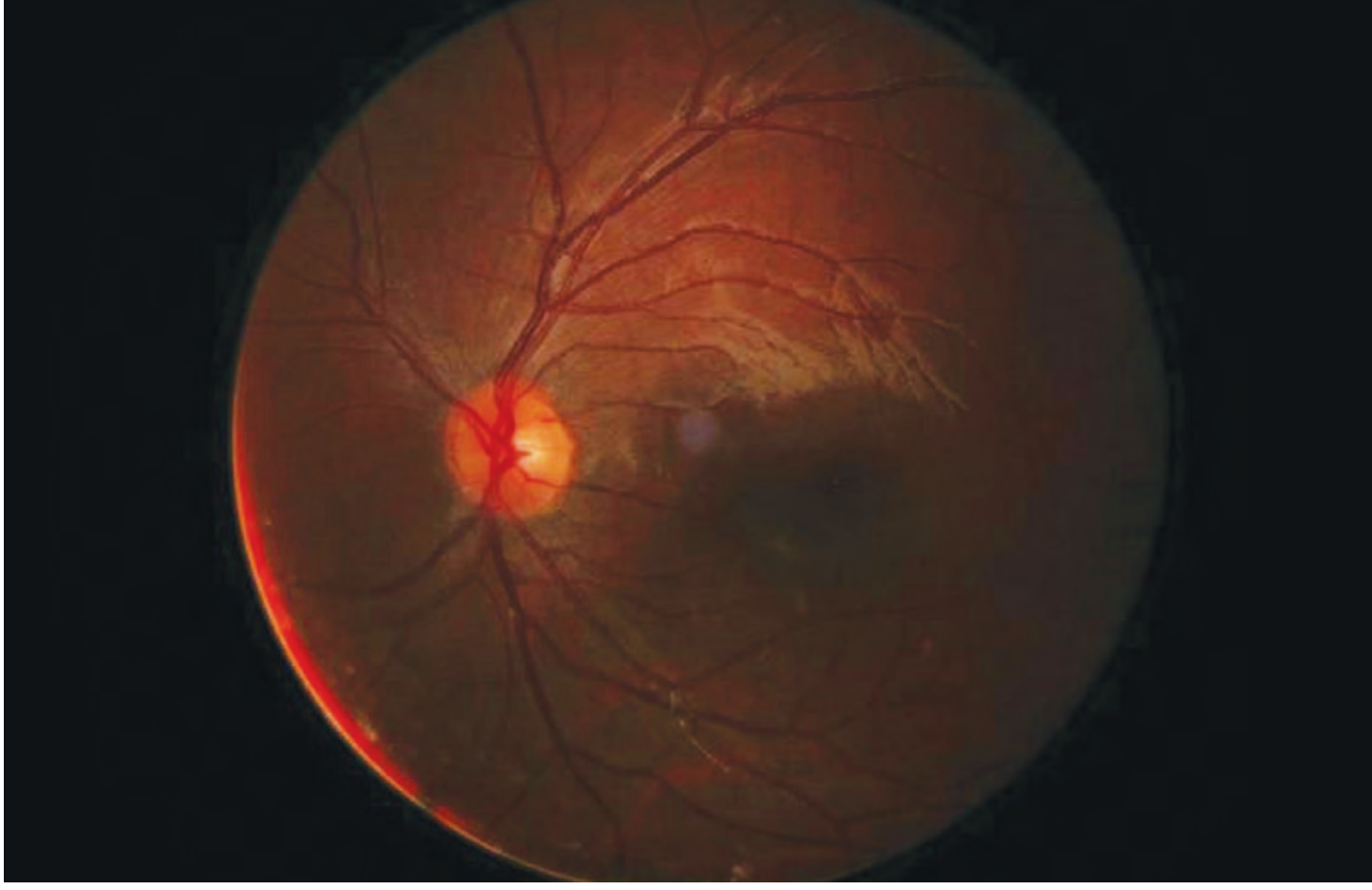
First, the team tried to "rescue" the deficient ion channel with readthrough drug therapy. Promisingly, some of the ion channel function was restored. Next, Pattnaik and his team tried lentiviral gene delivery. "It's a simple approach in theory but, practically, there are several caveats," says Pattnaik. "These proteins need to be made from the new gene, assembled correctly and trafficked to the cell membrane – and all completely functional. We knew that even 25 percent recovery would be sufficient to cure blindness but in this particular case, therapeutic gene therapy recovered the function by more than 50 percent," says Pattnaik.

The team hopes the findings could lead to a future LCA treatment, and believe a similar approach could be used to tackle other ion channel diseases, such as neuropathies and cardiac diseases.

In the meantime, Pattnaik wants to share a broader message: "It's important to convey that, in this era of precision medicine, we absolutely need to firm up the relationship between the patient, providers, and researchers."

Reference

1. *P Shahi et al., "Gene Augmentation and Readthrough Rescue Channelopathy in an iPSC-RPE Model of Congenital Blindness", Am J Hum Genet [Epub ahead of print]. PMID: 30686507.*



Ahead of the Curve

The science behind "self-curving" corneas

With a growing need for donor corneas, researchers are looking for new ways to meet tissue demand. Enter the self-curving cornea. Created by a team at Newcastle University's Institute of Genetic Medicine – responsible for the first 3D printed cornea – these "self-curving" biological tissues take just five days to develop. In the study, a flat circle of stromal cells – derived from limbal rings left over from corneal transplantation – were activated by a serum that caused the edges of the circle to contract at a different rate to the cells at the center. The result is a bowl-shaped structure similar to that of a human cornea.

So how did the idea come about? "A few years ago, we discovered that a particular peptide amphiphile had an RGD sequence similar to that of collagen, and that cells recognize peptides in that sequence and, as a result, bind readily to them," explains Che Connon, Professor of Tissue Engineering at the University. "We were making a gel of the RGD peptide amplifier and found that cells didn't contract very much – even in the presence of serum, whereas cells in a collagen gel without peptides will readily contract in a serum medium," says Connon. "We then thought: if you can spatially localize the peptides within a 3D gel, then you can infer shape into the contraction?" And that's what they did. Indeed, the team spent a lot of time investigating the effect that shape has on corneal cell function.

"The curvature isn't just important for refractive purposes. Recent papers have shown that corneal stromal cells actually change their type if they are grown in a curved environment. The cells have developed and evolved within a curved material and only behave appropriately (by which I mean, form aligned collagen, which is the structural part of the cornea) in a curved environment," explains Connon. "And that's why we created two forms of hydrogel – one that the cells can bind to and pull against, and another where the cells can't. If you position those hydrogels next to each other within a contiguous system, you will find that one half of the overall hydrogel will contract and the other half will not – it is this combination that infers a shape overall."

Though there are other ways of manufacturing corneas, such as 3D printing, a relatively simple approach to generating transplantable corneas is advantageous, says Connon. Though the concept is still in its infancy, the team hopes that the principle can be applied elsewhere in the body. "Imagine a tubular vessel, which could contract in response to certain factors flowing through that tube – like a stent placed into the heart," says Connon.

"Just the idea of being able to create complex shaped tissues in response to external environment is a game changer."

References

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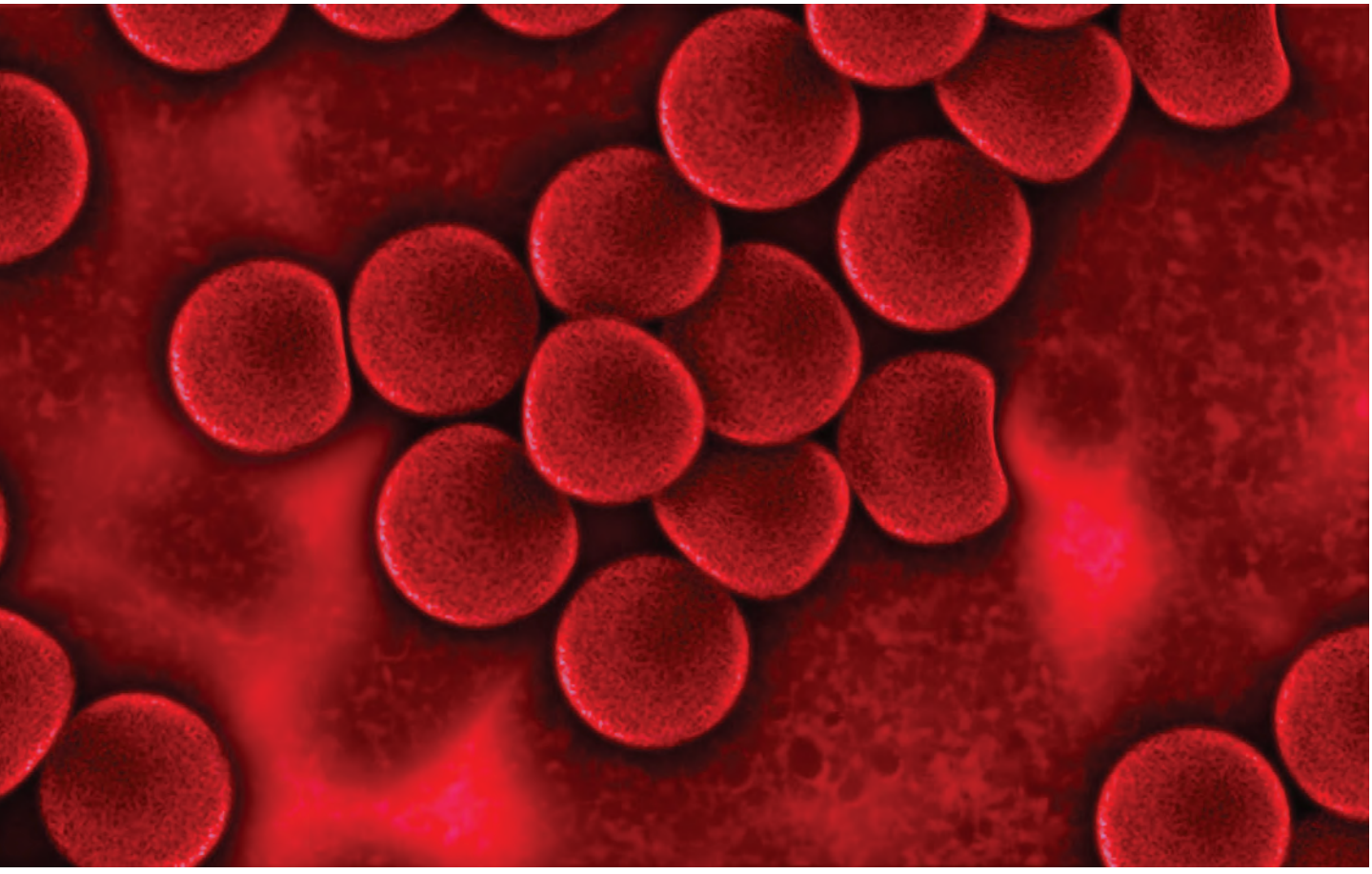

From iPSC to RPE to Therapy

Will stem-cell success in animals translate to humans?

For patients with advanced dry AMD, a long-awaited treatment may be on the horizon. Researchers at the USA's National Eye Institute (NEI) have successfully rescued retinal degeneration in rodent and pig models through cell-based therapy.

Kapil Bharti, Head of the NEI Unit on Ocular and Stem Cell Translational Research, led the investigation. He explains how the team used Nobel-Prize winning technology to pave the way for therapeutic success: "The blood cells are reprogramed using proteins that induce the expression of iPS cell genes. Within three weeks, blood cells start becoming iPS cells, where they are then expanded and used for making RPE."

These iPS cell-derived RPE cells are grown on a biodegradable scaffold, designed to promote the integration of the cells within the retina. Once matured, the cells are inserted between the RPE and the photoreceptors, using a purpose-built surgical tool. There, they rescue photoreceptors that would otherwise die in geographic atrophy – the late state of dry AMD.

So how long does the process take? "It takes 10 weeks – all in all – to make functional RPE cells from iPS cells. Once transplanted, the cells start affecting vision within a few weeks," says Bharti.

The team ran tests to confirm that the transplanted cells expressed RPE65 – the gene necessary for the regeneration of photoreceptors and an essential component for vision. The tests also showed that the RPE cells were pruning photoreceptors via phagocytosis – another RPE function that keeps photoreceptors healthy.

Importantly, the team also took special measures to develop oncogenic mutation-free clinical-grade iPSCs to increase the safety of the treatment. And because the approach is autologous, the chances of rejection are virtually non-existent.

Bharti and his team are planning to start a phase I trial later in 2019.

References

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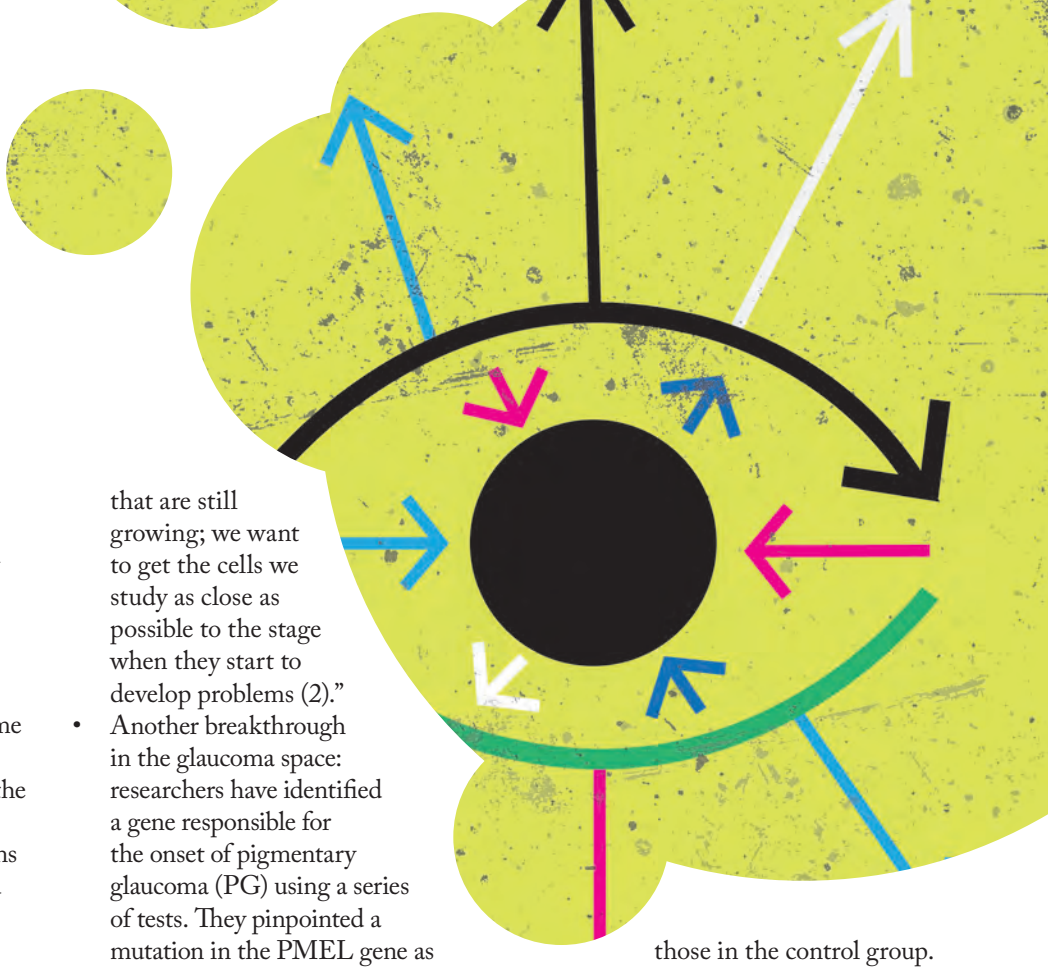

