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the Ophthalmologist™

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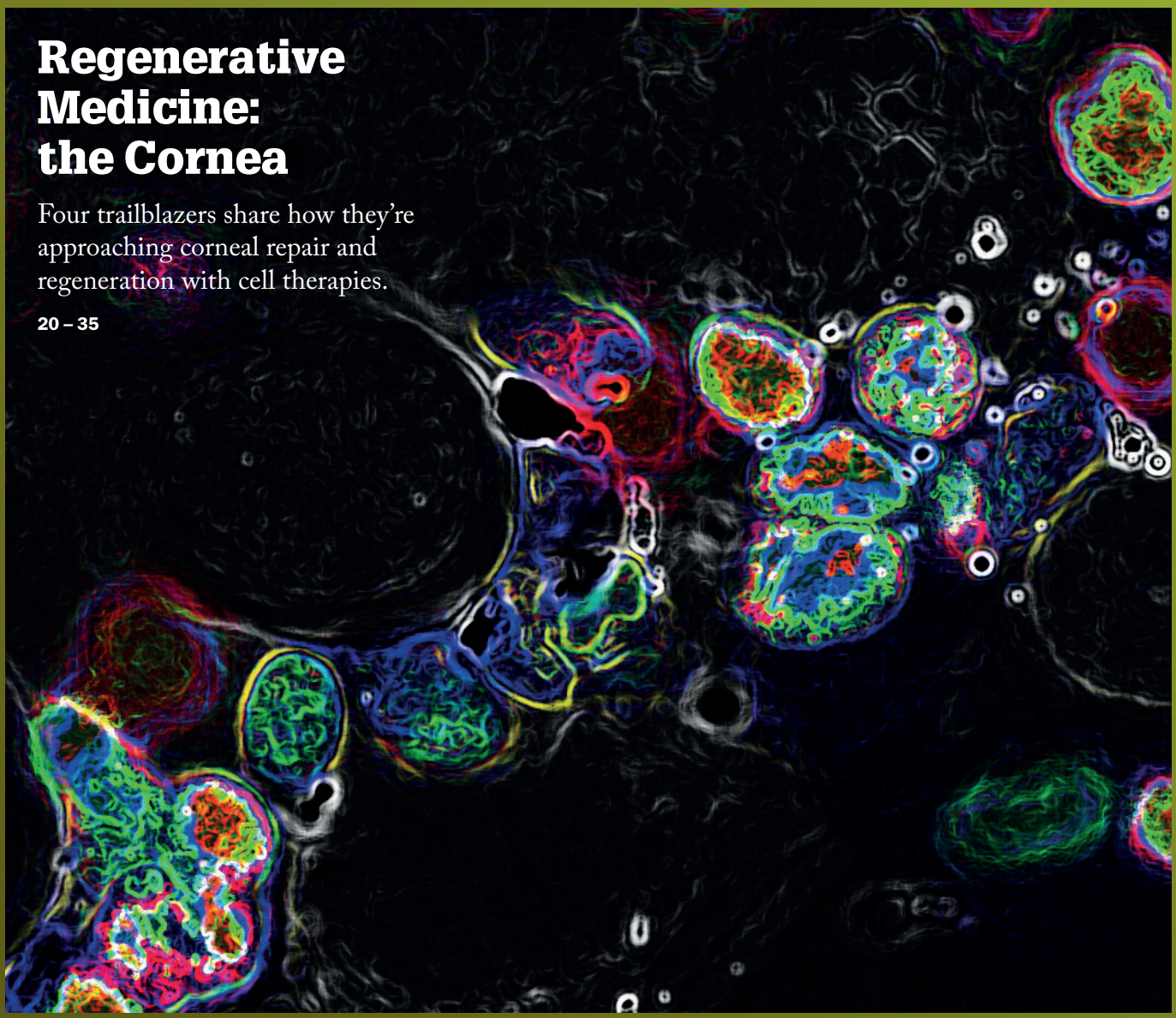

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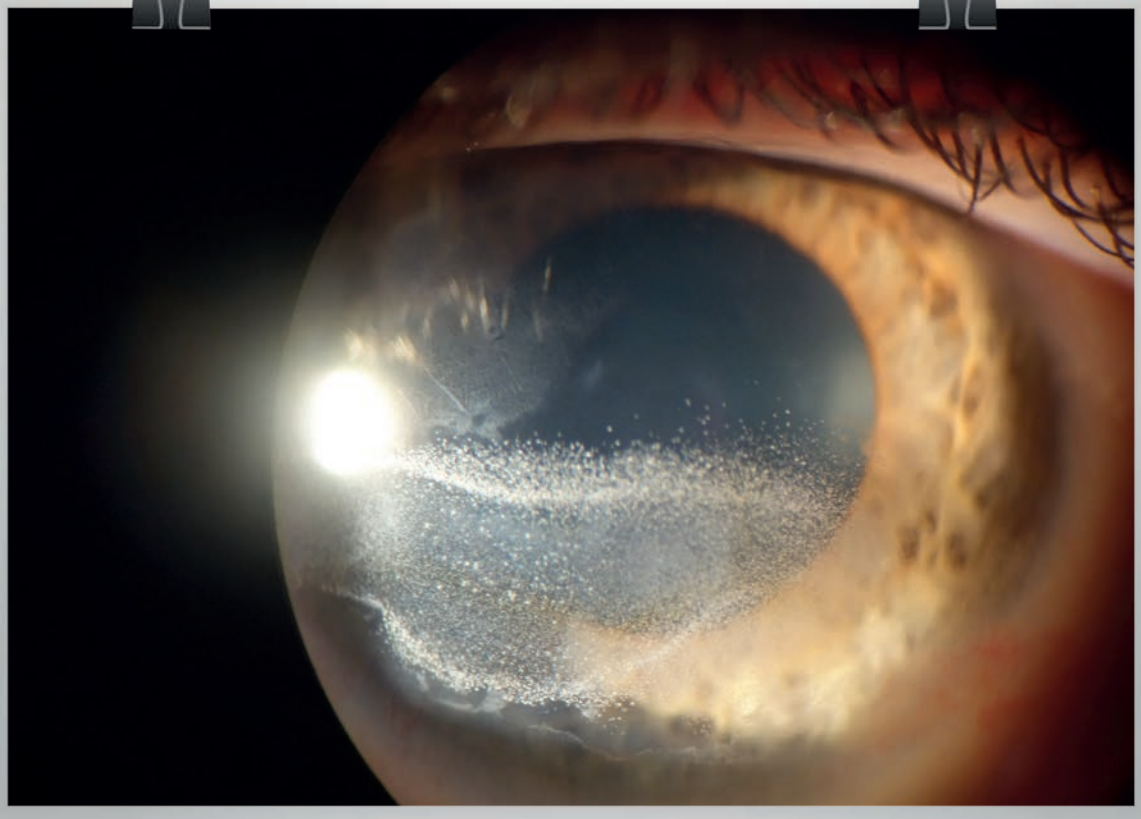

Corneal Cosmos

Aida Drljević and Amra Nadarević Vodenčarević share an image of corneal dystrophy in a female patient. Nadarević Vodenčarević says, "We both work in Health Center Tuzla, Bosnia and Herzegovina, and all our ophthalmic imaging is performed using equipment that's now more than 30 years old."

Image courtesy of Aida Drljević and Amra Nadarević Vodenčarević.

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

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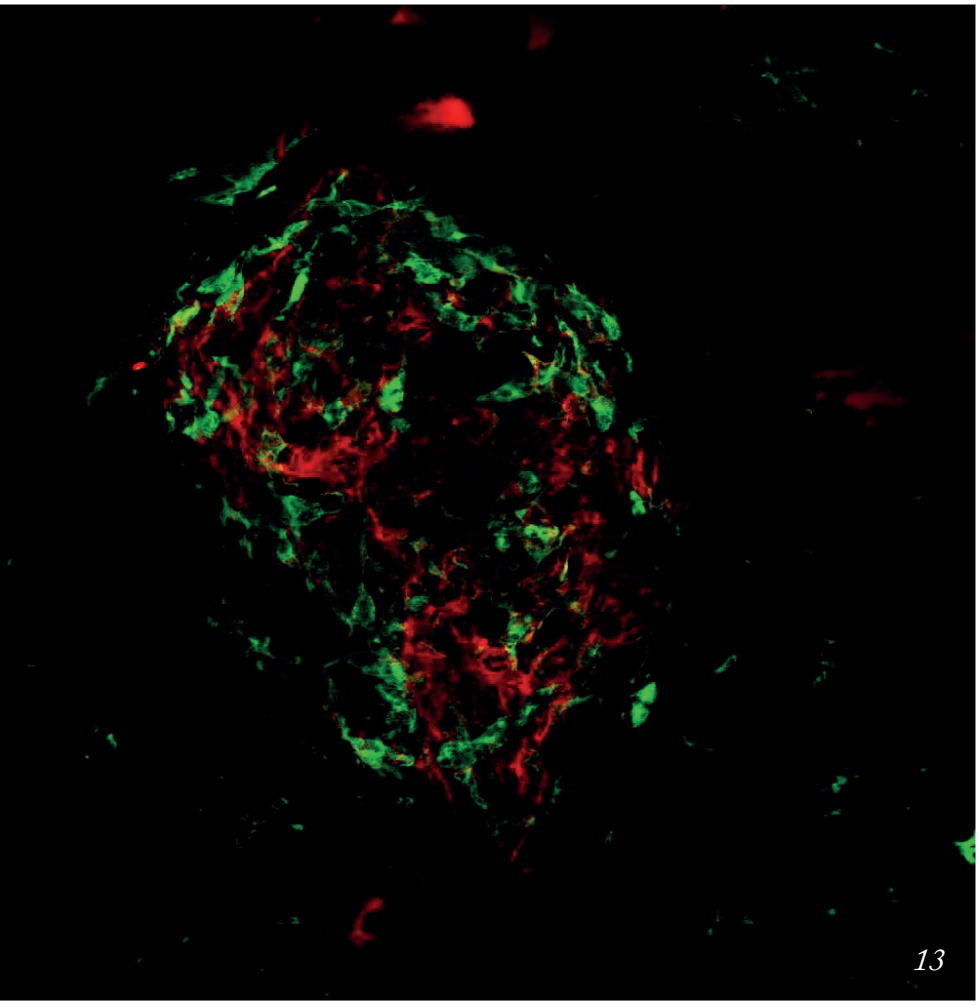

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Corneal endothelial cell basement stained in different neon colors. Credit: Wikimedia commons, User Zhigou.he

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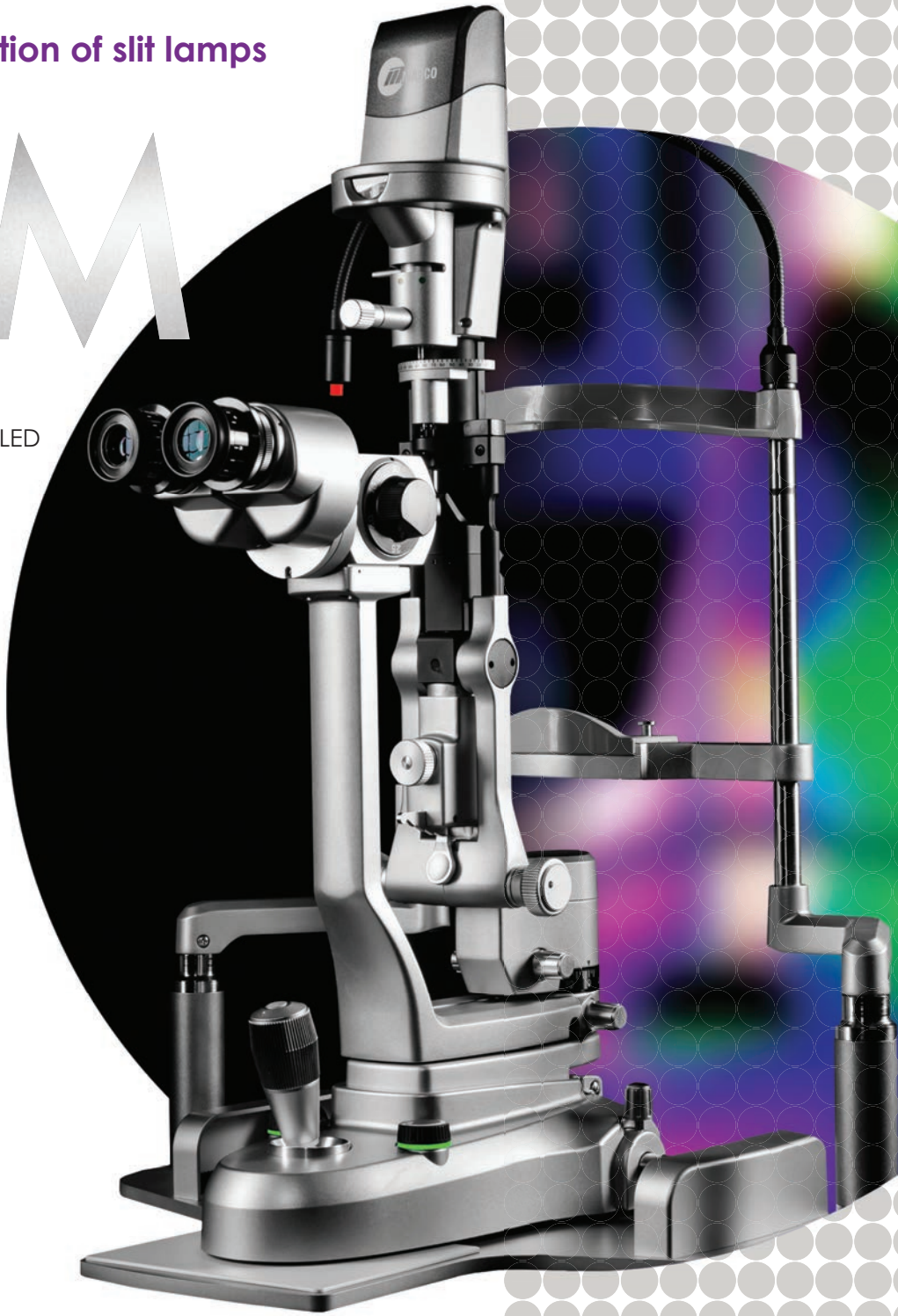

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Celebrating

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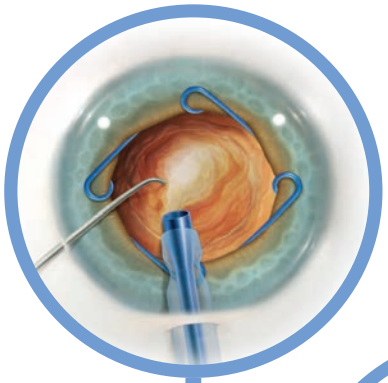
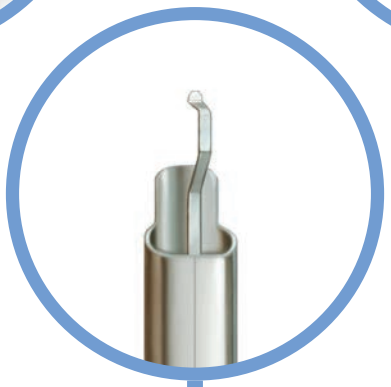
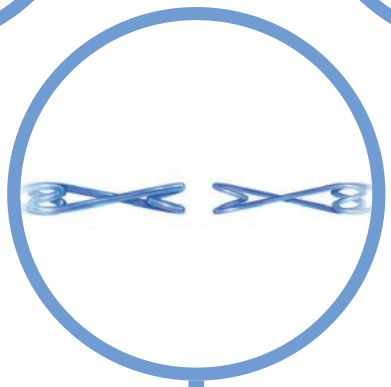


2007
Introduction of the Malyugin Ring

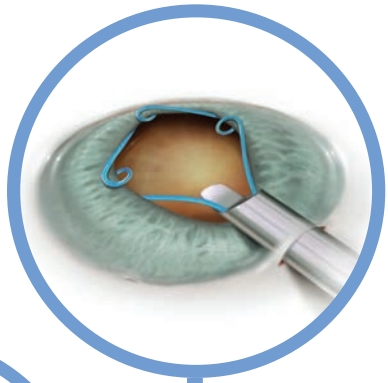


2014
Implementation of the Osher Modification

2014
1,000,000th Malyugin Ring Shipped



2016
Introduction of the Malyugin Ring 2.0



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International CXL Experts´ Meeting

Zurich, Switzerland
Nov 30 - Dec 2, 2017

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Abstract deadline:	Sep 29, 2017
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Regular registration:	Oct 31, 2017

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Friday, Dec 1
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Saturday, Dec 2
Scientific program. A comprehensive view on clinical and basic research findings related to the latest CXL protocols: thin corneas, customized, transepithelial, iontophoresis, CXL for ectasia, CXL Plus (combination with refractive surgery), PACK-CXL for infectious keratitis, new CXL technologies.

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Faculty
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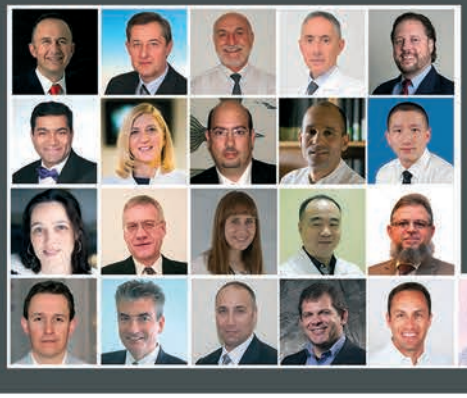

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The (Dark) Art of Public Relations!

It takes work. But it's more than worth it, when done intelligently.

For over a decade, I have spent the third Monday evening of each month in a local pub, where I run a SciBar. What is a SciBar? It gives local researchers the chance to present their work to the public; the scientists improve their communication skills, and the public gains a greater understanding of science. It's great fun.

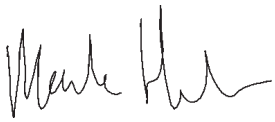
At the last SciBar, four PhD students presented: How Much Do You Trust a Science Headline? The highlight was the paper in Nature Communications: Fenamate NSAIDs inhibit the NLRP inflammasome and protect against Alzheimer's disease in rodent models (1), which turned into the headline: "Only 3p – the cost of the pill that could beat Alzheimer's" in the Daily Mail. The research group was inundated by calls from the press asking for interviews and, more sadly, from patients and their families in search of what the press was implying was a cure. Then the conversation turned to science communication in general: how do you get people to understand your work – especially when it's medical research – when the filter through the popular press distorts the message? I thought I'd share our ideas in the hope that some of you might find it useful.