Bitesize Breakthroughs

The latest ophthalmology news – in brief

- Researchers at Augusta University have discovered a potential treatment path for patients with optic nerve trauma. The team used a mouse model to show that removing the inflammatory enzyme arginase 2, which increases with injury, decreases neuron death in the retina, as well as the degeneration of nerve fibers that connect neurons in the brain. In fact, brain-derived neurotropic factor increased upon removing A2, suggesting that the axons were attempting to repair themselves and, ultimately, to reconnect with the brain. The team are now pursuing several new lines of investigation into the role of A2 in optic nerve injuries, for which there is currently no targeted therapy (1).
- Good news for glaucoma researchers – biologists have found a way to better mimic the environment in the human retina: more-mature models of retinal ganglion cells. Biologists at Indianapolis University-Purdue University discovered that introducing hPSC-RGCs to astrocytes, they can create cells that are more analogous to human RGCs – the cells primarily damaged by glaucoma. "What we found is that the astrocytes speed up the differentiation and provide a retinal ganglion cell that functions more appropriately and acts more like how we would expect these cells to function in the human retina," said Jason Meyer, Associate Professor of Biology at IUPUI. "Glaucoma doesn't develop in immature cells that are still growing; we want to get the cells we study as close as possible to the stage when they start to develop problems (2)."
- Another breakthrough in the glaucoma space: researchers have identified a gene responsible for the onset of pigmentary glaucoma (PG) using a series of tests. They pinpointed a mutation in the PMEL gene as responsible for the sight-threatening condition, which affects 150,000 people in North America alone. By introducing the mutation into zebrafish DNA, they noted altered pigmentation and eye defects very reminiscent to that of a human glaucoma patient. The team also identified unexpected similarities to other neurodegenerative diseases, such as Alzheimer's. The team hopes the findings will raise awareness of potential treatment avenues, with some of the methods used to treat Alzheimer's potentially being applied to glaucoma (3).
- In a world first, doctors have transplanted tissue created by donor stem cells into patients with limbal stem cell deficiency (LSCD). The randomized clinical trial, led by doctors at the University of Edinburgh and Scottish National Blood Transfusion Service, found that patients who had received the stem cells showed significant repair to their ocular surface over 18 months, which was not seen in those in the control group. Study leader Baljean Dhillon stated in a press release (4), "Our next steps are to better understand how stem cells could promote tissue repair for diseases that are extremely hard to treat and if, and how, they could help to restore vision."

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In My View

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

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

Contact the editor at edit@theophthalmologist.com

Can We Fix It? Yes, We Can!

When a patient comes to us with a calcified IOL, all is not lost. The solution is clear, but it requires care and skill

Sheraz Daya is an ophthalmic surgeon and Medical Director, Centre for Sight, London, UK

Recently, a series of patients who had received a particular IOL began to complain of deteriorating vision. Many underwent YAG capsulotomies thinking this was the cause of the opacity, but with no benefit. The reason? These patients had all received IOLs from batches that turned out to be prone to calcification. Fortunately, the incidence of lens calcification was low (0.08 percent), and the manufacturer asserts that the problem has now been solved; but that is of little comfort to the affected patients. Furthermore, other individuals with calcifying lenses may be identified in the future – so what can the surgeon do in these cases?

Calcified lenses can be relatively easy to dissect out, when the capsule is intact. That said, there is sometimes considerable fibrosis around the haptics; in this situation, I advise surgeons to use the viscoelastic to gently tease out the haptic: inject it in a plane between the anterior capsule and the haptic, from one end to the other, and then address the equator.

A critical part of the procedure is to separate the anterior capsule from the posterior capsule all the way to the equator. This process can take some time, but it is essential to ensure that the replacement lens will be accommodated within the bag without tilt or decentration. Be aware of the risk of zonular dehiscence, which can occur both intra-operatively and post-operatively. Once the lens is prolapsed into the anterior chamber, I insert a capsular tension ring (CTR) in the bag. This ensures the bag is open out to the equator. The calcified lens can then be moved to one side and the new IOL is implanted into the bag. Next, the calcified lens is cut into two pieces and removed from the eye.

In terms of replacement of IOLs, my experience is that most patients want an implant that gives them spectacle independence. Possibilities include trifocal diffractive implants from Physiol and Zeiss. But whatever model is implanted, I find it tremendously helpful to employ specially designed instruments (MicroSurgical Technologies, Redmond, WA) for manipulating and cutting the lens in the anterior segment.

Unfortunately, some patients with calcified lenses have already had YAG capsulotomy. In these individuals, remedial procedures are much more complicated, especially if the capsule opening is large. My approach is as follows. First, I very cautiously dissect the haptics from the equator of the capsular bag using a dispersive viscoelastic (Viscoat, Alcon, Fort Worth). During this step, I take great care to preserve the zonules and the anterior capsule opening. Also, I inject dispersive viscoelastic posterior to the lens; the idea is to fill the space between the lens and the anterior vitreous so as to avoid vitreous prolapse. Any prolapsed vitreous can be revealed with triamcinolone and removed by vitrectomy using a cutter and a separate irrigation port.

The surgical techniques I have described here are not easy, and carry some risks. But the "wait and see" strategy is also risky: a patient with an opacifying lens will likely experience further vision deterioration, and increasing calcification will further complicate surgery by restricting the surgeon's view posterior to the lens. In my view, knowing calcification is just going to progress, it is better to play safe and opt for earlier surgery.

Three and Out

Obamacare's uncertain future as we enter the third year of Trump's presidency

Brian Joondeph is a Denver-based retina surgeon and writer

Obamacare is approaching its 10-year anniversary. Like a marriage, the initial honeymoon phase has been squashed under the weight of work, children, family, and finances. And though some marriages grow stronger, others strain under the weight of new realities. Obamacare is in the latter category.

We saw major changes to the US healthcare system in 2018, as President Trump continued to pursue his campaign promise to repeal and replace Obamacare. Congress had other ideas. On a July night in 2017, the late Senator John McCain gave his famous "thumbs down" vote to the "skinny repeal" of Obamacare which then failed to pass by one vote. Congress did, however, manage to strike down the mandate that forced individuals to purchase healthcare insurance, whether they wanted it or not. In December 2018, a US District judge dealt Obamacare a potentially fatal blow, declaring Obamacare unconstitutional.

In 2012, the US Supreme Court ruled that Obamacare was indeed constitutional and that the individual mandate could be construed as a tax – a legitimate power of Congress. The problem is that the mandate is now gone, meaning that the tax is reduced to zero and can no longer be considered a tax. No tax means no mandate and, as such, the constitutional basis for Obamacare comes tumbling down, rendering the entire law invalid. It is worth mentioning that this lawsuit wasn't brought on by a rogue judge in a single state; it was brought by 20 states. This ruling is not final, however, and will be appealed.

We are now left with a national healthcare scheme that may not only be unconstitutional, but also deeply flawed. Insurance premiums have priced health insurance beyond the financial reach of many Americans. Cost sharing provisions – meaning deductibles and copayments – have made medical care unaffordable for those able to purchase, but not use, their insurance as intended. Narrow provider networks have separated patients from their doctors and hospitals, while insurance regulations and red tape are frustrating providers, leading to physician burnout and early retirement.

So what's next? As far as I can tell, 2019 will be shaped by a split Congress, with the House now under Democrat control and the Senate still in Republican hands. Given the hyper-partisan atmosphere in Washington, DC, it's unlikely that any meaningful reform will emerge from Congress. Many Democrats instead are pushing for a single-payer plan, called Medicare-For-All. Cost estimates for such a plan are daunting, even for a Congress quite comfortable spending far more money that it has, creating a national debt of over $20 trillion.

If single-payer came to be, the cost would be three quarters of the annual federal budget, leaving little money for anything besides healthcare. Funding would necessitate doubling of individual and corporate income taxes, smothering a currently robust American economy. Not only that, physicians would be paid 40 percent less than they are under current Medicare rates, driving most out of business and exacerbating an already present physician shortage. And these are all estimates – how many government programs actually meet projected costs?

The real Medicare system, when created in 1965, was predicted to cost $12 billion per year in 1990. The actual cost was $90 billion. Aside from this, the question remains: will Americans tolerate long waiting lists, limited drug formularies, and other care rationing that is common in countries with similar government run single-payer schemes? It is hard to say.

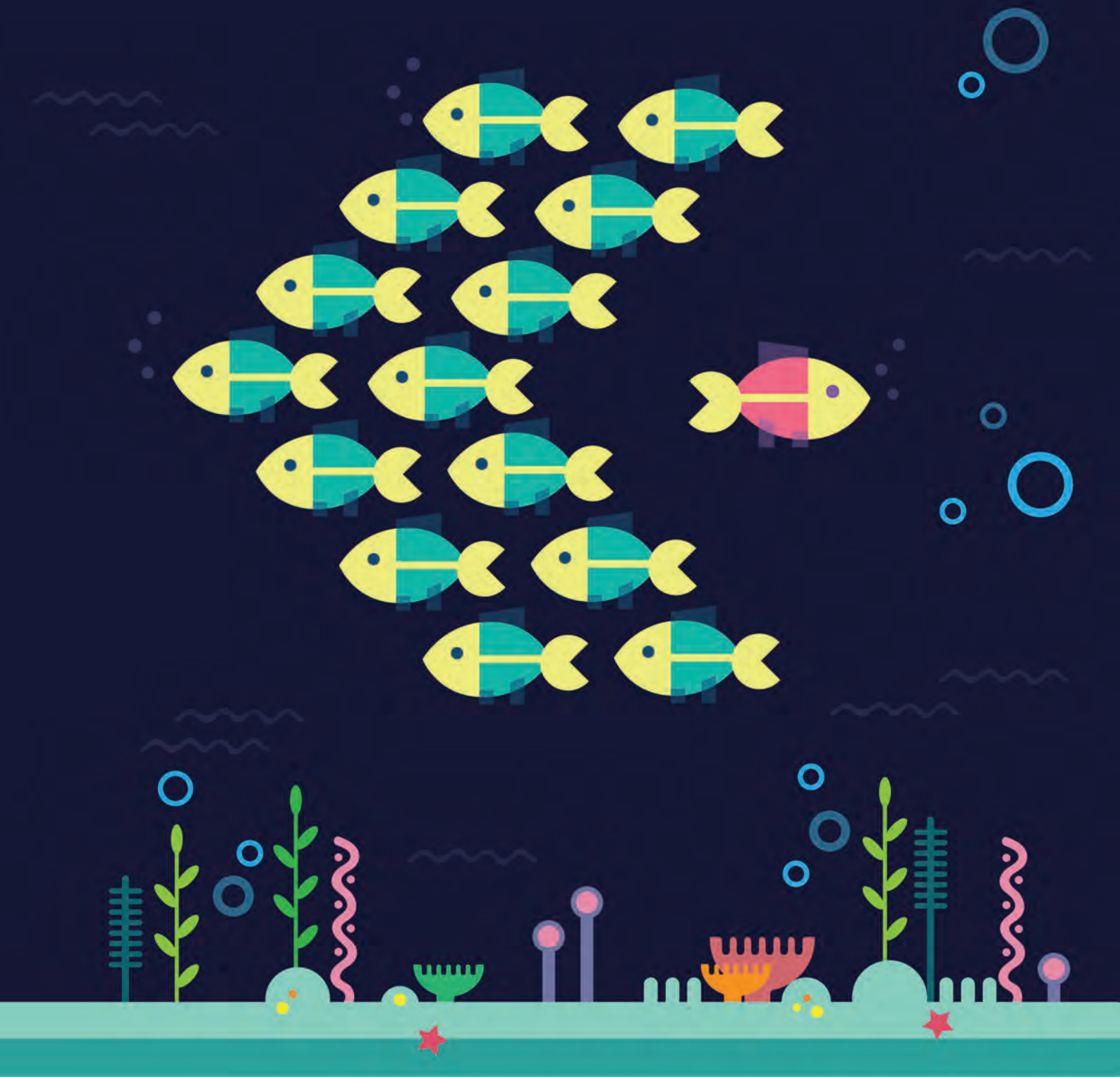
Ophthalmology faces its own challenges. Many insurance companies are mandating step care for intravitreal injections, requiring the use of bevacizumab first for macular degeneration or diabetic retinopathy. Branded, more expensive drugs can only be used after ill-defined "treatment failure," requiring ophthalmologists to waste time and effort jumping through hoops to the satisfaction of the payers. Meanwhile, there is continued regulatory scrutiny on compounding pharmacies, potentially limiting access to the same lower cost drugs that ophthalmologists are required to use first. It is a classic Catch-22 scenario.

Several new drugs or delivery systems are working their way through the FDA approval process, and are likely to be priced at or above existing therapies. With downward cost control pressure, these new options may not be readily available to patients. And let us not forget big data. Physician pay may soon be based on how we compare with our peers under cost and outcome metrics. Who will want to care for the challenging patients and their poorer outcomes then?

There are no easy answers to the questions I have put forward, but there is one thing I know for certain: we, as ophthalmologists, must be forward thinking to remain relevant in today's rapidly changing healthcare landscape. Good luck to you all.

SWIMMING AGAINST THE NUCLEOTIDES

Advances in cell and gene therapy herald exciting times for the world of ophthalmology – and specifically for retina specialists. With each new breakthrough come novel treatments – but also new issues and dilemmas. Here, we speak with four translational researchers, who describe their work – and their shared dream: to change the lives of patients with retinal disorders.

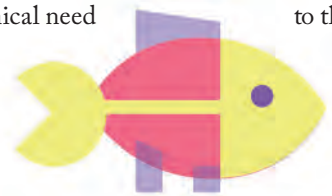


Rewarding Work

Tomorrow's cures for retinopathies will likely include advanced gene and cell therapies delivered by precision surgery

By James Bainbridge, Professor of Retinal Studies, UCL Institute of Ophthalmology and Moorfields Eye Hospital London

Translational research often requires both scientific and clinical input – and this demands collaboration between groups with complementary skill-sets. Developing gene or cell therapies for retinal disease requires sophisticated expertise in a range of disciplines, from molecular biology to microsurgery. Close collaboration was critical for the 2017 approval of a gene therapy for Leber Congenital Amaurosis (LCA), which is a form of childhood blindness that can be caused by the lack of a gene called RPE65. The contribution of our team at UCL/Moorfields was recognized last year, when the 2018 Antonio Champalimaud Vision Award was awarded to the four groups working to develop gene therapy for this condition. Working on a new therapy for an unmet clinical need is its own reward – but it's certainly an honor to receive such recognition!