Maximum result for minimum effort. Whether it's explaining the inflammasome or promoting your premium IOL practice, focus your efforts on what will give you the maximum exposure to your target audience. And today, that still means the mainstream media (MSM).

When you're dealing with the MSM, there are three key ways to get your message across. First, you should write the article yourself; find the best possible angle, pitch it at the level of the intended audience, and send it as a press release to every journalist and TV news producer you can find. Journalists often have to write at least 10 articles a day – make it easy for them by doing it for them. Second, a picture paints a thousand words. If you have a print-quality, simple and clear graphic that illustrates your work, use it. If you don't, make one. Place it on your website, and get it out with the press release. Third, take a leaf from the PR and communications agencies by writing what's known as an 'objection handler' – essentially a well-thought FAQ page. Try to guess all of the questions that might be asked, list them, and provide the answers. These will all help reduce the chance of your work being misinterpreted and misreported – and increase the chance of your work (or what your practice can do) being reported as widely as possible.

So, hijack the dark arts of PR, and use the inner workings of the MSM to educate to your advantage!

Mark Hillen
Editor



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1. *MJ Daniels et al, "Fenamate NSAIDs inhibit the NLRP3 inflammasome and protect against Alzheimer's disease in rodent models ", Nat Commun, 7, 12504 (2016). PMID: 27509875.*

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

The Importance of Being Early

Protocol I subanalysis suggests that earlier treatment of DME eyes with persistent edema maximizes visual benefit

There have been many clinical trials of anti-VEGF agents (and laser therapy) for the treatment of diabetic macular edema (DME) over the years – but still, some questions are unanswered; for example, what is the relationship between anatomic and functional responses to anti-VEGF therapy? Remember Protocol I (Figure 1a [1])? The Phase III multicenter, randomized trial (Figure 1a) showed that ranibizumab (with prompt or deferred focal/grid laser) resulted in superior visual acuity (VA) outcomes compared with laser alone through two years (1).

An early post-hoc analysis showed that sustained and early reduction of central retinal thickness (CRT) with ranibizumab therapy was associated with better long-term VA outcomes (2). And yet, asking a similar question, Phase III RIDE/RISE trial (Figure 1b) investigators saw a dissociation between early CRT reductions and visual outcomes (3). As RIDE/RISE also showed that delayed intervention with anti-VEGF therapy limits the scope for future vision improvement, Dugel and colleagues returned to the Protocol I dataset (4) to further characterize the anatomic response of the retina to ranibizumab, as determined by the average extent of edema over the 156-week period post-treatment initiation.

All Protocol I eyes with a baseline and at least one other CRT reading were included in the analysis (n=367). The extent of edema was calculated as the amount by which CRT exceeded 250 µm. Eyes were stratified into quartiles defined by the average extent of edema over the first 52 weeks post-treatment initiation (Figure 2). So what did they find?

Edema persisted after treatment initiation – and there was a significant correlation between the average extent of edema in the first and second 52 weeks after treatment initiation (r=0.673; p<0.001), and the average extent of edema that persisted

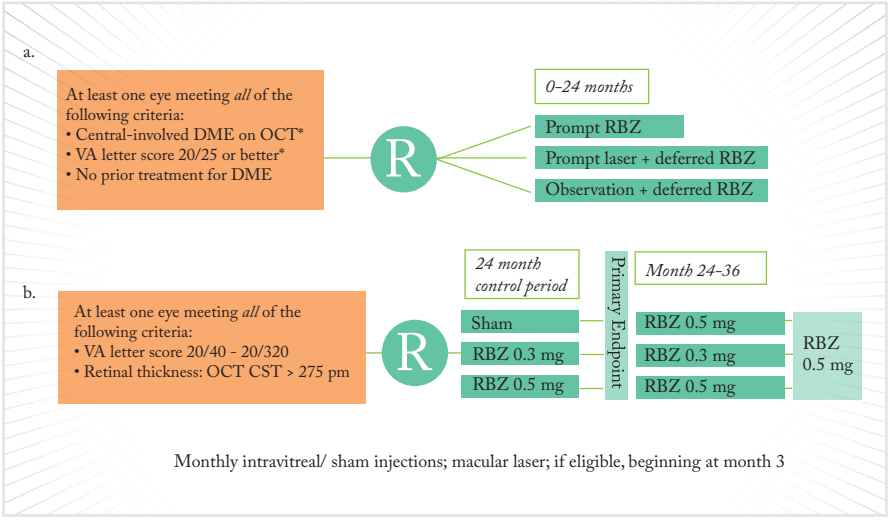

Figure 1. Protocol I (a) and RIDE/RISE (b) trial designs. RBZ, ranibizumab. CST, central subfield thickness. *Confirmed at 2 visits (screening and randomization 1–28 days apart).

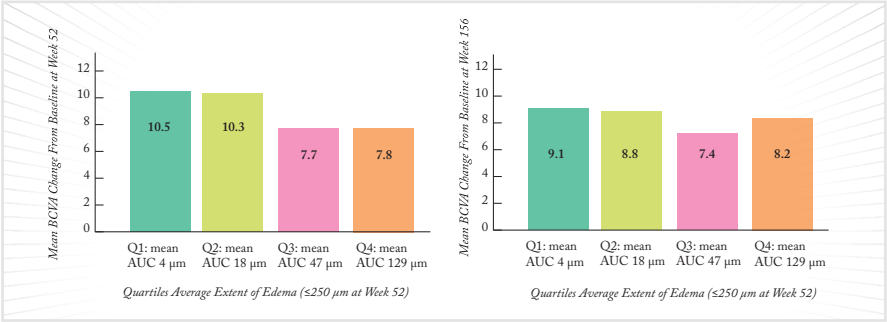

Figure 3. Mean (95% CI) BCVA improvement at week 52 (a) and 156 (b) among the quartiles. AUC, area under the curve; BCVA, best-corrected visual acuity, Q, quartile.

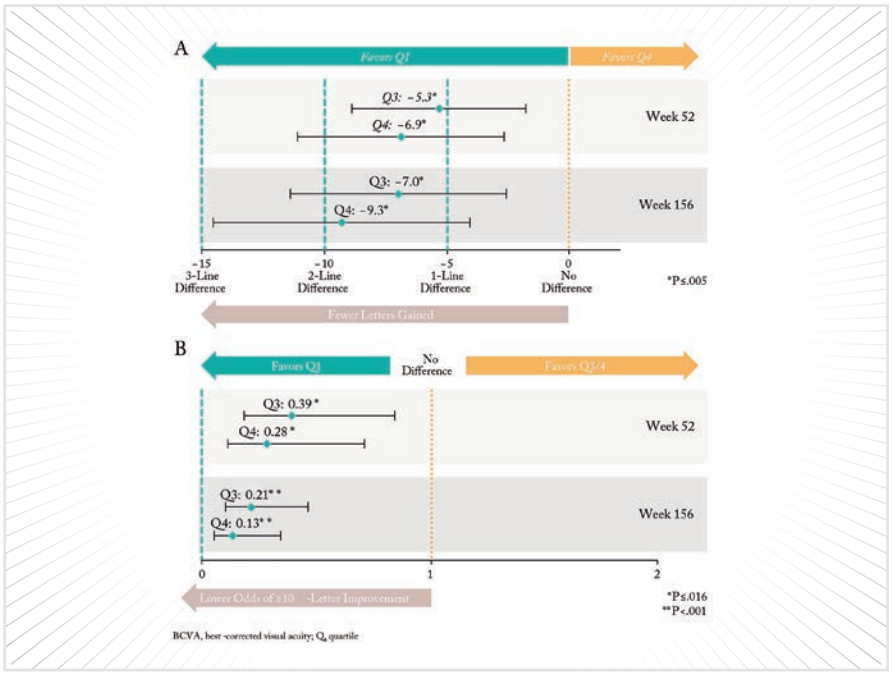

Figure 4. Estimated difference in long-term BCVA improvement (a) and adjusted odds ratio of ≥10 letter improvement (b) – Q3 vs Q1. BCVA, best-corrected visual acuity; Q, quartile.

between the first and second 52 weeks post-treatment initiation. In other words, if a patient had a thick macula to begin with, it's likely that would persist into the second year of treatment. What about VA?

In unadjusted analyses, there was no significant differences in mean BCVA change from baseline at weeks 52 (Figure 3a) and 156 weeks (Figure 3b) across quartiles (p=0.158 and 0.840, respectively). But when the data was split by 52-week quartiles, significant differences in several baseline characteristics (as well as treatment intensity) became apparent. Eyes with the least extent of edema (quartile 1) had better vision and lower CRT at baseline, whereas eyes with the greatest extent of edema (quartile 4) received significantly more ranibizumab injections and laser treatments over the study period.

After adjusting for potential confounders (including baseline BCVA and treatment intensity) eyes in quartiles 3 and 4 had a significantly lower estimated mean BCVA change from baseline vs quartile 1 eyes (Figure 4a). Likewise, quartile 3 and 4 eyes also had significantly lower odds of achieving a ≥10-letter improvement in BCVA compared with quartile 1 patients (Figure 4b).