Playing the long game

My involvement in LCA gene therapy began some 20 years ago, when I began working with Robin Ali at UCL – another of the Award winners – to develop surgical techniques for the delivery of gene therapy to the retina. We were under no illusion that retinal gene therapy would be a quick fix, but the rate of progress surpassed our expectations. The licensing of an approved treatment is an important landmark.

It has not been easy, however; getting to the stage of clinical application required many small incremental steps along the way, as well as a few critical step-changes. At first, we focused on efficient delivery of genes to the retina – solving this problem with AAV (adeno-associated virus)-based vectors was a key development that really enabled us to move forward. AAV is well-suited for gene delivery in the eye, since different serotypes vary in their affinity for different ocular cell types – you have an innate selectivity to play with. Once the delivery step was resolved, we turned our attention to the question of efficacy: what benefit could be derived from delivering functional copies of relevant genes to the retina? We answered this question in a mouse model by demonstrating that injection of a gene into the retina helped rebuild light-sensitive photoreceptor cells – another seminal advance.

A third critical milestone was reached when we took gene therapy into the clinic and found that it could improve sight in people with LCA. Media interest was intense - we even had a BBC film crew in theater for the first clinical trial surgery, which made things interesting!

Overall, it has been a wonderful journey, not least because of our patients who have all been trusting, and wholly confident in our efforts to do our very best for them. The patient who had the first surgery was particularly selfless, because he was the first ever to have gene therapy for genetic blindness. For him, the risks were unknown and the chance of significant benefit was small. He understood that we had to go one step at a time; his involvement – and that of others like him – has been critical for the therapy to get as far as it has.

The development of several of our gene therapies has been accelerated by essential commercialization with the founding of a UCL spin-out company and the support of MeiraGTx. The approved gene therapy was developed in the US by Spark Therapeutics and is being used there – it is currently being considered for use in the NHS. At present the drug is very expensive, owing to the high cost of development for this very new therapy, and the hope that it will provide lasting benefit from a single administration. In time, these types of therapy are likely to become more affordable.

Next steps

LCA isn't the only retinal disorder that could benefit from advanced therapies. About 10 years ago, we started working on gene therapies for other retinopathies – for example, achromatopsia – and three of these programs have now progressed to Phase I/II trials in both the UK and the US. We also intend to target other inherited retinopathies in the future, particularly severe conditions of childhood – partly because of the great need for a therapy for these patients, and partly because younger patients may benefit most from therapies that stop the disease before it progresses too far.

All the while, we should remember that gene therapy won't be applicable to all patients with retinal disorders – for example, in some the cells are too damaged to be corrected by a therapeutic gene. In these cases, we should consider rebuilding the retina by cell therapy. Regenerative therapies based on stem cells are very promising, and there are a number of active programs in this field. I personally have had some experience of using stem cell-derived material in macular degeneration (1); one of our key findings was that this cell therapy approach appears safe in people with advanced disease.

Images courtesy of Robert MacLaren

"We're looking at ways to transplant photosensitive cells – Robin Ali has been working on that for many years – and we are very excited by recent laboratory results."

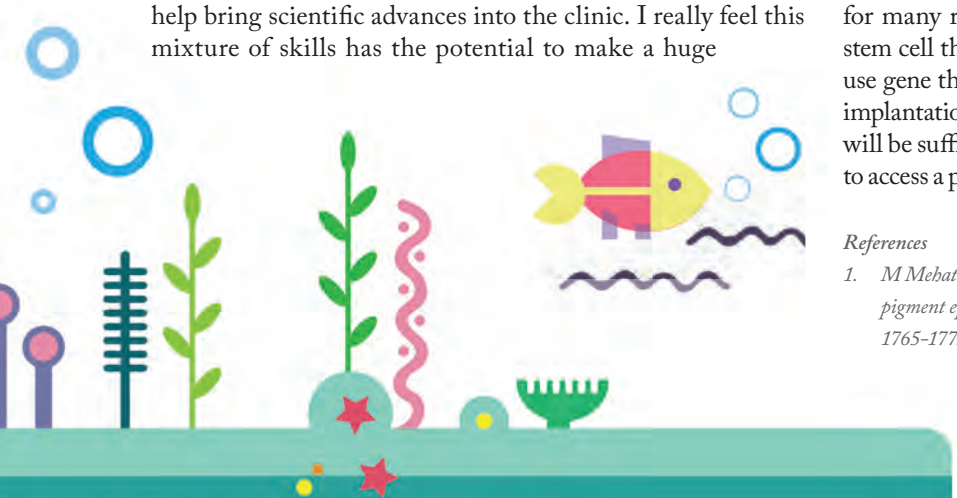
We're also looking at ways to transplant photosensitive cells – Robin Ali has been working on that for many years – and we are very excited by recent laboratory results. These include new methods for 3D culture of retinal cells, which mean that we don't need to grow retinal cells as 2D-monolayers any more – we can culture them in suspension, as spheres with different layers of cells which almost recapitulate the development of the eye. These structures are likely to make excellent models of disease development, and may provide a very useful source of photoreceptor cells for transplantation.

A mixed future – in a good way

I am a surgeon by training, and approach translational research from a surgical perspective. Surgery and molecular biology may seem an unlikely combination, but I see it as an amazing opportunity, and feel very fortunate to be in a position to help bring scientific advances into the clinic. I really feel this mixture of skills has the potential to make a huge difference to people's lives. I think others are starting to recognize the value of this combined approach.

Consider the actual delivery of the therapeutic genes into the retina. In principle this is straightforward; in practice, it's challenging. The procedure has the potential to be difficult, or even to cause patient harm, partly because degenerating retina can behave differently to normal retina – for example, it may be relatively fragile. These issues can complicate the precise delivery of therapeutic genes, and must be managed with appropriate care.

We're very confident that gene therapy will play a significant role in the treatment of inherited retinal diseases, and it is very exciting to see the regulatory authorities recognize the positive data generated by LCA gene therapy trials. Looking further ahead, the field of retinal regeneration by cell therapy is full of challenges and opportunities; it will take longer to get these products licensed, but such an approach may be the best option for many retinal disorders. In many cases, gene therapy and stem cell therapy will be used in combination – we may wish to use gene therapy to modify the patient's own stem cells prior to implantation, for example. No single approach or single skill set will be sufficient for most inherited diseases of the eye – we need to access a portfolio of expertise if we are to cure the retinopathies.



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Big Ideas

Gene therapies are no longer just hype – they provide tangible benefits to real patients, today. What disease will next fall to this powerful modality? For a clue, look at the biggest gene therapy trial in the world.

By Robert MacLaren, Professor of Ophthalmology, University of Oxford, UK

Gene therapy has been hyped for many years, in many therapy areas – but for now, it may be ocular disease that benefits most. Regulators have already approved a gene therapy for Leber Congenital Amaurosis (LCA), and similar products are currently being developed for several other diseases of the eye. Some of these are now in clinical trials and attracting commercial interest. Overall, the field is moving very quickly, and it's an exciting time to be involved, not least in my own field: gene therapies for choroideremia and X-linked retinitis pigmentosa.

REP-1 repair

Choroideremia is an X-linked retinopathy caused by deficiency in the REP-1 protein. The condition progresses to blindness, and there is no treatment. The need for a new therapeutic option is therefore acute. I have been working on a choroideremia gene therapy for several years; if successful, it will represent the first treatment for this problematic disease. Our approach involves the construction of a small retinal detachment so as to form a subretinal space, followed by injection of AAV2-vectored REP-1 sequences into this space. The method has generated very encouraging data from Phase I and Phase II trials: in brief, at the two-year follow-up of a 14-patient trial, treated eyes exhibited a median visual acuity gain of 4.5 Early Treatment Diabetic Retinopathy Study chart letters, while untreated fellow eyes showed a median decline of 1.5 letters (1).

These promising data enabled our choroideremia treatment to progress to the commercial stage – it is being taken forward by Nightstar Therapeutics, an Oxford University spin-out funded primarily by the Wellcome Trust. Nightstar has now initiated a clinical trial involving study sites spread across 11 countries. It's the biggest gene therapy trial anywhere – and we're very excited about it.

"I have been working on a choroideremia gene therapy for several years; if successful, it will represent the first treatment for this problematic disease."

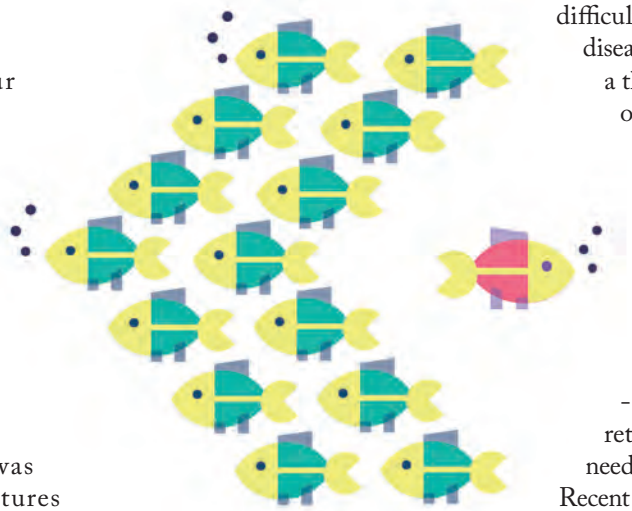
"At present, we rely on delicate surgical expertise – but to realize the full potential of retinal gene therapy, we'll probably need to develop new surgical techniques."

One down...

After Nightstar took on our choroideremia gene therapy, we set our sights on another target – X-linked retinitis pigmentosa (XLRP). This disorder, which primarily affects males, is associated with photoreceptor loss caused by mutations in the RPGR gene. Again, the condition leads to blindness and is at present incurable. We intend to change that.

This project, however, was complicated by inherent features of the RPGR gene. RPGR contains a purine-rich region, with highly repetitive nucleotide sequences, which is genetically unstable. In consequence, the cloning steps necessary to insert RPGR into a viral vector are associated with unpredictable recombination errors in this region. We solved this problem by developing a codon-optimized RPGR sequence which, when expressed from an AAV8 backbone, provides RPGR protein equivalent to wild-type protein. Thus, our XLRP gene therapy comprises an AAV8 vector carrying codon-optimized RPGR DNA.

That work cleared the way for the world's first XLRP treatment, trialed here in Oxford in March 2017. Since then, our XLRP gene therapy has progressed to larger-scale trials in various countries including the UK and the US. The forward momentum has been assisted by the clinical network we built up during our choroideremia program – the same surgeons that want to cure choroideremia also want to deal with XLRP. Again, this project is now being commercialized by Nightstar Therapeutics.



Reasons to be cheerful (Part 3 and beyond)

We have other programs in our pipeline, including AMD gene therapy. Looking further ahead, some aspects of glaucoma may have a genetic predisposition, suggesting a role for gene therapy in this condition too. And although most of our efforts at present are directed at low-hanging fruit in the gene therapy tree – which is to say, augmentation of non-functional genes – I think the future will see us go after more difficult targets. These include dominant diseases where we must not only provide a therapeutic sequence but also remove or disable the original dysfunctional sequence. The CRISPR gene-editing system has obvious applications in this approach.

In all cases, however, we should remember that an essential part of retinal gene therapy is delivery of therapy to the retina! At present, we rely on delicate surgical expertise - but to realize the full potential of retinal gene therapy, we'll probably need to develop new surgical techniques. Recent developments include intra-operative OCT – which, for example, allows us to carefully monitor the iatrogenic retinal detachment step in our choroideremia gene therapy – and robot-mediated ocular surgery. But whatever developments tomorrow brings, it is clear that exciting days lie ahead for ocular gene therapy.

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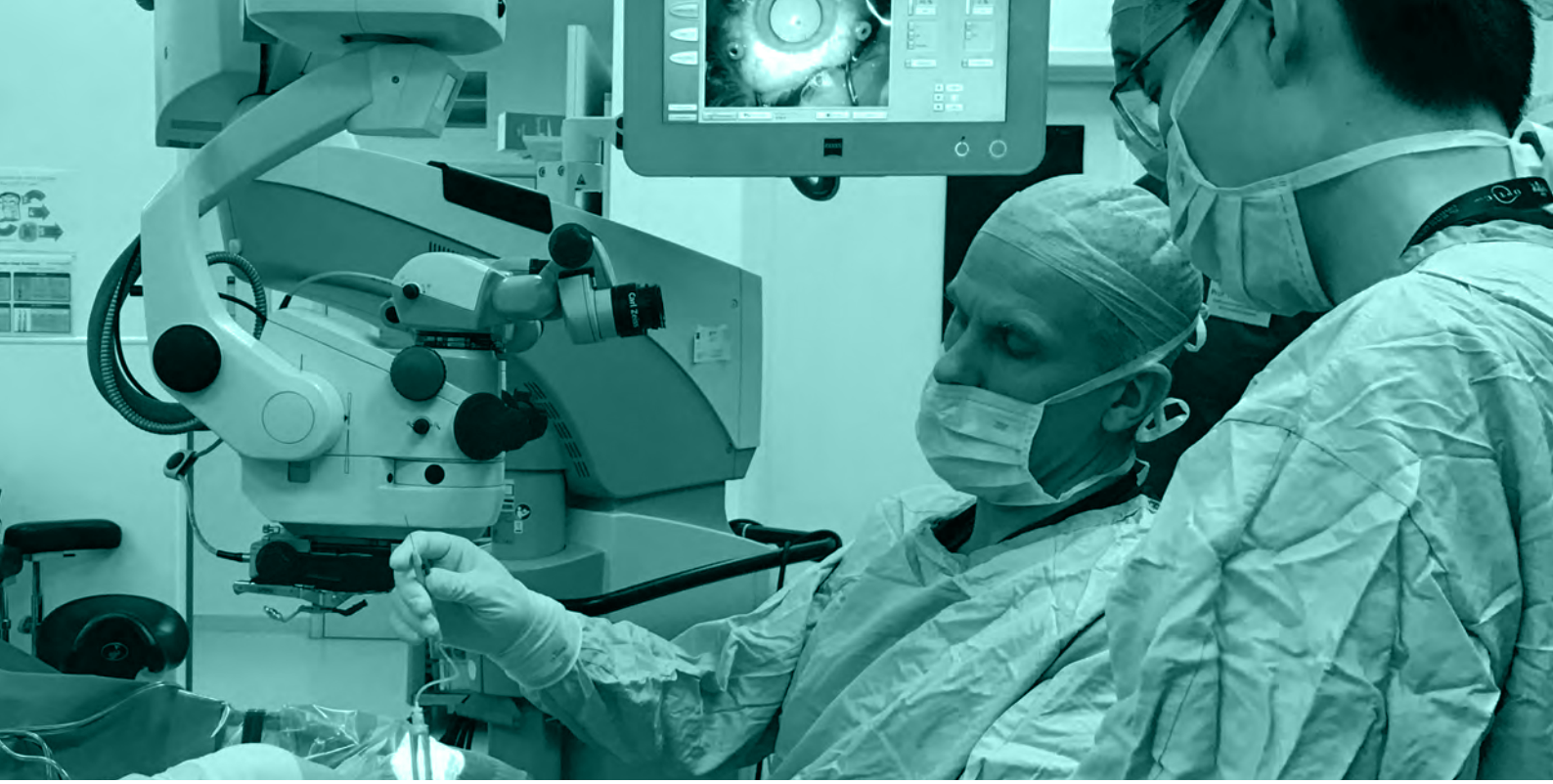
The author is a consultant to Nightstar Therapeutics, Spark Therapeutics and Gyroscope Therapeutics. He sits on the UK Department of Health evaluation committee, which assesses new retinal gene therapy treatments.

Images courtesy of Robert MacLaren



The Test of Time

Reflecting on the past – and future – of gene therapy

By Michel Michaelides, Consultant Ophthalmic Surgeon, Moorfields Eye Hospital, London, UK

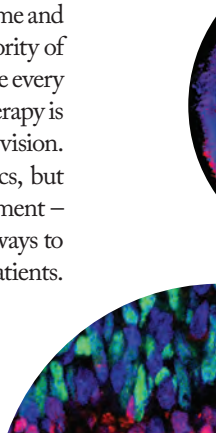
My interest in inherited retinal disease (IRD) began in 2001, with my research degree. I had always been passionate about retinal disease, but I found IRDs to be even more fascinating. There are over 300 known diseases, each one heterogeneous – both clinically and genetically. Despite this, the field remains at the forefront of innovation, with novel treatment types lending us to an unprecedented level of understanding.

The biggest transformation I have seen in my 20 years in the field has been our ability to establish a genetic diagnosis. We have gone from being able to molecularly characterize a minority of patients to being able to characterize the majority. We have also gone from relatively low-level resolution to ultra-high-resolution imaging – so much so that we are now at the point where we can image individual receptors. Of course, you cannot have a conversation about change without acknowledging the huge technological advancements that have shaped the field, especially in gene therapy. In my mind, these three factors have conspired to create the ideal landscape for treating IRD.

Today, I work mainly in gene identification, which involves genotyping the patients to establish their molecular diagnosis and potentially match them to a trial. I'm currently a PI on four trials: achromatopsia caused by CNGB3; achromatopsia caused by CNGA3; another for X-linked retinitis pigmentosa caused by RPGR, and a trial for RPE65 associated retinopathy, as well as a study of Leber Congenital Amaurosis caused by ALP01 – all sponsored by MeiraGTx. Which brings us onto our next point: what's stopping us from finding the perfect solution? The answer: money – or, should I say, the lack thereof.

Running trials is a multi-million-dollar endeavor, and the regulation surrounding them is onerous, slow and multi-faceted. Unless you win the lottery, the only way to find funding is through a commercial partner. And though there are benefits to a partner of this kind – an understanding of researcher's needs and an ability to accelerate progress – there are challenges too. The same goes for technology. Though it has undergone iterative changes over the last decade – and I am sure progress will continue in the years to come – what we have now isn't flawless. Still, I would say the greatest challenge to clinicians and researchers in the field is more fundamental: to really see change, we need to develop new therapies for dominant disease and create more sophisticated gene-editing approaches.

In the next five years, we should have half a dozen phase three trials ongoing and at least two to three approved therapies. The dream outcome, of course, is to establish an intra-vitriol gene therapy. Unlike sub-retinal delivery methods, this approach lasts a lifetime and prevents retinal degeneration – more than that, the vast majority of patients are responders. Even if it takes another 20 years, I have every faith that we can create a viable therapy. In my mind, gene therapy is more advanced than stem cells, neuro protection or artificial vision. The only therapy that shows greater promise is optogenetics, but for all its benefits, it won't address all kinds of visual impairment – only gene therapy can do that. I can only hope that we find ways to intervene earlier and thereby derive greater benefits for our patients.



Images courtesy of Robert MacLaren

(Not) Going Viral

Plasmid vectors are gaining traction as a viable alternative in gene therapy delivery

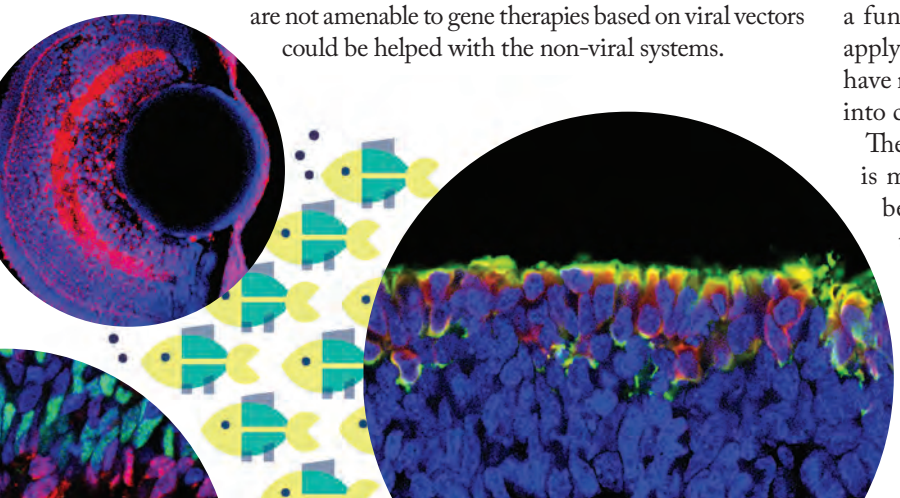
By Mariya Moosajee, Consultant Ophthalmologist and Associate Professor, Moorfields Eye Hospital, Great Ormond Street Hospital for Children and UCL Institute of Ophthalmology, London, UK

I'm currently working on non-viral gene therapy, which – I believe – will be the second wave of therapies in this field. This alternative approach uses plasmid vectors, which are composed of entirely human elements that can package the gene, and deliver it to target organs. Non-viral gene therapy has not traditionally been considered as effective as the use of viral vectors because of the cell's ability to silence plasmid vectors after a short time, meaning that they are no longer able to express the gene of interest.

Special formula

Fortunately, we have managed to find the missing ingredient: the scaffold/matrix attachment region (S/MAR). These molecules serve as anchor points for our DNA, mediating the structural organization of chromatin and playing a role in gene expression. If you place an S/MAR into the plasmid vector, it allows it to sit in the nucleus alongside our existing genome. There, it can express the gene without being silenced.

These non-viral gene therapy delivery systems are able to carry genes of any size; this is important because there are inherited retinal diseases caused by genes that are larger than the size limit of viral gene delivery (which is around 8000-9000 kilobases). A key example is Usher syndrome, the most common cause of deaf-blindness worldwide, where the most prevalent causative gene is USH2A, this is around 16,000 kilobases in size, and mutations in this gene also contribute to non-syndromic retinitis pigmentosa (RP). In other words, a significant number of patients who are not amenable to gene therapies based on viral vectors could be helped with the non-viral systems.



Reducing risks

Currently, those patients undergoing gene therapy treatments require steroids administered before and after the surgery to reduce inflammation and the risk of an immune response to the virus. Luxturna is licensed for single administration, the potential immune system response to a second dose is still difficult to predict. As the plasmids are made from human components, the chance of an undesirable immune response is significantly lower. Those patients undergoing viral gene therapy today may need a non-viral alternative in the future.

In the past, the early viral vectors integrated into a patient's genome, sometimes resulting in insertional mutagenesis – another risk, but this is less so with newer adeno-associated virus (AAV) vectors. The S/MAR plasmid vectors sit alongside our DNA in the nucleus, so there is no risk of mutations occurring.

Taking these aspects of non-viral gene therapies into account, researchers consider them to be safer and more effective – and perhaps the non-viral approach will become the standard delivery system for all gene therapies in the future. But, at the moment, we are only at the preclinical stage – working with animal models and stem cells to show that they are having the required effect.

Stop that nonsense

Another research area that I focus on is in mutation-based genetic therapies, and in particular nonsense mutations, which are responsible for up to 70 percent of human genetic diseases. In ophthalmology, nonsense mutations can account for between 30 to 50 percent of cases in some disorders, such as aniridia, choroideremia, RP and Leber congenital amaurosis. We have been testing a range of small molecule drugs with the ability to bind to our ribosomal protein-making machinery; if it comes across a nonsense mutation, it helps override this and form a functional protein. The results of our preclinical work on applying these drugs to the field of inherited retinal diseases have now been published, and we are in the process of moving into clinical trials.

The ophthalmic gene therapy field is extensive, and research is moving at an incredible pace. The networks developing between scientists and clinicians are really strong, and there is a great feeling of working together to develop a smooth pipeline for the translation of these therapies.

Images courtesy of Mariya Moosajee

Figure 1. Cluster Trend Analysis is part of the Octopus perimeter - shown here is the Octopus 900 perimeter.

THE IMPORT OF SPACE AND TIME

During glaucoma progression, subtle changes can be masked by background fluctuations – and, therefore, entirely missed by standard monitoring methods. Fortunately, there is an alternative.

Glaucomatous visual losses typically appear as "clusters" of adjacent defects corresponding to pathways of affected retinal nerve fiber layer (RNFL) bundles. To better reflect this observation – and thus improve the sensitivity of glaucoma progression monitoring – Haag-Streit developed its Cluster Analysis system, which is based on the distribution of nerve fibers in the retina (1).

Cluster Analysis works by grouping together visual field test locations innervated by adjacent RNFL bundles (2) – and, as the names suggests, analyzes them in those clusters. Each cluster contains at least four visual field test locations; by measuring visual losses per cluster and calculating the mean cluster defect – Cluster MD – the system is able to identify even very low-level visual deterioration. The high sensitivity is derived from an averaging procedure that cancels out variations associated with measurements from single locations within the cluster. The result? Cluster Analysis is more sensitive to glaucomatous change than systems based on point measurements.

The process sounds complex, but interpretation of the system output is simple: Cluster MDs that are similar to the norm ($p>5$ percent) are marked with a '+' symbol, while values that differ significantly from the expected range are marked in orange ($p<5$ percent) or red ($p< 1$ percent). The system also provides a visual representation, with cluster fields shaded light to dark according the degree of difference from the norm.

To assess disease progression, physicians employ the Cluster Trend Analysis capability, which – by methods similar to those used in Cluster Analysis – compares cluster values over time. Worsening at $p<5$ percent and $p<1$ percent is indicated with, respectively, open and solid red arrows, and the rate of change (dB/year) is indicated by a numerical value. This technique has been shown to be more sensitive than MD Trend Analysis and

HAAG-STREIT DIAGNOSTICS

local event analysis. As Jonathan Myers, Chief of the Wills Eye Glaucoma Service in Philadelphia, US, commented: "This type of progression software saves the clinician a lot of time and helps them pick up subtleties they might miss (3)."

With Cluster Analysis, we can pick up tiny defects without needing to identify and count individual abnormal sites; and with Cluster Trend Analysis, we can quickly and objectively identify the extent of progression.

In short, these two innovations enable faster, more precise and less subjective glaucoma assessment.

Case study: visual field series in a patient with primary open-angle glaucoma

In Figure 2, we can see that MD analysis confirms slow progression (0.5 dB/year), but provides little information regarding the location of the change. Conversely, grayscale representations reveal a superonasal expansion; this approach, however, is not ideal for quantifying the speed of progression. Cluster Trend Analysis, by contrast, provides the clinician with objective information regarding both the location of defects and the speed of their progression. In Figure 2, we see how the system illustrates defects in the superonasal and superior clusters, and quantifies their progression (2.5 dB/year and 1.1 dB/year respectively). Statistically significant ($p<1$ percent) change is indicated with a red downward arrow; near absolute sensitivity loss is indicated with a black symbol (inferonasal cluster). Fundus images show rim thinning and RNFL loss spreading from the 1 - 2 o'clock position towards the 6 o'clock position. This correlation between fundus and visual field changes confirms glaucomatous progression.

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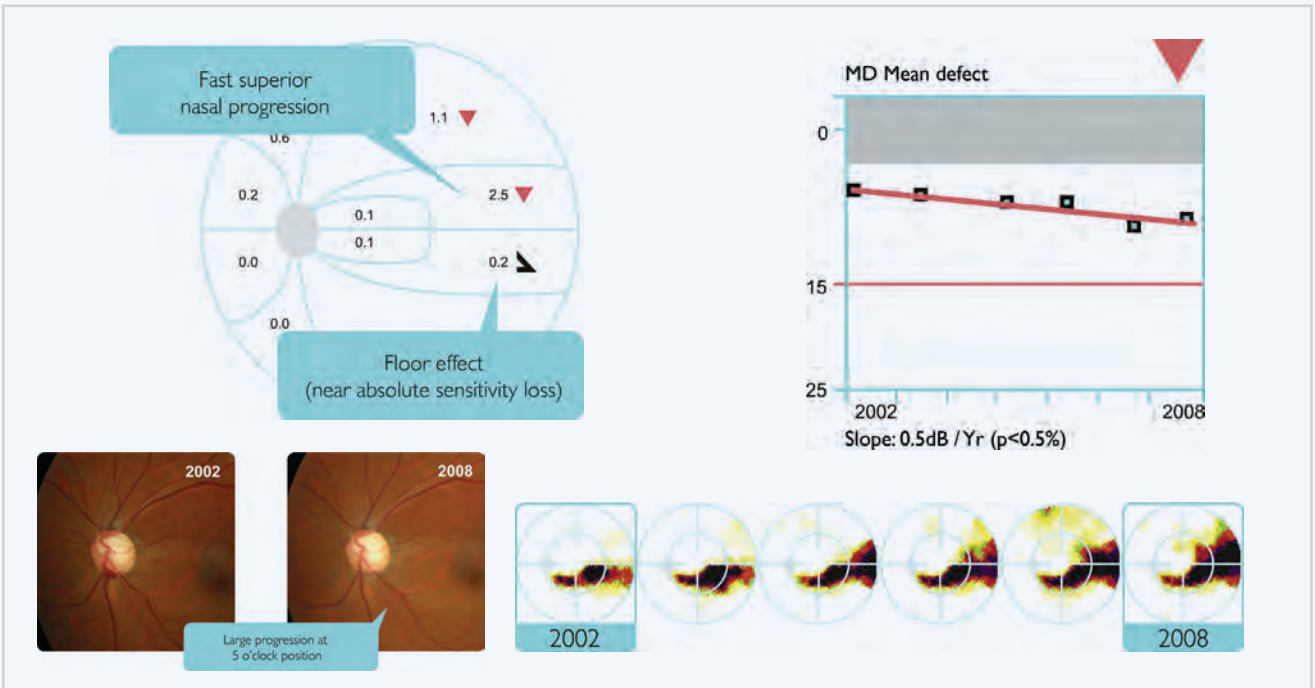

Figure 2. The advantages of Cluster Trend Analysis. Unlike other methods, Cluster Trend Analysis evaluates glaucoma progression in both space and time.

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Defusing the Myopia Time-Bomb

A myopia pandemic is unfolding before our eyes; its future consequences include a significant increase in sight-threatening conditions. To avert tomorrow's explosion of blindness, we have to defuse this time-bomb – today.