The authors' conclusion? It's of paramount importance to control for the differences in baseline characteristics between patients with and without an anatomic response. As eyes with the least amount of edema had better baseline VA, the team's findings

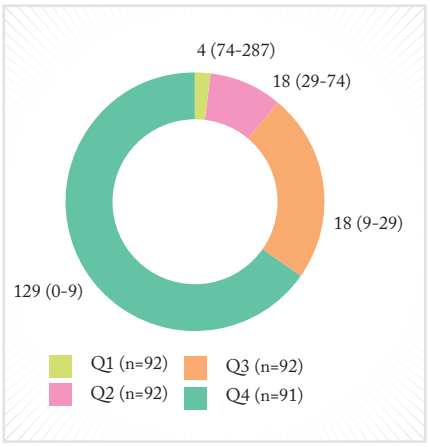

Figure 2. Distribution of study eyes, by average extent of edema [range] during the first 52-week post treatment initiation period. Q, quartile.

may reflect a "ceiling effect," where eyes with better vision at baseline (on average) have less room to improve. Ultimately, it confirms what RIDE/RISE suggested previously: you should consider additional disease management strategies earlier in eyes that show evidence of persistent edema to maximize potential vision benefit. *MH*

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2. *SB Bressler et al., "Factors associated with changes in visual acuity and central subfield thickness at 1 year after treatment for diabetic macular edema with ranibizumab", Arch Ophthalmol, 130, 1153–1161 (2012). PMID: 22965591.*
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"May I Enjoy Life and Art"

... so states the Hippocratic Oath – and now research shows that art training can improve ophthalmologists' observational skills

"Observation is a pivotal skill in medicine, especially in the field of ophthalmology, but medical education does not focus explicitly on teaching students how to observe," says Gil Binenbaum, attending surgeon in the Division of Ophthalmology at Children's Hospital of Philadelphia, Pennsylvania, USA. To explore how observation skills training might improve the medical – and more specifically the ophthalmological – observational skills of students, Binenbaum and a multi-center team performed a randomized controlled study. "We looked to the fine arts, a field that excels in its observation training," says Binenbaum.

Thirty-six first-year medical students were randomized into either art training or control groups. The 18 students in the training groups attended six art observation sessions at the Philadelphia Museum of Art over a three-month period; the control group was given free membership to the museum. Pre- and post-training, the students' observation skills were assessed by description testing (where they described works of art, retinal pathology images as well as external photographs of eye diseases) and emotion recognition testing.

Did the art training improve their observation skills? "Yes, it did!" says Binenbaum. The training group showed significantly improved observational skills compared with the control group ($p<0.001$). Furthermore, the training group scored significantly higher scores in all subsets of the description testing. "We believed that learning observational skills related to fine arts would allow students to hone general observational skills, but we were surprised by the extent to which they translated to medicine," says Binenbaum, adding that the results "highlight the art of medicine and encourage us to think outside the box when it comes to bridging across disciplines to improve medical training."

And does this team practice what they preach? Senior medical student and coordinator of the study, Jaclyn Gurwin, has herself participated in the art training in its first iteration and is now an ophthalmology resident. She commented: "It was incredible to see the training at work and how the medical students participated and expressed themselves in a way that I was not used to seeing in the medical school classroom. It seemed as though the students felt more of a freedom to share their own ideas and opinions, and they quickly built upon techniques they were learning."

Binenbaum hopes that their findings will help encourage medical schools and graduate medical education programs to recognize the importance of teaching observational techniques, and perhaps even incorporate this type of art observation training into their curricula. "As a result of our study, The Perelman School of Medicine at the University of Pennsylvania has already created two medical student elective courses in art observation training," says Binenbaum. Next, the team are planning to study the effect of art training on physician empathy, and have begun to pilot art observation training for post-graduate trainees. Binenbaum comments: "We hope that improved observational abilities from this training will translate to improved clinical effectiveness and empathy, and ultimately, make better physicians." It seems the medical schools of the future may place a little more emphasis on the finer points of the Hippocratic Oath. *RS*

Reference

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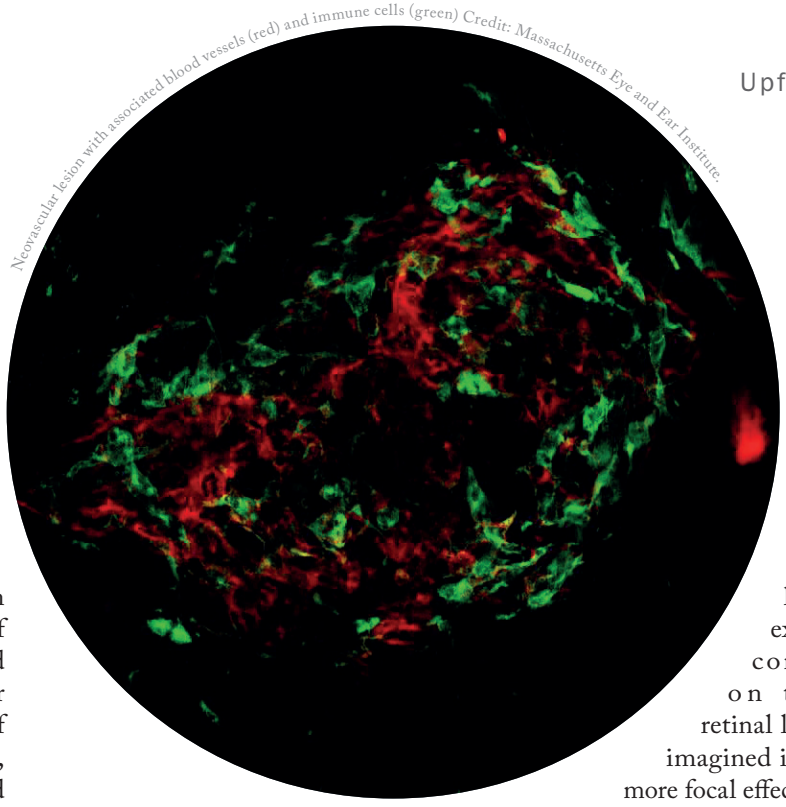


Neovascular lesion with associated blood vessels (red) and immune cells (green) Credit: Massachusetts Eye and Ear Institute

Magic Metabolites

Bioactive lipids show promise in protecting against the development of neovascular disease

Age-related macular degeneration (AMD) is the most prevalent cause of blindness of the elderly in the developed world, and the search for new and better therapeutic interventions is the subject of intense research. Despite these efforts, researchers still don't fully understood how the disease advances. It's known that choroidal neovascularization (CNV) goes hand-in-hand with advanced disease, and it is also thought that inflammation might also play a role in driving AMD pathology. And though treatment with VEGF inhibitors blocks the process of vascular growth and leakage, they do not lead to complete regression of abnormal vessels, and they largely ignore the role of immune cells. A team from the Massachusetts Eye and Ear Institute may have found a way to target both aspects that drive the pathology: via a subset of bioactive molecules that can resolve CNV by modulating inflammation. Kip Connor, corresponding author on the associated paper (1), tells us more about their work.

What inspired this research?

We wanted to perform this research because identifying additional mechanisms that regulate abnormal blood vessel growth in the eye could open a range of possibilities for new research and treatments for AMD.

What were your key findings?

In the present study, we demonstrated that specific bioactive products from the cytochrome P450 (CYP) pathway, a major family of enzymes, could reduce the development of CNV and vascular leakage by altering how immune cells were recruited to areas of disease and injury. Specifically, we isolated and characterized two key mediators of disease resolution from the CYP pathway: 17,18-epoxyeicosatetraenoic acid (17,18-EEQ) and 19,20-epoxydocosapentaenoic acid (19,20-EDP). These bioactive metabolites reduced disease severity in a mouse model of neovascular AMD.

Did you encounter any hurdles?

There are always obstacles (other than funding) that come up in research! We initially struggled to identify whether the bioactive lipids exerted their effects locally in the retina or systemically. It turned out to be a little of both: they modulated the damaged vasculature at the site of injury as well as systemic inflammatory immune cells. Such challenges make our jobs so exciting and rewarding because they really make us think about the science and push us into new areas that we may have overlooked before. I am very fortunate to be part of an amazing team, and together we overcame the challenges encountered along the way.

Did you have any surprising results?

I was surprised at the degree by which systemic immune cells were affected by these bioactive lipids and the extent of their contribution on the local retinal lesions. I had imagined it would be a more focal effect.

What impact do you hope your research will have?

Our study offers new insights into bioactive lipid metabolites as regulators of systemic inflammatory immune cells and mediators in CNV resolution, and it also shows the promising therapeutic potential of these bioactive products for neovascular AMD – as well as other major conditions that involve angiogenesis and inflammation, such as atherosclerotic disease and cancer. Given the high prevalence and progressive nature of neovascular eye disease, the ability to stabilize bioactive lipids that mitigate or halt disease is of great and increasing therapeutic significance. We hope that emerging technologies and future studies will expand on our work and ultimately lead to safe, targeted, and cost-effective therapies that markedly improve visual outcomes and quality of life for patients suffering from these debilitating ocular diseases.

Reference

1. *E Hasegawa et al., "Cytochrome P450 monooxygenase lipid metabolites are significant second messengers in the resolution of choroidal neovascularization", Proc Natl Acad Sci USA, [Epub ahead of print], (2017). PMID: 28827330.*

Know Thy Patient

How do patients really feel about their disease and their treatment – and how do they differ?