By Bhavin Shah

Myopia is increasing in prevalence quicker than ever before. Extrapolating current trends, over half of the world's population will be myopic by 2050, and one-tenth will have high myopia (1). In some parts of the world, the prevalence is extraordinary: in South Korea, for example, 96.5 percent of 19-year-old males are myopic (2). Furthermore, myopia progression is associated with the development of sight-threatening conditions (Table 1): thus, refractive errors as low as -3.00DS significantly increase the risk of cataracts, retinal detachment and myopic macular degeneration. Indeed, recent studies (3) indicate that over 32 percent of adult Chinese-American myopes have a significant – and untreatable – risk to vision due to myopic macular degeneration. Similarly, myopic macular degeneration is now the leading cause of monocular blindness in Japan (4) and of new cases of blindness in China (5). Hence, myopia soon will be the major factor in sight loss among older people.

Most concerningly, in many countries the pandemic now extends into younger cohorts; thus, the incidence of myopia in UK children has more than doubled over the last few decades, and now stands at 20 percent. Given that uncorrected childhood myopia can hinder education, it is particularly important to effectively manage

Level of myopia	*Increased risk factor*		
	Cataract (6)	Retinal detachment (7)	Myopic maculopathy (8)
-1.00 to -3.00	2.1	3.1	2.2
-3.00 to -6.00	3.1	9.0	9.7
-6.00 to -8.00	5.5	21.5	40.6

Table 1. Higher myopia increases the risk of ocular pathology.

At a Glance

- *Myopia is becoming more prevalent, and it increases the risk of developing sight-threatening conditions, such as cataracts or myopic macular degeneration*
- *Children are increasingly suffering from myopia, which can have an impact on their education and future prospects*
- *Four main groups of factors – genetic, environmental, accommodative/vergence and peripheral retinal hyperopic defocus – contribute to development of myopia*
- *Identifying patients at risk of myopia and acting early can help prevent or delay progression of the condition.*

"At present, we cannot treat the genetic factor – it can only inform our efforts to identify at-risk children."

this group of patients. Unfortunately, this is not always easy – about 40 percent of myopic children are self-conscious about – or generally dislike – wearing glasses (9).

The implication is clear: managing the pandemic requires treatment not just of older myopes, but also of younger ones who may progress to high myopia and serious sight-threatening disease as they age. What can we do about it? Rational choice of treatment strategies requires that we understand the causes of myopia and that we can identify those children most likely to benefit from treatment.

What makes a myope?

The multifactorial etiology of myopia comprises four main groups of factors: genetic, environmental, accommodative/vergence and peripheral retinal hyperopic defocus (Figure 1). All of these may contribute to an increase in the axial length of the eyeball and hence poor distance vision.

The genetic contribution to myopia is well-established; where both parents are myopic, the child has a significantly higher risk of myopia (10). At present, we cannot treat the genetic factor – it can only inform our efforts to identify at-risk children. Environmental factors, by contrast, are relatively easy to address; most importantly, the known protective effect of sunlight on the eye and retina (11, 12) suggests a health benefit to outdoor pursuits. Current advice is that children should spend at least two hours outside each day, but this target is rarely reached – in fact, children today spend less time outdoors than ever before. Lack of sleep is also thought to contribute to myopic progression (13), and may be influenced by environmental factors.

Accommodative/vergence factors seem to be important in myopia progression. For example, accommodative lag increases during progression; an increased lag may be evident up to two years before myopia onset (14). However, it is not yet clear whether the lag plays a causative role or only predicts myopia. Other functions of accommodation – such as amplitude, facility and response to blur – also have been implicated as factors or indicators in the progression of myopia (15). For example, we know that accommodation induces an increase in the axial length of the eye (16), the increase being proportional to the amount of accommodation exerted. This suggests that children should avoid holding reading/visual material too close to the eye. Accommodation may also impact myopia via an effect on IOP, as accommodative effort increases pressure (17), which may in turn contribute to myopia progression. Also, the under-accommodation associated with near-vision esophoria may contribute to or predict myopia (18, 19, 20). Thus, bifocal or progressive spectacle lenses have been reported to control myopia progression in esophore children (21). Similarly, some studies suggest that myopia progression may be controlled by spectacles that under-correct myopia (22), although other work indicates the opposite effect – myopia progression and axial elongation (23, 24).

For the purposes of myopia control, however, the most important factor may be peripheral retinal hyperopic defocus. In brief, studies have shown that spectacle-mediated correction of myopia (and uncorrected and undercorrected refractive error) induces hyperopic defocus on the peripheral retina. This defocus stimulates eyeball growth and increases axial length (25), possibly as an attempt at emmetropization. Reduction of hyperopic defocus and induction of myopic defocus is therefore an increasingly important topic in myopia control.

Tomorrow's high myopes, treated today

To avoid the significant individual and societal impact of myopia progression and related conditions, we should identify at-risk patients in childhood, where possible, and act to prevent or delay progression. Diagnosis of at-risk individuals is informed by genetic factors; by presence of esophoria; and by apparent accommodative/vergence difficulties (26). Age of onset is also significant: early onset myopia (6 to 7 years of age) is associated with high myopia

What to tell patients – and their parents

1. Get outside: at least two hours per day is essential, especially before the onset of myopia
2. Get some variety: reduce screen time or near-vision work, and take breaks (remember the 20/20/20 rule – focus on something 20 feet away for 20 seconds every 20 minutes).
3. Get further away: don't hold books or devices close to the eyes.
4. Get more sleep: ideally, more than nine hours per day for children.
5. Get professional help: children with a high risk of myopia (and especially if they have early onset) should be assessed and offered a myopia control program if appropriate.

Figure 1. Major factors that contribute to myopia

(>6DS) as an adult. However, the most reliable predictor of myopic onset and progression is a shift away from the normal hyperopic refractive error: future myopes have significantly less hyperopia compared with the average for their age. Furthermore, this diagnostic indicator may be present up to four years prior to the onset of myopia, and a faster shift from the norm is often seen one year before myopia onset (27).

Given the links between myopia and other ocular conditions, parents of all children at risk of myopia or myopia progression should be fully advised regarding available interventions. Today, we have a number of options for myopia control (Figure 2), including pharmaceutical intervention, vision training, and specialized contact or spectacle lenses.

Pharmaceutical intervention

The only approved drug relevant to myopic progression is atropine. Its mechanism of action is not fully understood, but it is known to be effective (28): one percent atropine slows myopia by 0.68DS/year. That said, atropine has side-effects including blurry vision and reduced accommodation, and there is evidence of rebound myopic progression after treatment cessation (29). In practice, therefore, the application of one percent atropine is rather limited. Lower concentrations, however, may be more useful: 0.01 percent atropine has fewer side effects and less rebound myopia; therefore, it may provide longer duration benefit, albeit at the price of slightly lower myopia control (0.53DS/year). Recent studies also indicate that other low doses may be more appropriate (0,05 percent and 0.025 percent (30)). Unfortunately, these lower-strength formulations are not widely available and must be compounded specially. There have recently been concerns and mystery about the action of atropine. From the ATOM and LAMP studies (31), despite reducing the rate of progression of myopia, it does not appear to reduce the rate axial length growth. This lengthening of the eyeball is largest risk factor in myopia related pathology. So, the risks of myopia may still be present.

Vision training

The involvement of accommodative/ vergence factors in myopia progression suggests that vision training therapy may be an effective intervention. A recent study (32) indicated that accommodation training

Figure 2. Intervention options for myopia control

slows myopia progression compared to controls, at least in younger subjects, but only for a limited period of time. My own experience is that children undertaking vision training for accommodative/vergence difficulties often exhibit reduced myopia progression. Furthermore, this type of training is of broader benefit to these young patients in that it supports reading and studying.

Specialized contact lenses

The orthokeratology approach involves use of reverse-geometry, rigid, gas-permeable (RGP) lenses; when worn overnight, these devices reshape the cornea and provide transient (36 to 48 hour) relief from myopic refractive error. Furthermore, RGPs reduce axial length growth, thereby reducing myopia progression by 40 to 50 percent compared with no intervention (33). Traditional (day-wear) lenses did not show a similar suppression of eyeball growth, suggesting that the RGP mechanism is likely to be reduced hyperopic defocus on the peripheral retina.

Overnight placement of RGP lenses, however, increases the risk of serious infections, such as microbial keratitis, by 2 to 6 times as compared with day-wear soft contact lenses (34). This risk is minimal when the device is chosen with appropriate regard to lens design, is carefully fitted, and when the patient is provided with appropriate aftercare. In fact, the rate of contact lens-related events and complications for children is very low (35) – and lower in ages 8 to 11 than in older children and adults. Nevertheless, parents considering RGPs for their children should be fully informed of all possible outcomes.

Today, however, there is a new contact lens option for inhibiting myopia progression: single-use, disposable soft contact lenses, such as Coopervision's 'MiSight' device (36). These dual-focus, multifocal contact lenses work by presenting the peripheral retina with hyperopic defocus, thus reducing the drive for axial elongation, and reduce myopia by about 50 to 60 percent compared with controls wearing single-focus contact lenses (37). This outcome is similar to that of orthokeratology; the risk to ocular health is slightly lower when using daily disposable lenses compared with overnight wear. I believe that this soft contact lens advance is one of the most exciting innovations in myopia control.

Specialized spectacle lenses

Spectacle lenses for myopia control fall into two broad categories: (i) bifocal/progressive lenses, and (ii) lenses which alter peripheral defocus. Bifocal/progressive lenses (for example, Myopilux), especially those with a prismatic correction in the near segment, appear to be more effective in children with low accommodation lag and/or esophoria at near. Early reports suggested their effect was not clinically significant, but more recent studies, indicate reductions in myopia progression of up to 50 percent (38).

More exciting, however, is the new generation of spectacle lenses that induce peripheral defocus. The Myovision lens (Zeiss) has had some success, but greater effects are seen with the Defocus Incorporated Multiple Segments (DIMS) spectacle lens. This device, developed by a team at Hong Kong Polytechnic University, is reported to reduce myopia progression by 60 percent (39).

Bomb disposal

The high and increasing incidence of myopia, together with the close link between myopia progression and a number of sight-threatening conditions, points to an explosion of ocular disease in the near future. Defusing this bomb requires that likely pre-myopes are assessed as early as possible, taught good visual habits, and encouraged to decrease the risk of myopic progression by behavioral interventions (for example, by increasing outdoor time). This strategy should slow or prevent myopic progression in at least a proportion of patients.

Once myopia has become established, however, its control requires more significant intervention. First steps include a full assessment of accommodative and vergence factors; patients should be offered vision training where appropriate. Reduction in myopia progression also may be effected by soft contact lenses (such as Misight), or spectacle lenses, such as the new DIMS device. Some patients may benefit from orthokeratology, provided they have access to an experienced practitioner, and with the proviso that parents should be fully informed of the nature of the intervention and appropriate consent obtained. Finally, pharmaceutical intervention may have a role in myopia retardation in the future; for example, if atropine 0.01 percent becomes more widely available, and could be used in parallel with the interventions described above.

Broad and consistent application of the above tactics should enable ophthalmology clinics to minimize the force of the myopia explosion, and shelter patients from the fallout.

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PCO Secrets: Out of the Bag

IOL implantations restore sight to millions of cataract patients annually – but many patients subsequently lose their renewed vision to posterior capsule opacification. Now, an in vitro lens capsular bag model promises to both reveal the mechanisms behind this troublesome condition and also suggest novel means of preventing it.

By Michael Wormstone

At nearly 30 million operations per annum, cataract removal and intraocular lens (IOL) implantation is the most common surgical procedure in the world. There are good reasons for this: cataract surgery is phenomenally effective at restoring sight to patients. But imagine how frustrating it would be for an IOL recipient to find their sight disappearing all over again. Unfortunately, this is precisely what happens to those patients who experience posterior capsule opacification (PCO). After two or three years, their decline in vision is such that they need yet another procedure – laser-removal of light scattering areas. This is not only inconvenient, but also associated with a degree of risk. Obviously, patients and surgeons alike want to avoid this situation.

Developing rational approaches to inhibit or avoid PCO, however, requires some understanding of the processes at work. What causes PCO? In brief, it is the consequence of a natural wound-healing mechanism in the eye, which itself is a response to the trauma of cataract surgery. A key aspect of post-surgical wound-healing in the eye is stimulation of lens epithelial cells to proliferation and migrate. Some of these cells invade previously cell-free areas of the lens capsular bag and can grow over the IOL, which interferes with the passage of light to the retina. Consequently, many patients start to lose their vision within months or years of having cataract surgery. We know that much about PCO – but we still have a lot of questions to answer. What molecular pathways are involved, and how might we modulate them? Which IOLs are inherently less susceptible to PCO and why – and can we build on this to design IOLs that can better prevent PCO?

At a Glance

- *Posterior capsule opacification (PCO) occurs as a result of natural post-surgical wound healing in the eye, and can lead to patients losing some of their vision months or years after undergoing cataract surgery*
- *The new in vitro capsular bag model, developed by University of East Anglia scientists and West Norwich Hospital ophthalmologists, benefits from spatial organization and cell types found in real-life patients*
- *Researchers are working on improving the human model, replicating regenerative features of PCO and examining a range of IOLs to determine the best outcomes for patients.*

Comparing new IOL brands

Michael Wormstone and colleagues at UEA, in collaboration with HOYA, have developed an in vitro model of PCO (1) based on explanted human eyes and a graded culture regime.

How can we most accurately represent the environment that gives rise to PCO? One way is to use human capsular bags implanted with IOLs in vitro, and to maintain them in a way that reflects the normal anatomical relationship of IOL and capsule. Such a model provides a very close representation of the clinical situation with regard to physical and cellular parameters. To reflect post-surgical reality even more closely, we can provide this model with an environment that changes over time: the initial pro-inflammatory culture medium is gradually replaced with minimal, non-activating medium.

The model

- Capsulorhexis and lens extraction performed on human donor eye to generate capsular bag attached to the ciliary body by the zonules
- Ciliary body pinned to silicone ring, such that bag containing IOL is suspended by zonules over ring lumen (thus enhancing IOL-capsule interaction)
- Preparation maintained in experimental culture medium for 28 days
- Experimental medium comprised:
  - (i) serum-free medium throughout; or
  - (ii) graded culture regime in which initially high levels of human serum and TGFbeta decline over time (medium is serum-free by day 15)
- End-point measurements include cell coverage, matrix contraction, matrix deposition, light scatter and myofibroblast expression

Our theory is that this graded culture regime should better mimic the post-surgical environment, by providing an initial protein-rich, stimulatory environment that subsequently declines to a non-activating environment. It is known that a number of growth factors, such as FGF, HGF and VEGF can promote wound healing, leading to PCO following cataract surgery. Many of these factors become elevated in the eye following a breakdown of the blood aqueous barrier, and thus addition of serum to our cultures mimics this process. TGFβ2 elevation following surgery is fundamentally a local event, so TGFβ2 is specifically added for this reason. Graded culture enhances growth, increases myofibroblast expression and promotes matrix contraction and matrix deposition relative to serum-free culture (Figure 1).

Our graded culture model therefore seems to reflect the PCO-favoring environment of the post-surgical eye. Our next step was to use the model to assess marketed lenses. What can the model tell us about the inherent ability of IOLs to influence PCO progression?

IOL comparison

- Alcon Acrysof or Hoya Vivinex IOLs were implanted in matched capsular bags (derived from the same donor)
- Matched preparations were maintained under the graded culture regime for 28 days
- Outcomes were compared with regard to: cell coverage on the posterior capsule, coverage of the IOL and light scatter within the visual axis.

The results? Vivinex IOL was more resistant to PCO (as represented by the outcome measures) than Acrysof. Specifically, although both lenses had equivalent cell coverage by day 28, cell coverage with a Vivinex implanted occurred at a slower rate and resulted in lower levels of light scatter. Moreover, cell cover of the IOL surface was less pronounced with a Vivinex IOL than Acrysof (Figure 2). These results add weight to previous observations that IOL choice may have an impact on PCO.

In conclusion, our in vitro capsular bag / graded culture regime provides investigators with an advanced PCO model that mimics the dynamic inflammatory environment of the post-surgical eye. Furthermore, it can identify differences between IOLs with regard to susceptibility to surrogate measures of PCO, and therefore serves as an excellent system to evaluate and develop IOLs, which will limit this costly and frustrating phenomenon.

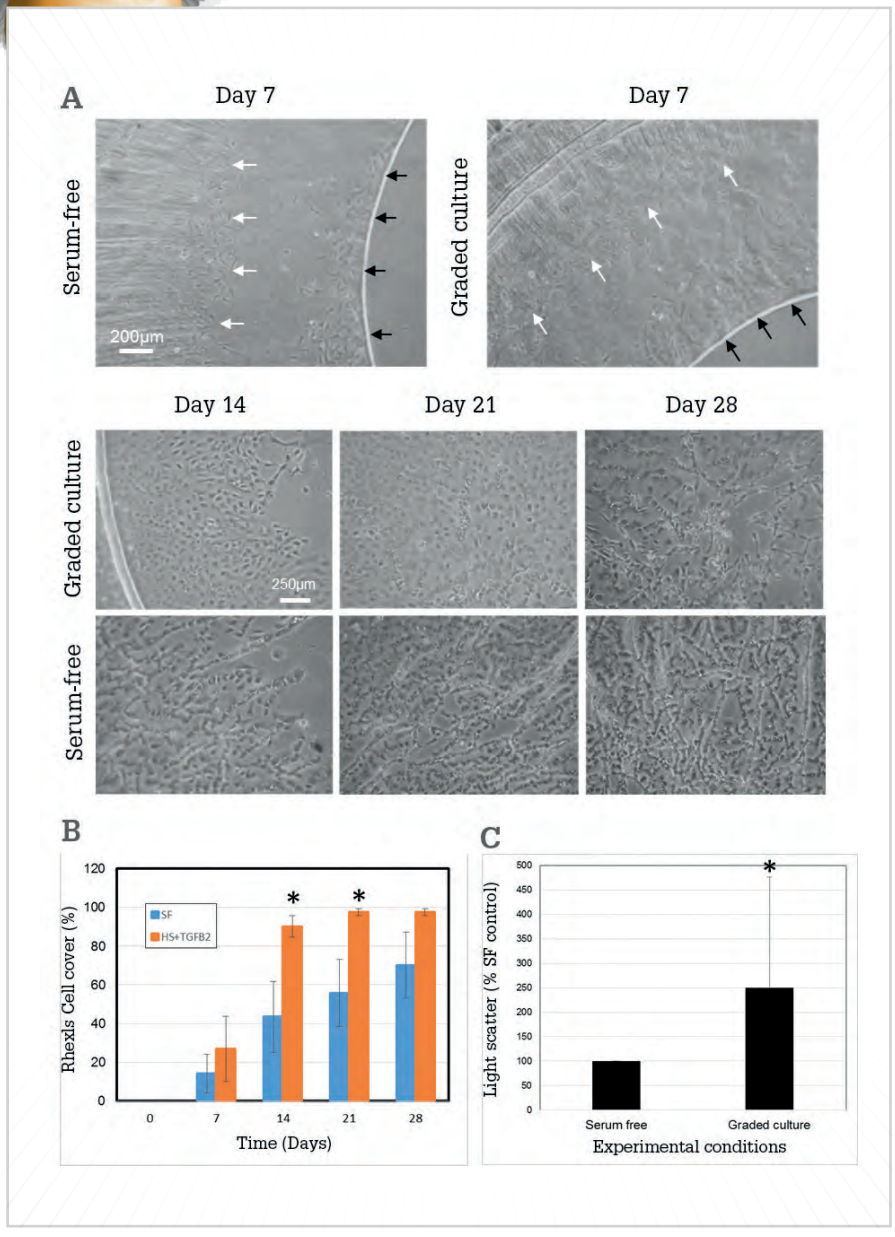

Figure 1. Graded medium regime enhances cell proliferation and migration. (A) Progressive migration of cells (white arrows=leading edge) over peripheral posterior capsule (Day 7); and beyond the rhexis margin (black arrows) onto the central posterior capsule (days 14, 21 and 28). (B) Cell coverage of the central posterior capsule (within the rhexis margin) in serum-free and graded culture conditions. (C) Light scatter in central posterior capsule after 28 days. Figures reproduced from the original study (1).

"Essentially, we began by performing bench-top cataract surgery on human donor eyes."

Model answers

We developed our in vitro capsular bag model with the above questions in mind, and with the over-arching objective of making a difference to clinical practice and patient outcomes. And to have the best chance of making a real difference, our view was that the model should reflect the human situation as accurately as possible. Other PCO models exist, from cell cultures to whole animals, but ours is the only fully human capsular bag model, and we believe it is the system most likely to be predictive of events in real patients.

It all started with a collaboration, initiated in the mid-90s, between University of East Anglia scientists and two ophthalmologists – Christopher Liu and Peter Davies – at the West Norwich Hospital. Essentially, we began by performing bench-top cataract surgery on human donor eyes. This meant that our system benefited from the same spatial organization and cell types that you find in real patients – and that seemed like a logical approach to the study of human PCO. Since then, we have modified the basic system in various ways and for different purposes. In particular, we have experimented with a range of culture conditions – minimal media, sustained high levels of supplements, timed addition of specific activators – to investigate the role of specific molecular components and pathways, which is an excellent way of teasing out the key factors that drive PCO in patients. We've also improved the way the artificial lens is mounted – in the latest model, the IOL is suspended – and we have made the whole system more reflective of real life by using human serum and human growth factors in the culture medium. We've always aimed to

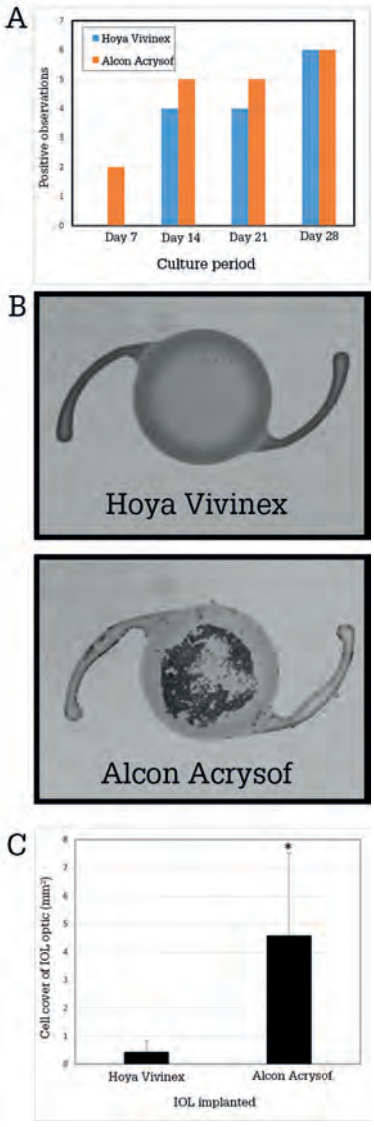

Figure 2. Comparison of HOYA Vivinex and Alcon Acrysof. (A) Cell outgrowth on IOL anterior surface: note no cell growth on Vivinex at Day 7. (B) Appearance of cell coverage per IOL at day 28. (C) Area of anterior surface covered by cells per IOL, day 28 (pooled data, n=6).

mimic post-surgical inflammatory events as realistically as possible, and we believe the latest version of our model (1; Box) goes a long way to achieving that.

Another advantage of our system is that we work with two matched eyes per experiment – that is, both eyes from a given donor are used, each receiving a different IOL. This dual approach enables us to compare the influence of different IOLs on PCO within a given donor, thus removing inter-donor variability from the system, which gives us much more confidence in predicting which IOLs are most likely to resist PCO in real patients.

Moving on

We're continuing to improve the model; for example, by mimicking longer-term changes associated with PCO following cataract surgery. In particular, we want to replicate regenerative features of PCO, such as the three-dimensional structures known as Elschnig's Pearls and Soemmerring's Rings. Both are known to cause light scatter and impaired vision; to prevent their development, we really need a model that allows us to better understand the etiology and test preventive mechanisms. To that end, we are working on ways to replicate these events within the time window permitted by our model. We also intend to examine a broad range of IOLs: different manufacturers, different shapes, different materials. The idea is to identify modifications that correlate with PCO resistance and which therefore should result in better outcomes for patients. It's very gratifying that we have received funding, from HOYA Surgical Optics and the Humane Research Trust, to develop our model – I am convinced that a system based on human tissues and growth factors is the best way to model human PCO.

Modeling a better future

It's not perfect of course – there's not an endless supply of cadaver eyes, so we don't always have as much material as we would like. But we're very grateful for every donation: each one allows us to move things forward a little, and each iteration of the model is an incremental step forward – an evolution that makes it better and more clinically relevant. And that's the point; we're trying to make a difference at the clinical level. Today, we are identifying marketed IOLs that are less susceptible to PCO, but tomorrow we will be helping develop next-generation IOLs with advanced resistance to a range of unwanted post-surgical sequelae. Time will tell!

"We intend to examine a broad range of IOLs: different manufacturers, different shapes, different materials."

Michael Wormstone is Professor of Ophthalmology at the School of Biological Sciences, University of East Anglia, Norwich, UK.

The author reports that he is currently funded by and acts as a scientific consultant for HOYA Surgical Optics.

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Solving the PRP Puzzle – an Inventor's Story

When it comes to patient comfort, sometimes the doctor knows best! Here's the tale behind the non-contact PRP solution.

By Alexandre Pedinielli and Francesca Amoroso

Like most stories of invention, ours is one of persistence. It started when we were working together at the CHI de Créteil Eye Clinic in France. The clinic had been in possession of a Navilas laser since 2016, and we were lucky enough to get the chance to use it. It had real benefits over conventional lasers, such as the precisely pre-planned laser positioning and faster PRP sessions (using a contact lens). A non-contact treatment option was provided for the focal laser delivery. Still, such a solution was not available when it comes to the periphery – something that would really improve patient comfort.

At a Glance

- *While working at the CHI de Créteil Eye Clinic, Alexandre Pedinielli and Francesca Amoroso came up with the idea for a non-contact PRP solution and asked OD-OS if they could incorporate it into their Navilas laser*
- *Upon being told no, they designed their own device from a lens and plumbing pipe – creating the first ultra wide-field non-contact PRP treatment approach*
- *The doctors collaborate with OD-OS to turn the concept into a widely-available commercial solution.*

As ophthalmologists, we want to see as much of the retina as possible – and that includes the periphery. So why wasn't non-contact PRP an option on the Navilas? We decided to go to the source – OD-OS, the creators of Navilas – and ask them: "Why don't you have a non-contact widefield objective?" They told us that it wasn't possible, which we didn't believe. We thought we knew better – and we resolved to create one ourselves.

The major stumbling block? Neither of us had ever tried to build such a device before. Our only combined experience of inventing something was a computer program developed by Alexandre in the early days of OCT-angiography. Back then, the focus was on qualitative data, but Alexandre was more interested in quantifying vascular density. Alexandre decided then that instead of trying to adjust someone else's software, he would just invent his own. And that's what we tried to do with the PRP solution – think outside the box to make something new.

Puzzle solving – Mario style

We came up with a design and visited a plumbing store (!) to find a pipe with the right dimensions. We took a lens usually used for fundus exams and fixed the two together to create a rudimentary non-contact device. We couldn't wait to try it out. Would it work at all?

Thankfully, it did; we had found a way to see the periphery without touching the eye at all.

Excited, we took our device to OD-OS. The initial reaction was that this solution might not work out. Undeterred, we asked again. And for a second (and possibly third) time, they said it wasn't possible. It took us some time to convince the company but

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The other side...

with OD-OS Clinical Project Manager, Ulrike Rahn

What stopped you from creating a non-contact PRP solution?

We actually had a non-contact PRP objective similar to our current focal non-contact objective in our very early product versions. Though it was good in a certain number of requirements (such as distance to the eye), it was not truly successful, as it made it too difficult to treat the far periphery. We only found our first widely used product for peripheral applications when we turned back to a contact lens solution. The doctors were perfectly trained to use these lenses, and to manipulate the lenses in a way to get out far enough. With that success, we dropped any idea around a non-contact peripheral treatment.

What did you think when you were approached by Pedinielli and Amoroso?

Not possible! That was the very first (and second?!) thought. But Dr Pedinielli and Dr Amoroso kept insisting that this idea would work and be a really great addition to the laser. We decided to take a look at the imaging and simulations taken with their "hand-made" objective. We started to ask them about critical aspects, such as field of view. Question by question, they convinced us.

Did it take long to turn their idea into a reality?

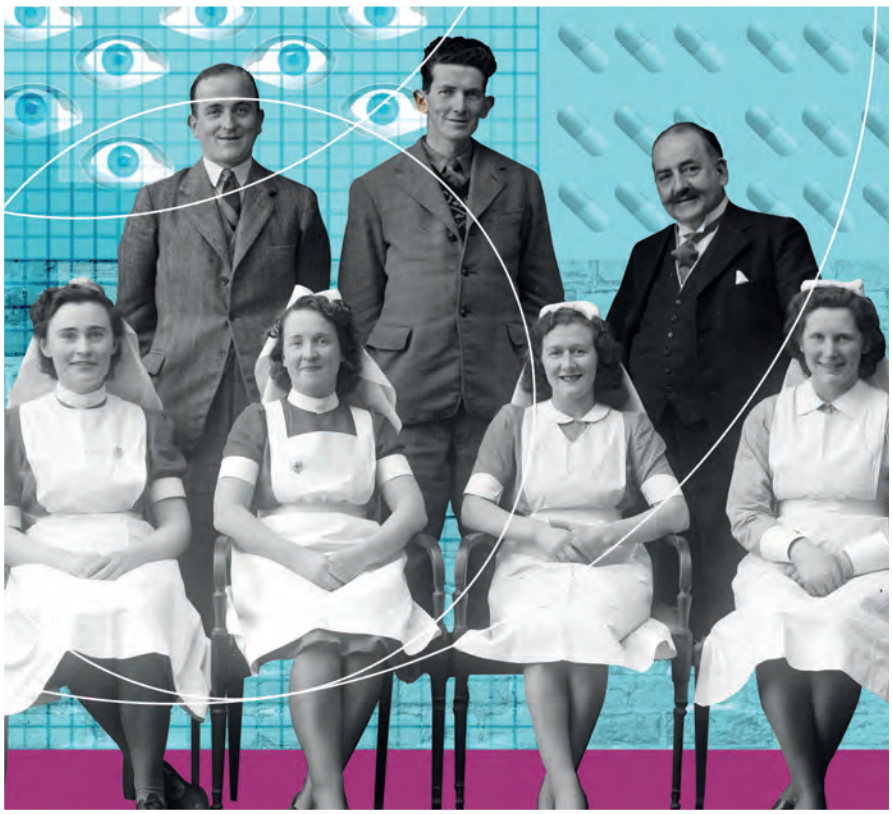
Yes and no. It took a while to get everyone at the company convinced that it could work – and to find the right team to make it happen. Once this was done, it was relatively fast.