Clinical trials may address the all-important aspects of safety and efficacy, but patients have feelings and expectations. Recently published research (1) has delved into the more personal aspects of medicine in the context of neovascular AMD and intravitreal anti-VEGF therapy.

In the multicenter, non-interventional, prospective cohort study, a total of 332 patients with neovascular AMD were observed over a 12-month period; patients were over the age of 50 years and had received at least one intravitreal injection of anti-VEGF therapy prior to enrolment. Patients were enrolled from 23 different treatment centers, including hospitals, office practices and outpatient clinics.

Over the course of the study, patients participated in three 30 minute telephone interviews, each structured by a pre-defined questionnaire. The first interview (two months after enrollment) included assessments of patient well-being and their quality of life; the second (five to six months after enrollment) included assessments of knowledge, awareness and expectations of their disease and treatment; and the third (12 months after enrollment) questioned aspects such as beliefs, expectations and preferences. Key results are highlighted in the infographic (1).

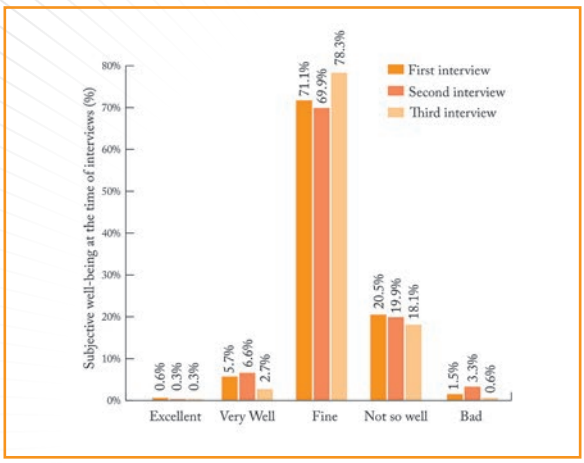
Based on the findings, the team were able to identify five significantly different clusters of patients:

- Cluster 1: optimistic patients without fear of injections or side effects, and a below average knowledge of their disease and treatment.
- Cluster 2: as Cluster 1 but with a better knowledge of their disease and treatment.
- Cluster 3: patients not afraid of injections or side effects, have good disease awareness and average knowledge of treatment, but are pessimistic with regards to expectations of therapy.
- Cluster 4: patients have "non-awareness" of disease, and do not use self-tests or pay attention to diet.
- Cluster 5: patients are afraid of injections and/or side effects.

Writing that patients differ in terms of treatment optimism, disease awareness and knowledge, and fear of injections or side effects, the team recommend "the development of separate patient communication strategies for the five patient clusters identified." Coupled with the finding that only a minority of patients reported being aware of the chronic nature of neovascular AMD (16.6 percent), the team conclude that using communication strategies suited to individual patients might help motivate patients with neovascular AMD to accept the necessary long-term treatment for their condition. *RS*

Reference

1. *S Müller et al., "Treatment of age-related neovascular macular degeneration: the patient's perspective", Graefes Arch Clin Exp Ophthalmol, [Epub ahead of print], 2017. PMID: 28776095*



Subjective assessment of vision between interview 2 and 3

32.2%, *deterioration*

31.9%, *no change*

19.6%, *improvement*

57.8% *stated they are "generally in need of help"*

***9.6%** are afraid of injections in general*

***66.3%** would prefer tablets or eyedrops*

Disease and treatment knowledge

***87.3%** named their disease correctly;*
***43.1%** named their administered anti-VEGF*
***31.1%** paid attention to their diet because of their disease*

***Only 16.6%** were aware of the chronic nature of nAMD*

Adapted from (1).

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

All Together Now

Glaucoma management works best as a team approach – with the patient at the helm

By Simon Skalicky, Consultant Ophthalmologist and ophthalmic surgeon, Senior Lecturer at the University of Sydney and University of Melbourne, and Chair of the Ophthalmology Committee for Glaucoma Australia

Patients typically value clinicians who establish a good relationship, listen to their concerns, and counsel them about their disease. It's not simply crowd-pleasing behavior; quality doctor-patient interaction can enhance the therapeutic value of administered treatments (1). And yet its perceived importance may have diminished in our era of modern technology medicine.

Thankfully, the pendulum is beginning to swing back – a shift in focus reflected by FDA guidelines that stipulate quality of life (QoL) metrics must be a key endpoint for all new randomized clinical trials (RCTs) in ophthalmology (2). Our fundamental job is to evaluate and improve our patients' QoL, not simply treat their disease; a holistic framework that considers psychosocial dimensions is required.

Counseling empowers patients to make their best possible health choices. It informs them of the resources available, the different treatment options, as well as the likely side effects and strategies to minimize them. And it may also alleviate unspoken fears for the future (3). Although I take the time to counsel patients during clinical practice, I also encourage patients to seek further information from a third party, such as a patient advocacy group. There is only so much a patient can absorb in a medical consultation, especially when stress from a recent diagnosis might impair their comprehension. I believe it is beneficial for patients and family to hear the information again from an alternative, independent source and have an opportunity to ask further questions. Selected Internet resources can be useful as well. These approaches improve clinical care: patients who acquire information from sources external to their doctor often have the best medication adherence (4).

Glaucoma Australia is a not-for-profit organization that provides a free patient advocacy service, including access to counseling, leaflets, support groups, regular glaucoma newsletters, and it is currently building an informative and interactive website.

One of the first of its kind, a short-term RCT was published recently measuring the impact of glaucoma-specific counseling on glaucoma knowledge and disease-related anxiety (5). The standardized verbal and written information provided by Glaucoma Australia to new patients was evaluated. A total of 101 newly diagnosed open angle glaucoma patients from 13 centers across Australia were randomized 1:1 into the intervention arm (usual clinical care from ophthalmologist with counseling from Glaucoma Australia) and the control arm (usual care from ophthalmologist). After four weeks, the intervention arm but not controls had improved knowledge levels ($p=0.02$ vs. control); intergroup analysis revealed a significant reduction in anxiety from the intervention ($p=0.02$ vs. control). So, third party counseling might not only improve medication adherence, it might also improve glaucoma-knowledge and reduce anxiety, at least in the short term.

How might this change clinical practice? In an ideal world we always counsel patients well; in reality, there are multiple conflicting pressures that often hamper

our performance. Time constraints, overbooked clinics, administrative needs, teaching requirements and technological demands can all detract or distract from our core role as quality care providers. Everything is a juggle, a compromise – and we do best with what we value the most. We must remember our roles as teachers, care providers, listeners and advocates. We must also remember we don't have to do it alone; there are important services at our fingertips to help.

As we move forward, we need to evaluate further what kind of counseling is appropriate – what are the right things to say and the right times to say it. We must train our junior doctors in the art of clinical interaction, not just the science and skills of medicine and surgery. We should embrace new technology to improve patient education and communication, harnessing the wonderful opportunities provided by sophisticated networking, personalized devices and digital media. Building bridges with advocacy groups and other healthcare professionals, and strengthening the bonds of the glaucoma health team can only be beneficial to our patients.

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Looking Beyond the Eyes

Lessons in taking a more active role in diabetes care

By Bobeck S Modjtahedi, Ophthalmologist, Southern California Permanente Medical Group (SCPMG), Baldwin Park, CA, USA

We exist in an era of increasingly specialized medical care where most providers carve out a narrow niche. But to provide the most complete care, ophthalmologists should to try to broaden their attention beyond strictly eye issues and take the opportunity to address underlying systemic diseases as well.

The prospect to do more is perhaps greatest in the area of diabetes care – if patients are unable to properly manage their diabetes, they will never be able to extricate themselves from the perpetual downward spiral of complications. In addition to the clear systemic benefits of tightened control, intense treatment of glycemia can slow retinopathy progression (1). Many diabetic patients spend more time with their ophthalmologists than any other healthcare provider, and all of that chair time gives us the chance to improve diabetes control. The problem? Indirect evidence suggests we may not be realizing the full potential of our time. Even though it may seem intuitive that diabetic patients subjected to potentially uncomfortable, repeated, and time-consuming interventions may be "scared straight" into doing a better job with managing their diabetes, it has been shown many times that patients undergoing intravitreal anti-VEGF injections do not undergo clinically meaningful improvement in systemic measures, such as blood pressure and hemoglobin A1c (2–4). Many patients may not understand that injections and lasers should ideally be thought of as a mechanism to "bridge the gap" until the benefits of the improved systemic control can take effect – something that may take years to achieve. It behooves ophthalmologists to try to take a more active role despite the ever-present obvious limitations in time, expertise, and resources.

But extrapolating from the non-ophthalmic literature, it's clear that there are several incremental steps that ophthalmologists and their clinic staff can take to help tangibly improve diabetes control (5–7):

1. Most patients (and many physicians) fail to appreciate the strong correlation between ophthalmic findings and long term systemic risk to patients.

The eye is truly the "canary in the coal mine." In addition to discussing the well-established risk of vision loss from

diabetic eye disease, providing patients the broader implications of their eye findings can highlight the seriousness of their condition – especially when they remain asymptomatic. For example, all-cause mortality is 133 percent higher in patients with diabetic retinopathy than diabetics without retinopathy (8).

In patients with type 2 diabetes, all-cause mortality is 38 percent higher in those with non-proliferative diabetic retinopathy and 132 percent higher in those with proliferative diabetic retinopathy (8). Patients undergoing pars plana vitrectomy for tractional retinal detachments have a mean survival of 2.7 years. At 10 years, these patients have a 48.7 percent all-cause mortality rate – compared with 2 percent in diabetics with minimal to no retinopathy (9)! Telling a young patient who requires tractional retinal detachment repair that they only have a 50 percent chance of living 10 more years with an average life expectancy of approximately three years is a sure way to get their attention; however, the initial shock value of these figures often fades and patients slide back into bad habits unless there is a way to channel their new found motivation into meaningful change. And that is why the next point is critical.

2. Close coordination of care with primary care physicians is invaluable.

A two-way street of communication allows primary care doctors to gain a better view of their patients' diabetes control and can also allow ophthalmologists to better understand the changes taking place in a patient's management. It would be helpful to know if a sudden improvement in blood sugar pre-dated a new diagnosis of diabetic macular edema. Additionally, ophthalmologists can provide the appropriate nudge that may help convince patients to adhere to their primary care doctor's interventions – such as finally convincing a patient to start an overdue insulin regimen. It is not uncommon for patients to view their ophthalmologist as their primary source for healthcare. A surprising number of patients have not seen their primary care doctor for years, and commonly, patients first establish care with an ophthalmologist before finding a primary care doctor. Simply ensuring patients are returning to see their primary care doctors for continued systemic management can hold significant value.

3. Health education classes and support groups are a valuable resource.

Such programs have been shown to improve diabetes outcomes – and many are either covered by insurance, provided in the community at little to no cost, or exist online. Several online programs have already been vetted and are certified by professional societies or physician groups. Being familiar with these opportunities provides an easy way to direct patients to potentially fulfilling resources with minimal effort on the part of the ophthalmologist.

4. Repetition and reinforcement are critical to modifying patient behavior.

Medication reconciliation can be used as a mechanism to remind patients of the importance of medication adherence. Encouraging and reminding patients to diet and exercise at each visit can eventually start to influence behavior. For example, patients who received telephone calls every 4–6 weeks to encourage medication adherence and lifestyle modification had improved diabetes control compared with those provided only print literature (6). Retina clinics regularly see patients at similar intervals and could use their staff to employ similarly simple interventions.

On the surface, these steps may seem unrealistically burdensome for a busy ophthalmology practice; however, many tasks only take a few minutes and can be done by ancillary staff during intake or check out. Ultimately, these relatively small interventions may serve as a long-term investment in the general and ophthalmic wellbeing of our diabetic patients.

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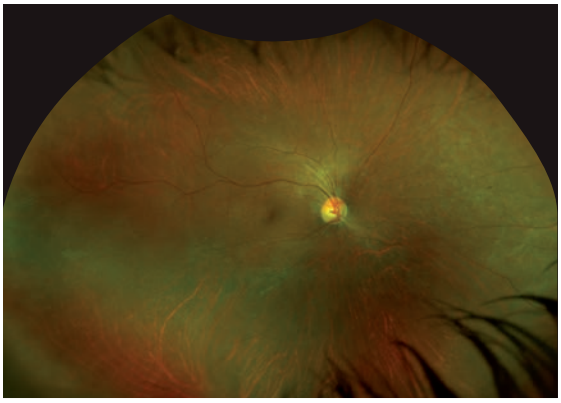

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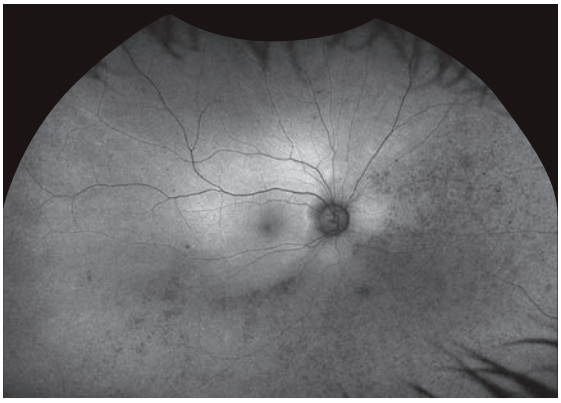

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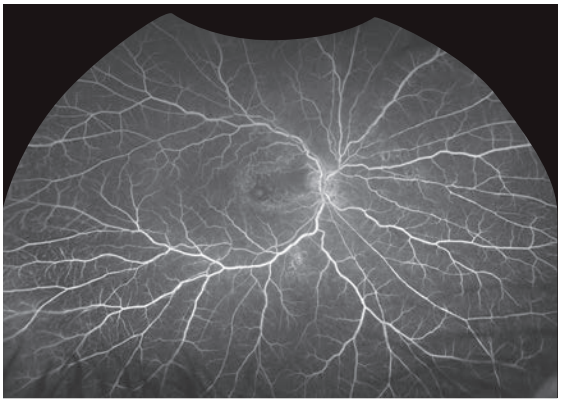

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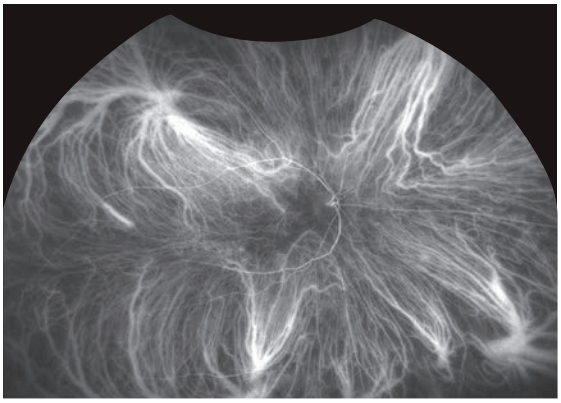

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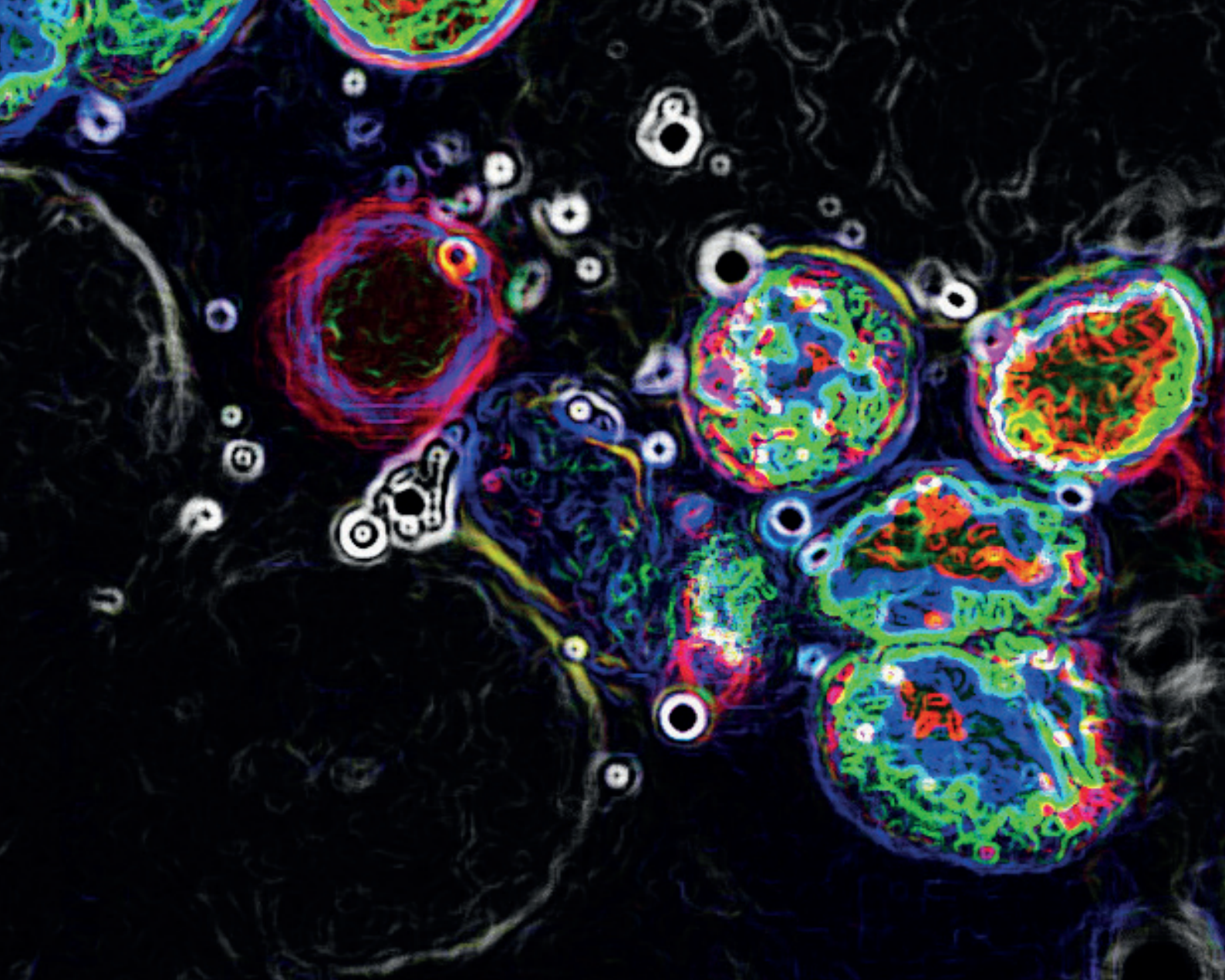
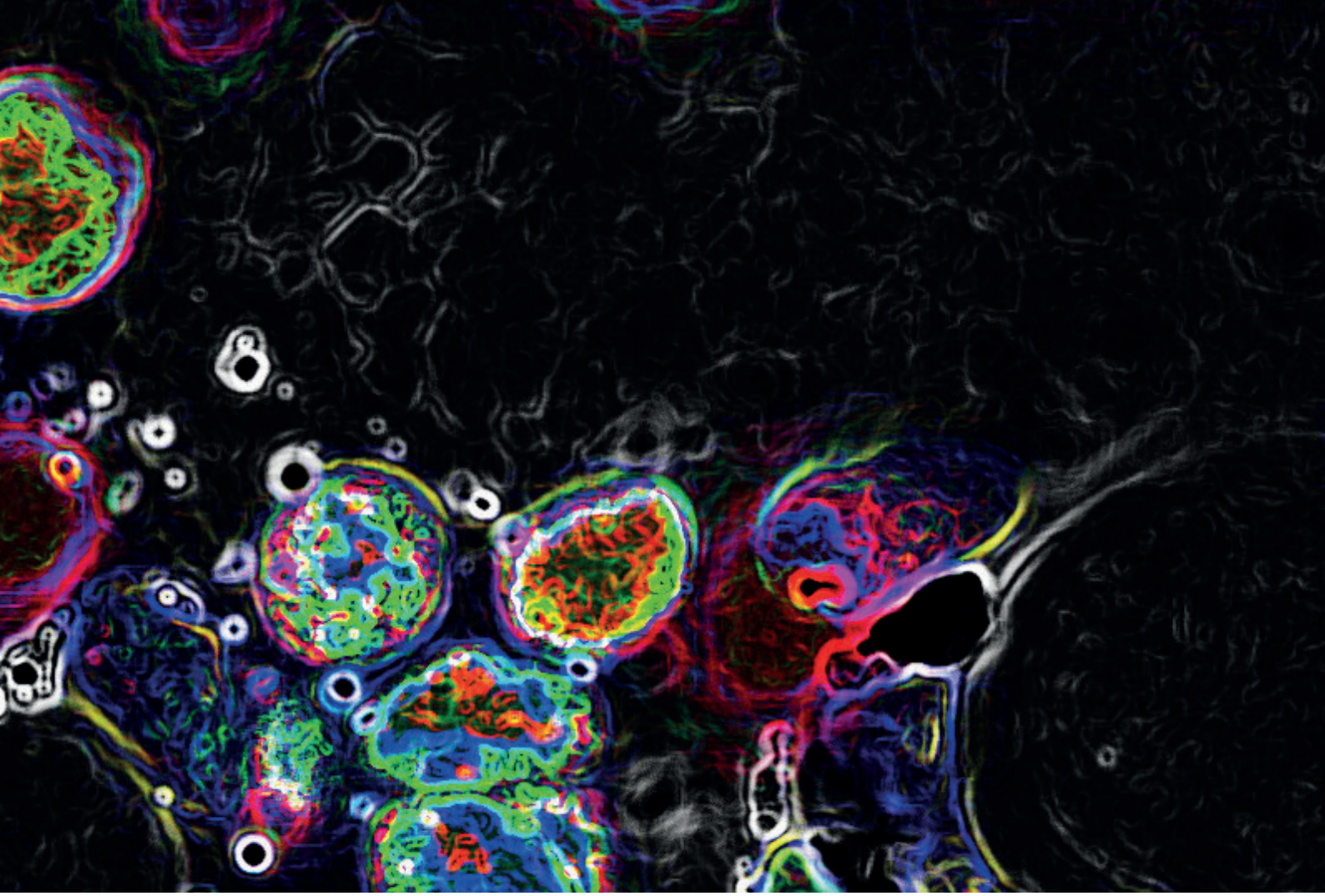