Would you consider working with the doctors again?

Definitely! It is always a pleasure to work with enthusiastic and clever people. It was amazing how patiently they answered all our questions again and again. I am looking forward to a continued cooperation with them in the future.

How can clinicians offer new perspectives to companies?

Clinicians usually know better than companies what they need. In other words, they can more easily detect where an improvement can be made, either to usability or to the treatment itself. Although usability issues can be noticed by employees, doctors might be able to propose a solution – "it would be nice if…" – something that is impossible to know from observation alone. Therefore, all medical device companies are in need of ongoing user feedback – positive as well as negative – to make products even better. Clinicians usually have a much more objective opinion of how good a solutions really is!



finally, they liked what we had done and asked to incorporate it into a commercial design. Of course, we said yes. Together, we came up with what would later become the non-contact widefield objective – a navigated non-contact PRP solution, with flexible, pre-planned spot positioning. It works the same as the Navilas contact PRP solution for Navilas, but with one added benefit: comfort. For the patient, it means no longer having to keep a lens on your eye. For the clinician, it requires you to simply sit behind the device and simply press the pedal with your foot.

Of course, there is always room for improvement. The current solution is a fraction slower than a conventional contact lens, as the precision eye tracking Navilas software sometimes pauses to find the correct registration and spot positioning. Still, I am confident we could make it as fast, if not faster, with a few slight modifications. We are currently running a study to measure the reliability, comfort, and safety of non-contact PRP compared with conventional contact lenses. We chose these three treatments parameters because they are the most important for patients and clinicians. Seven people are taking part in the study, although 20 have been treated using the non-contact PRP without any problems, and we hope to publish the final results later this year.

Be proactive and persistent

If our story tells you anything, let it be this: as physicians, we should stop taking "no" for an answer. Navilas had tried to make a non-contact PRP solution before – but didn't succeed because they didn't have the focus as we have as clinicians. Working with patients gives us an understanding that companies just don't have – it's our job to share that insight. If you see something that could be improved, improve it – don't let "no" stand in your way. We should all be striving to make ophthalmology better. Remember, you don't have to be an inventor to create something worthwhile; sometimes all it takes is a clinician who thinks outside the box, and a partner who is willing to listen.

60 seconds with co-creator, Francesca Amoroso

Why did you decide to develop a non-contact PRP device?
To try to go beyond the limits of contact lens laser technique and create something new to improve the comfort of patients during treatment.

What is the key benefit of a non-contact solution?
The treatment is more comfortable for the patient – and for the doctor, too.

Why an ultrawide-field lens?
It allows us to see all the way into the far periphery of the eye. I know that because I tested it on myself during the creation process – in training mode, of course!

Would you call yourself an inventor?
Dr Pedinielli and I tried to find something new to ameliorate the conventional laser technique, so… I guess we are!

Do you plan to create anything else in the future?
We will focus on this project for the moment, but maybe in the future… Why not?!

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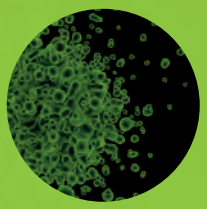

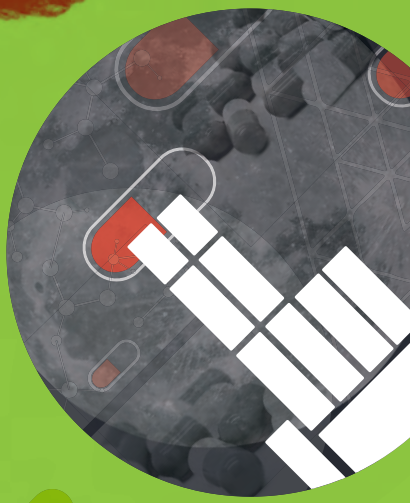

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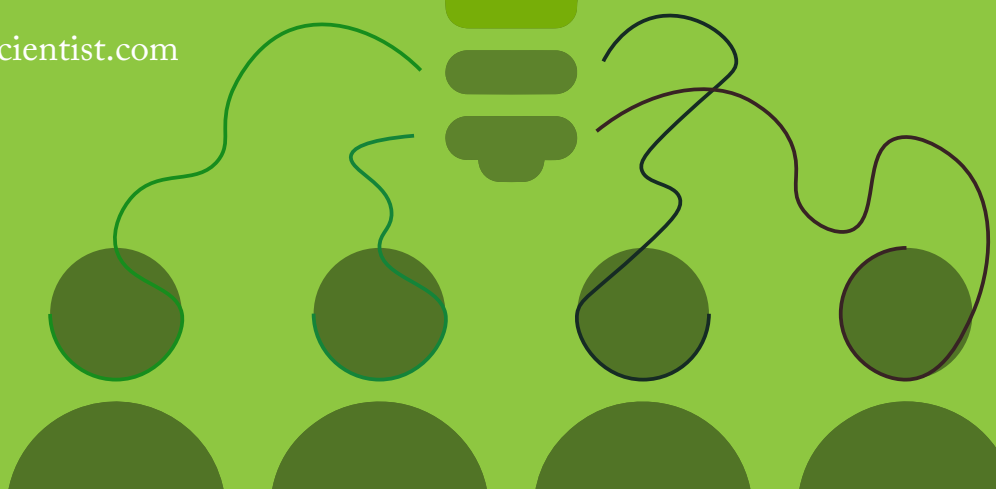

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Amos Twinamasiko reflects on his legacy as founder of a pioneering ophthalmology department.

With Tú Trần, Arlene Bobb-Semple, and Simon Arunga

Figure 1. Prof Twinamasiko and Dr Arunga.

Mbarara University of Science and Technology (MUST) is not the largest university in Uganda – it is not even close. Set over two campuses on the banks of the Rwizi River in southwest Kampala, MUST has just 3,000 students, yet is recognized as one of the best training institutions in East Africa – teaching ophthalmologists from Uganda, Burundi, Democratic Republic of Congo, Ghana, Guyana, Rwanda, Sierra Leone and South Sudan. The reason why can be attributed, almost entirely, to one professor: Amos Twinamasiko.

Twinamasiko founded the MUST Department of Ophthalmology in 1993 and has been devoted to it ever since. He transformed MUST from a makeshift office to what is now a free-standing eye hospital, providing excellent patient care, a vibrant residency program and multi-year funded research programs in microbial keratitis and diabetic retinopathy.

In Sub-Saharan Africa, one of the most commonly referenced human resources challenge is the unequal geographic placement of providers, especially of specialists. Twinamasiko could have stayed in the capital, Kampala, where he qualified in medicine and ophthalmology, but he chose to return to his home region and commit himself to the public sector. His decision shaped the lives of more than just his patients. Arlene Bobb-Semple, winner of the 2017 ophthalmology resident research award – a prize recognizing research among the regional College of Ophthalmology of Eastern, Central, and Southern Africa (COECSA) – credits her success to Twinamasiko. "When I was a student, I admired his excellent work ethic and his humility," she says. "I aspire to be an exemplary ophthalmologist who can leave a legacy in my country, upholding my ethical duties and responsibilities while remaining humble." Bobb-Semple went on to train as a vitreoretinal surgeon in Tanzania, and has since returned to Guyana to practice. Day in day out, she maintains the philosophy and approach to patient care that Twinamasiko instilled in her and all of his mentees.

As the Department nears its 25th anniversary – and as Twinamasiko approaches his retirement – Bobb-Semple and fellow mentees, Simon Arunga and Tú Trần, interview him about his inspiring career.

At a Glance

- *Professor Twinamasiko is the founder of the Mbarara University of Science and Technology Department of Ophthalmology, responsible for training ophthalmologists from east African countries and beyond*
- *He also started a residency program with the Ruharo Eye Centre, and admitted the first resident in 2003*
- *Professor Twinamasiko managed to secure funding for the department, and develop the infrastructure*
- *In May 2019, the largest group of graduates since its conception will leave the department.*

What were the major obstacles f or establishing and expanding the department?

AT: At the start, I felt like being asked to cultivate the fields without any tools. It was up to me to figure out how to take care of patients. Infrastructure was lacking. We had one room as an office that I shared with another lecturer, and another room that doubled as the clinic and teaching space for medical students. In time, we were given a bigger room, and later a second room when I took on an administrative role. Eventually, the government provided a fair amount of ophthalmic equipment, but we could not deploy it without an operating theater space.

Recruiting ophthalmologists was another major challenge. Not only was there a ban on recruitment of additional faculty because of a shortage of funds, the job contracts that did exist were so poor that nobody would apply. For several years, I was the only full-time faculty member. To train medical students and residents, we depended on

Figure 2. Humble beginnings: A medical student learning to measure IOP using a Shiotz tonometer in the old eye clinic. The same room acted as an office, consultation room, minor procedures room, and storeroom.

in-service training, and we admitted the first resident in 2003.

To expand the faculty beyond just me, Christoffel-Blindenmission (CBM) agreed to support the first one to two years of faculty salaries, then transition them to the university payroll. One of the first to join was Professor Kenneth Kagame. Later, the fourth faculty member was added when MUST hired a resident who graduated from our program.

In July 2013, the Ophthalmology Department moved into the Mbarara University and Referral Hospital Eye Centre (MURHEC). This was a game changer that could have not been achieved without the Eastern Africa College of Ophthalmologists (EACO), which has since merged with the Ophthalmological Society of Eastern Africa (OSEA) to form COECSA. The EACO received a European Union/Sightsavers/Light for the World grant that included infrastructure development. This grant allowed us to establish an eye hospital with space for outpatients, inpatients, operating theaters, investigations, imaging and teaching. It opened up opportunities for expansion that we never had before. With new facilities, we could offer a wider variety of eye care services to a greater number of patients, we could attract more applicants to the residency program and more international collaborators, who have helped in the training of both faculty and residents, provided more equipment, and opened up opportunities for research collaborations. Of course, not all is perfect. A major challenge is the shortage of dedicated morning, evening and night shift nurses, which greatly affects quality of care.

Figure 3. Professor Twinamasiko performing a slit lamp exam in new clinic. (Above)
Figure 4. Professor Amos Twinamasiko. (Left)

the grace of Dr. Keith Waddell and the other ophthalmologists at Ruharo Eye Centre, which is a storied, church-based eye hospital a few kilometers away from MUST. I realized the only way to attract and retain ophthalmologists was to start a residency program. Ruharo Eye Centre generously offered to host residents for

During the Department's first decade, donors turned you down because they didn't see the need for another eye service when the well-established Ruharo Eye Centre was nearby. What changed?

Figure 5. Professor Twinamasiko in South Africa learning ECCE (2004).

We have to be thankful for the former EACO. Approaching international donors as a united consortium of university eye departments made all the difference. Indeed, potential donors initially felt that there was no need to develop another eye unit in Mbarara when Ruharo was doing so well. Most donors thought training ophthalmologists was too expensive and the focus should be on training mid-level providers. In 2000, I was invited to a WHO meeting that brought together representatives from different university eye departments and major NGOs involved in eye care. The meeting resolved in a call for increased output of ophthalmologists and harmonization of quality, but the NGOs would not entertain funding requests from individual institutions. Hence, EACO was launched in 2005 to mobilize financial support and harmonize training programs. For the first time, the eye departments came together to present a united proposal for the development of ophthalmology departments at universities in East Africa. Even the oldest residency program at University of Nairobi needed support to develop further.

Establishing an eye hospital to house an academic ophthalmology department has broadened our horizons massively, leading to a more self-sustaining system. We can now train and retain ophthalmologists within Southwestern Uganda, leveraging our new capacity to build partnerships with the Church of Jesus Christ of Latter-Day Saints, Massachusetts Eye and Ear Infirmary, Orbis, and the Fred Hollows Foundation. We have also sustained outreach for high volume surgical camps with support of the Pentecostal Church in the USA.

Acquiring the funding for infrastructural development was a battle, but implementing the project was also taxing on you. Can you tell us about that experience?

It took a high degree of vigilance and persistence. I served as an accounts auditor, architectural consultant and even a quantities surveyor. I cared for our eye hospital as if it was my personal home. Towards the latter stage, 90 percent of the funds were paid but only 60 percent of the promised work had been done. After an audit of the books, we concluded that the consultant and contractor had conspired to defraud the funding agency. Our construction project was not the only one succumbing to this, but to overcome this obstacle, our selfless friends at the Kilimanjaro Christian Medical College (Moshi, Tanzania) gave us a share of their allocated grant budget for construction. This allowed us to finish the building and purchase furniture, equipment and supplies.

Any construction project involving multiple beneficiary countries, international donors and diverse stakeholders is susceptible to being slowed by bureaucracy. I must congratulate the MUST university administration for working expeditiously to seize this opportunity. They promptly signed the commitment to participate in the project, allocated us land, and supported us at every stage of the construction, so that we were able to get the most benefit from the project. I will forever be grateful.

You have welcomed many international collaborators over the years. What makes a successful partnership?

For a collaboration to work well, it must be mutually beneficial. Partners from more well-resourced institutions may mobilize resources and provide sub-specialty and technical support. In return, they enhance their professionals by exposing them to a wider working environment, which provides them with opportunities to expand their research fields and to make a greater contribution to humanity. The Church of Jesus Christ of Latter-day Saints and the National Health Service Bristol Hospitals are the most recent examples; they procured posterior segment lasers for us, and will bring their specialists to train our faculty and residents. In the future, foreign specialists and trainees can rotate through our department to provide this treatment. Lastly, the European Union authorized this project in 2009, not long after the 2008 Great Recession. What we have been able to achieve is a reminder of what good their support has done for humanity, despite the challenges and instability their nations faced.

What were the most influential moments in your early career?

My first career turning point was moving to the Church of Uganda Kisiizi Hospital in April 1981. I qualified as a doctor from Makerere University in 1980, during some of the most difficult days of Uganda. The country was transitioning from Idi Amin's rule and several government changes in a short period. Like all other sectors, the medical services were run down. It was difficult to practice medicine in the public sector and Kampala was very insecure. While on vacation, I rotated at a church-based hospital in southwestern Uganda:

Figure 6. Professor Twinamasiko with colleagues at Kisiizi (early 1980s).

Kisiizi Hospital. I learned that they were looking for a Ugandan doctor to join the two expatriates running the hospital. I was attracted to the superlatively high-quality services they offered and the positive attitude they had, even under difficult conditions. I requested to be posted to Kisiizi after medical school, and it was there I learned many aspects of medicine and surgery.