REGENERATIVE MEDICINE: THE CORNEA

How three leading lights and one CEO are tackling corneal disease through pioneering research and development

Ophthalmology is at the forefront of many fields of biomedicine, including diagnostics, drug development, and gene therapy. Understandably so – despite all of the incredible advances in eyecare over the last 50 years, there's still a huge unmet need for sight-saving and sight-restoring interventions. If new or better therapies can be developed that meet these needs, particularly within the context of aging baby boomers with age-related eye disease, it will be of huge benefit to healthcare systems and society. Another field that vision science is trailblazing is regenerative medicine. Many research groups are focused on treating retinal diseases with cell therapy and have rightly received a great deal of coverage. But what about the cornea? We caught up with three leading researchers and one CEO to find out how they are approaching corneal repair and regeneration, and how these potentially life-changing therapies are being brought to patients.



From Liposuction to New Stromal Collagen Production

The first clinical trial of autologous adipose-derived adult stem cells placed in an intrastromal pocket shows great promise for the treatment of corneal ectatic disorders

By Jorge Alió and Jorge Alió del Barrio

The biggest challenge in combatting corneal disease is repairing the stroma. It makes up nine-tenths of the corneal thickness and imparts most of the strength, shape and even the transparency of the cornea. Dystrophies, ectactic disorders and even scars disrupt the stromal anatomy and physiology, destroying its transparency and leading to vision loss. Being able to repair it would be a game-changer but, until now, the only option has been to replace it through corneal transplantation. Efforts have been made to recreate the stroma in vitro, but they've all met with failure (1). The stroma may be mostly collagen, but its complex ultrastructure has meant that recreating it, or finding a suitably strong and transparent replacement, has been impossible to date. An alternative approach – recreating the stroma with stem cells – has shown far more promise.

Corneal stromal stem cells (CSSCs) do exist, and at face value, they're a great option for treating corneal dystrophies, scars and ectasias. They're already corneal cells, with a more directed differentiation profile (2). However, there are three problems with CSSCs: i) few are present in any given cornea, ii) they're more technically challenging to harvest (and doing so damages the cornea), and iii) they're more difficult to cultivate and expand in cell culture – all of which precludes their autologous use. Compare this with extraocular mesenchymal stem cells (MSCs). MSCs (from both ocular and non-ocular sources) have already shown great promise: in rabbits, human MSCs can survive, differentiate into adult human keratocytes and produce new human collagen within the rabbit stroma, without an inflammatory reaction (2–6). Further, mouse MSCs (in mice) have been shown to improve corneal scars by stroma remodeling, and to improve corneal transparency in animal models of corneal dystrophies and metabolopathies through collagen reorganization and catabolization of accumulated proteins, respectively (7–12).

In terms of potential clinical application, human adipose-derived adult stem cells (ADASCs) could be the MSC of choice;

*Box 1: Inclusion and exclusion criteria**

Inclusion	Exclusion
• Advanced keratoconus (Stage ≥IV RETICS classification) • Age ≥18 years • Negative serologies for HIV, hepatitis B and hepatitis C • No history of malignancy	• CDVA <0.1 in contralateral eye • Active concomitant inflammatory eye disease • Other ophthalmic comorbidity (e.g. cataract, glaucoma, retinal disease) • Previous ocular surgery including CXL (other than cataract) • Previous corneal hydrops or central corneal scars • History of cognitive impairment/ dementia • Any immunodeficiency/ immunosuppressive therapy • Pregnancy or breast-feeding
Five patients, 1 LTFU Mean age: 34.2 (30–42) years 3 ♂, 2 ♀; 2 OD, 3 OS.	

*Keratoconus progression was not considered as an inclusion or exclusion procedure.

CDVA, corrected distance visual acuity; CXL, corneal collagen cross-linking; HIV, human immunodeficiency virus; LTFU, long-term follow-up; RETICS, Spanish Network of Research in Ophthalmology.

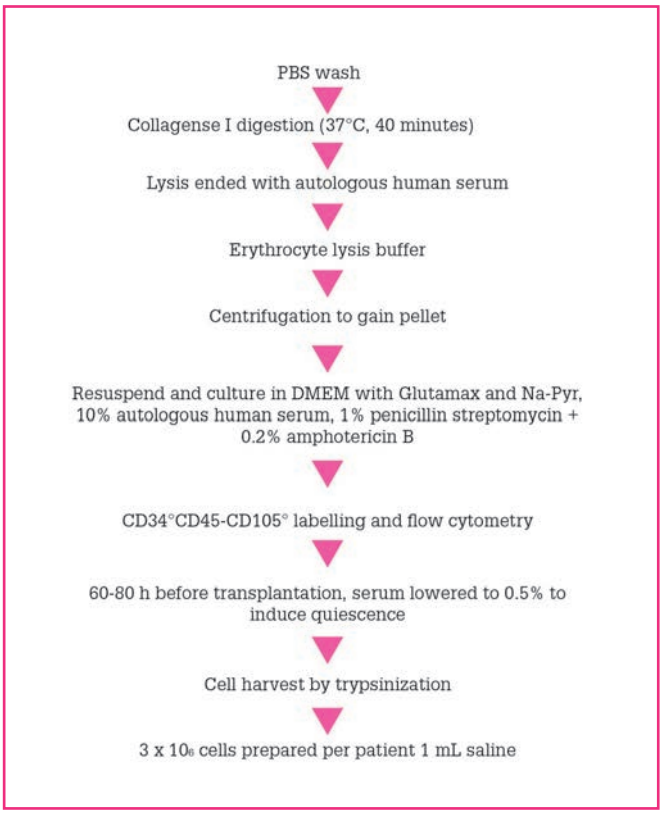


Figure 1. From liposuction aspirate to adipose-derived adult stem cells (ADASCs). DMEM, Dulbecco Modified Eagle Medium, PBS, phosphate buffered saline.

not only can they differentiate into multiple stem cell types, but also the source material, adipose tissue, is easily obtained by liposuction – and ADASCs can be retrieved with high efficiency (2). In other words, a patient can undergo liposuction, have their own ADASCs harvested, and have those stem cells applied to the cornea – in theory. The big questions are: can it work? And is it safe? My colleagues and I decided to perform a small, phase I safety and tolerability clinical trial in five patients with keratoconus (see Box 1: Inclusion criteria) as a first step to finding out (13).