While contemplating how to further my career, we were visited by an ophthalmologist from CBM, the late Dr. Joseph Taylor. He offered me a six-month trial training as a cataract surgeon in Mvumi Hospital in central Tanzania under the enthusiastic lead ophthalmologist, Dr. Allen Foster. Realizing the shortage of ophthalmologists in East Africa, I saw it as an area where I had the potential to make a real impact. I then returned to Kisiizi Hospital to strengthen the eye care services we already offered. We ran many mobile outreach clinics and surgical camps throughout southwestern Uganda and it was then I made up my mind to train as an ophthalmologist.

The second career-turning point was my move to MUST. CBM sponsored me to undergo one-year training at the University of Zimbabwe, and later residency training at Makerere University. Upon finishing, I was committed to move to Mbarara to work at Ruharo Eye Centre. CBM determined Ruharo was the optimum base to provide coverage for the Southwestern region, but Ruharo was not ready to receive me. By chance, I discovered MUST needed an ophthalmologist. I hesitated slightly because working conditions in government hospitals at that time were notoriously bad for healthcare providers. Nevertheless, I had no desire to work in Kampala. So, with my heart set on rural Uganda, I moved to Mbarara and became the sole MUST ophthalmology faculty member in December 1993. The first piece of equipment I used was borrowed from Kisiizi Hospital.

What advice do you have for young ophthalmologists in Uganda and other low- and middle-income countries?

I should start by saying there are greater opportunities for training and career improvement than there were 25 years ago. In Uganda, the potential for improved welfare is also rising with renewed interest in health insurance. However, the profession is also becoming more demanding, with the emphasis shifting from quantity to quality. For those in training institutions, the focus is now on workload analysis. There is also increased emphasis on having more formal research training through PhDs and publications.

Ophthalmology is still one of the marginalized specialties in Uganda. We need to keep pressing to raise the profile of ophthalmology, as we have tended to sit back and let other specialties and non-healthcare professionals determine our course. Ophthalmologists should advocate for the elevation of health care in general, with ophthalmology having a role in public health.

Much as there is potential for better earning capacity for ophthalmologists in the near future, the practice of medicine always involves sacrifice. Even as a more senior practitioner, you will always find times where you are required to serve much more than you will be remunerated for directly. But do not worry; you will be blessed in other ways. Always remember to find a career and other aspects of life like family, health, and faith. In the final analysis these determine the quality of your life.

In 2014, you gave up your position as Head of Department. What motivated your decision?

I transitioned the Head of Department position to a younger ophthalmologist: Dr. John Onyango. It was appropriate because I had a colleague who was extremely qualified to take over and thus, share the responsibility, so I could pay attention to other aspects of professional life that had lagged behind because of my administrative duties. It is very gratifying to see the department running at a faster pace under such young, enthusiastic leadership.

As my retirement approaches, I feel comfortable that the department is in good hands and supported by active ophthalmologists who will be able to take it to greater heights, especially with the ever-increasing opportunities for international collaborations. I am confident that, under Dr. Onyango's leadership, we will realize the vision of MUST Ophthalmology Department to become a center of excellence for training eye care professionals and research. Last year, we treated nearly 9,000 patients, operated on 464, and examined 1,513 patients in outreach. In May 2018, we graduated a class of six residents – the largest in our history. We will also graduate six in May 2019. The future is bright.

Tú Trần is an MD student at the University of Minnesota, USA.

Arlene Bobb-Semple is a MMed alumna of Mbarara University of Science and Technology, Uganda and is now a practicing Vitreoretinal surgeon in her home country, Guyana.

Simon Arunga is a Clinical Lecturer in Ophthalmology at Mbarara University of Science and Technology, Uganda, and PhD Student at London School of Hygiene and Tropical Medicine, UK.

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Imaging the Future of Retina

Sitting Down With… Paulo Stanga,
Consultant Ophthalmologist and Vitreoretinal Surgeon, Manchester Royal Eye Hospital; Professor of Ophthalmology and Retinal Regeneration, University of Manchester; Director of the Manchester Vision Regeneration (MVR) Lab at NIHR/Wellcome Trust Manchester CRF, Manchester and Lead Vitreoretinal Surgeon, London Vision Clinic Retina, London

Why ophthalmology – and why vitreoretinal surgery?

My medical degree taught me that I didn't want to pursue general medicine! But as for what to do after qualifying, I couldn't decide between ophthalmology and plastic surgery: both require some artistry, which appeals to me. After all, doesn't the definition of medicine refer to the 'art' of healing? Anyway, I loved looking inside the eye, and when I was told that vitreoretinal surgery was the most complex subspecialty in ophthalmology, I knew it was the one for me. It was the challenge, I think.

You are currently based in Manchester and London, where have you practised previously?

Since graduating in 1990, I've been on the move: first, New York, and then London, Liverpool and Manchester, and now back in London. I made the move back down to London recently because of the exciting opportunity to work alongside Professor Dan Reinstein and his team in opening London Vision Clinic Retina.

"I loved looking inside the eye, and when I was told that vitreoretinal surgery was the most complex subspecialty in ophthalmology, I knew it was the one for me."

How has your focus shifted over the years?

In New York, during my clinical research fellowship with Harvey Lincoff, I worked on ICG angiography for visualizing choroidal disorders, and on interferon (IFN) alpha 2a (IFN) pharmacotherapy for age-related macular degeneration (AMD) and choroidal neovascularization (CNV). At that time, IFN was usually administered subcutaneously, but Harvey had developed a novel balloon delivery device with a double-lumen catheter, which could deliver IFN directly under the macula. We showed that this procedure stabilized CNV for six months; given that the standard treatment at the time involved photocoagulation of subfoveal CNV, which is quite traumatic, this finding perhaps should have received more attention. Unfortunately, at the time we were all looking for a permanent cure, something we do not even have at present.

Subsequently, I started working on time-domain OCT technology with Zeiss Meditec, and then got interested in Topcon's spectral domain OCT. Swept-source technology is marvelous: it enabled Prof. David McLeod and me to image the cortical vitreous in vivo for the first time. We could see the optic nerve, the macula, and areas temporal to the macula, all in a single scan – and we could visualize structures, such as the Bursa Premacularis and the Space of Martegiani. The variation in cortical vitreous anatomy could perhaps partly explain why not all patients respond to enzymatic vitrectomy – efficacy that perhaps depends on how much posterior hyaloid remains attached. It was just fascinating. Incidentally,

"Swept-source technology is marvelous: it enabled Prof. David McLeod and me to image the cortical vitreous in vivo for the first time."

I suspect that study may have had at the time the widest age-spread of any vitreous imaging study– our patients ranged from four to one hundred years old!

Familiarity with imaging systems was a great help in my later work, not least when we set up a monthly Paediatric Retinal Regional Service with Susmito Biswas in 2010. We developed a new treatment for exudative retinal detachment in Coats' disease: namely, scleral/transchoroidal drainage of the subretinal fluid followed by ultra-widefield fundus autofluorescence angiography-guided laser treatment and anti-VEGF therapy. It has been very rewarding to see this technique being adopted by other hospitals. Furthermore, our widefield, swept-source OCT imaging studies revealed abnormalities in the fovea of the fellow eye – a novel finding that suggests we may need to rethink Coats' disease, which has traditionally been considered a unilateral condition.

"Vitesse uses a needle that oscillates at 1.5 million times/minute; essentially, it liquefies the vitreous by breaking up the collagen fibers into tiny fragments."

What are you working on now?

I am still interested in ultra-widefield imaging, but I can't do everything, so at present I am focused on two main fields of work. I am UK Chief Investigator in a collaborative project with Professors Robert MacLaren and Graham Black focusing on gene therapy for X-linked retinitis pigmentosa. The approach requires complex surgery – creating a bleb in the retina for vector placement – but our Zeiss microscope-mounted OCT system is a great help, and everything is going very well.

The other main project is part of my long-standing collaboration with Bausch and Lomb, which started with work on improving small gauge transconjunctival vitrectomy and the development of the Stellaris platform in Europe, and then moved on to the development of the Vitesse hypersonic vitrectomy system. Vitesse uses a needle that oscillates at 1.5 million times/minute; essentially, it liquefies the vitreous by breaking up the collagen fibers into tiny fragments. We started working on this system in 2012, beginning with cadaveric eyes (porcine and human) before moving onto experimental surgery. Since then, I have performed the first ever hypersonic vitrectomy in humans in 2017 and then the first ever in Europe in 2018. The FDA approval for Vitesse was based on work we did in Manchester, at the University of Manchester and the Manchester Royal Eye Hospital; we had to, amongst others, do histopathology and electron microscopy studies after the use of both a guillotine and a hypersonic vitrector to study how the vitreous and the retina reacted to hypersonic energy, something not previously done, optimize vacuum settings, and determine how effectively it removed vitreous compared to a guillotine vitrector, and so on. It required a large, collaborative team effort, and was a great achievement. Certainly, a fascinating time in my career.

Over the course of 2018, I gradually expanded my private practice to 138 Harley Street, Central London. As my children are living in the South, this means I get to visit them more often and I am now finally seeing my patients here at London Vision Clinic Retina.

What next?

The team and I at London Vision Clinic Retina will continue working on expanding and enhancing the services we can offer to our patients.

I think I will always maintain an interest in medical and surgical retina, cataract surgery, eye trauma, R&D of new therapies, imaging, laser and surgical technologies – watch this space!

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use VYZULTA safely and effectively. See full Prescribing Information for VYZULTA.

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024%, for topical ophthalmic use.

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17) in full Prescribing Information]*.

5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS

The following adverse reactions are described in the Warnings and Precautions section: pigmentation (5.1), eyelash changes (5.2), intraocular inflammation (5.3), macular edema (5.4), bacterial keratitis (5.5), use with contact lens (5.6).

6.1 Clinical Trials Experience

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

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 µg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose) *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

Embryofetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose, on a body surface area basis, assuming 100% absorption). Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA in human milk, the effects on the 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 VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

8.4 Pediatric Use

Use in pediatric patients aged 16 years and younger is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

8.5 Geriatric Use

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per dose, bid. The systemic exposures are equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

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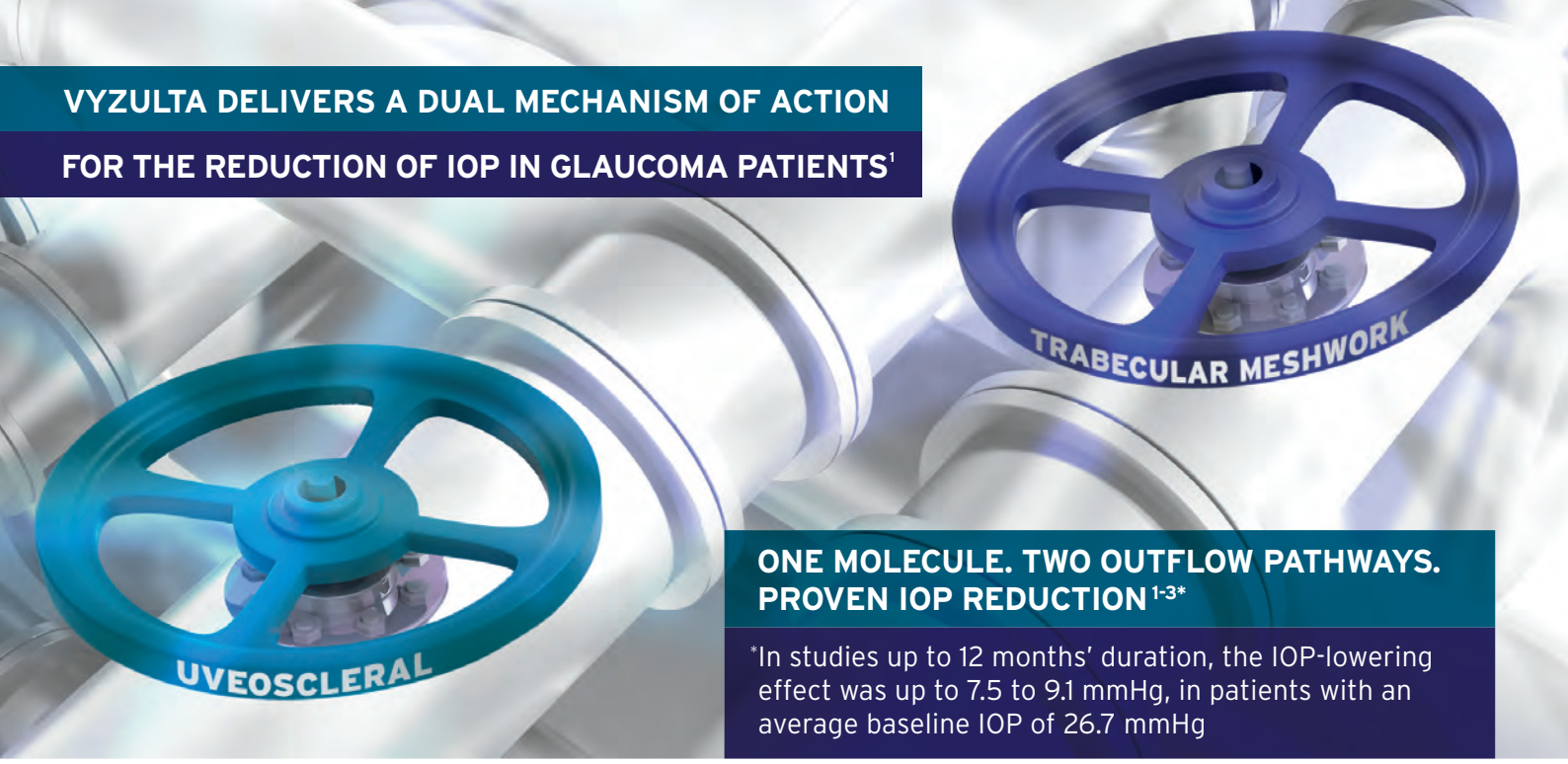

VYZULTA DELIVERS A DUAL MECHANISM OF ACTION FOR THE REDUCTION OF IOP IN GLAUCOMA PATIENTS[1]

ONE MOLECULE. TWO OUTFLOW PATHWAYS. PROVEN IOP REDUCTION[1-3*]

*In studies up to 12 months' duration, the IOP-lowering effect was up to 7.5 to 9.1 mmHg, in patients with an average baseline IOP of 26.7 mmHg

INDICATION

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

- Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent
- Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation
- Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation
- Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema

IMPORTANT SAFETY INFORMATION (CONTINUED)

- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients
- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration
- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

For more information, please see Brief Summary of Prescribing Information on previous page.

References:

1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. 2017.
2. Weinreb RN, Sforzolini BS, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology*. 2016;123(5):965-973.
3. Medeiros FA, Martin KR, Peace J, Sforzolini BS, Vittitow JL, Weinreb RN. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR study. *Am J Ophthalmol*. 2016;168:250-259.

For more information about VYZULTA and how it works, visit vyzultanow.com

BAUSCH + LOMB

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(latanoprostene bunod ophthalmic solution), 0.024%