The process of ADASC cell harvesting is described in Figure 1 and the microscopic appearance of these cells is depicted in Figure 2. Once we had prepared the stem cells – three million in 1 mL of saline – we used a 60-kHz IntraLase iFS femtosecond laser to create a 9.5 mm diameter, half-depth (of an OCT-determined thinnest pachymetry point) intrastromal pocket, which ended with a 30° anterior side-cut as a corneal incision. Next, we opened the pocket by blunt dissection with a lamellar dissector, and a 1-mm corneal paracentesis was made to reduce IOP and increase the volume of cells that could be introduced

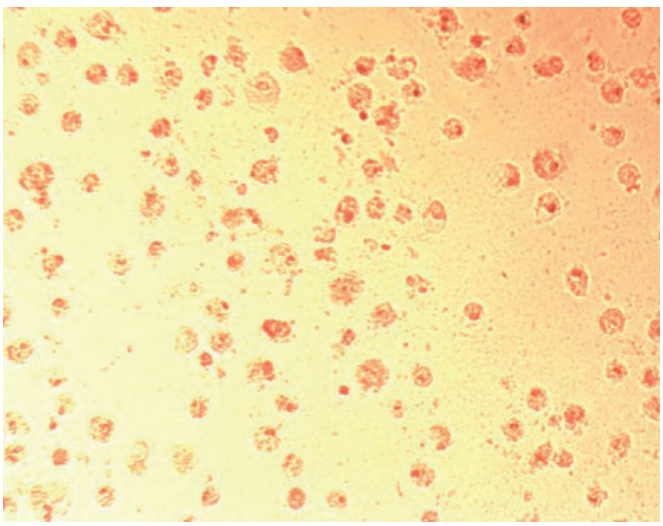
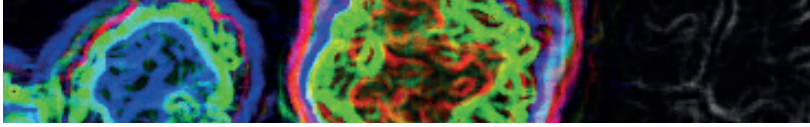


Figure 2. Microscopic appearance (phase-contrast photographs) of autologous adipose derived adult stem cells after trypsinization and before transplantation (×10 magnification).



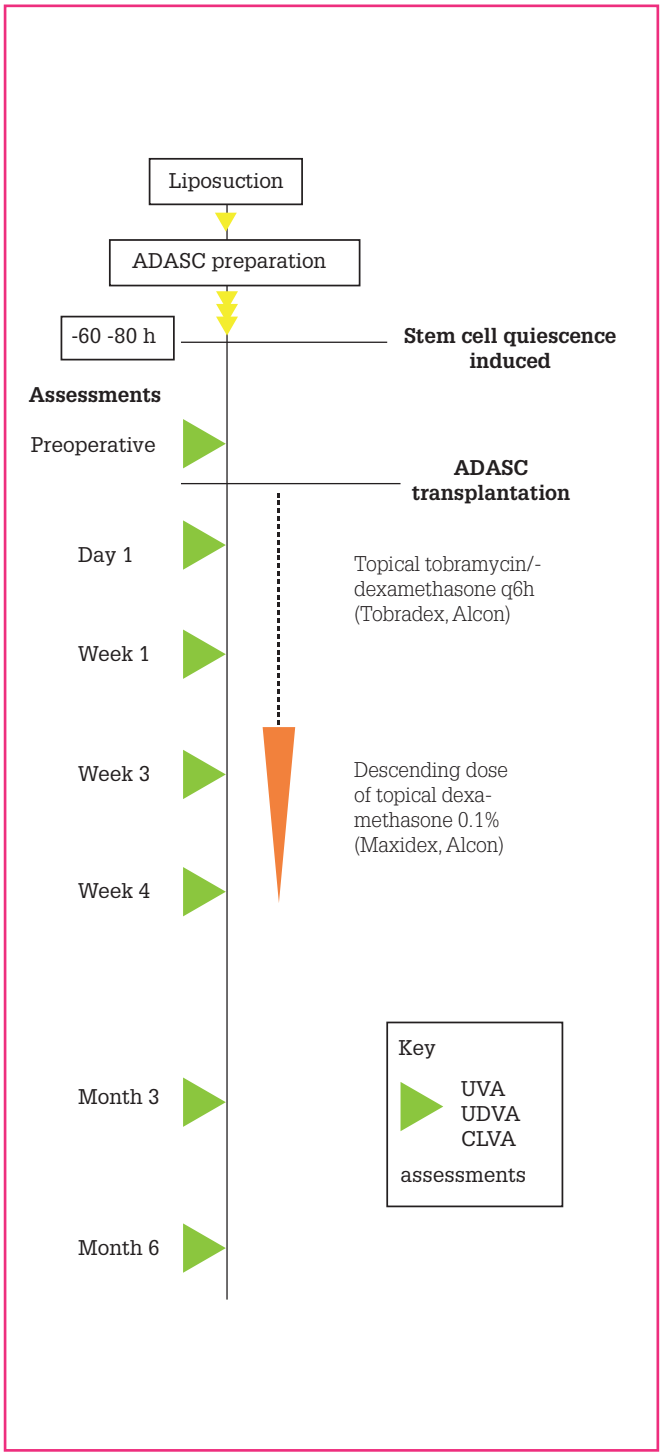


Figure 3. Timelines: treatment and assessment regimen. ADASC, adipose-derived adult stem cells; UVA, uncorrected visual acuity; UDVA, uncorrected distance visual acuity; CLVA, distance rigid contact lens visual acuity.

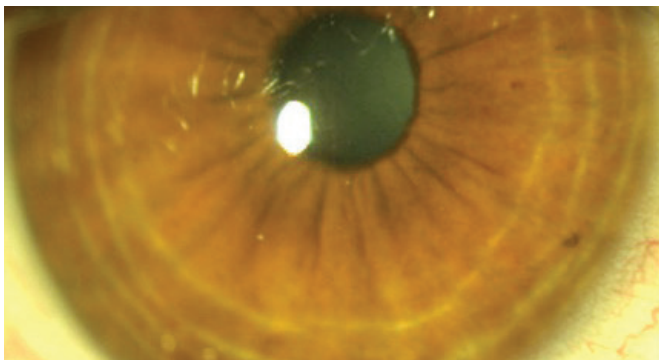


Figure 4. Slit lamp picture of a patient 24 hours after the procedure.

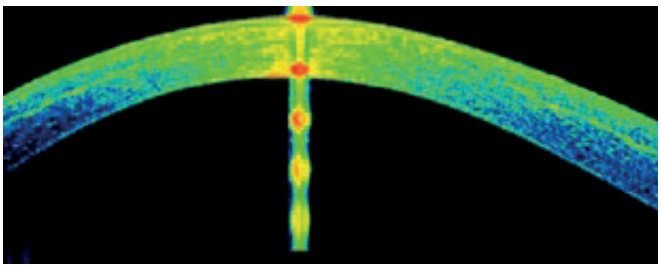


Figure 5. Corneal OCT picture from a patient 6 months postoperatively. Note the patched hyper-reflective areas (white arrows) at the level of the stromal pocket compatible with areas of new collagen production.

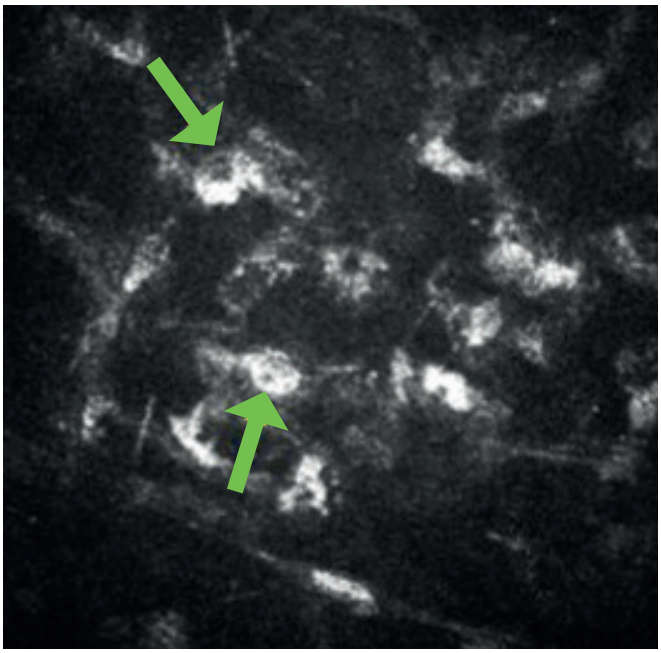


Figure 6. Corneal confocal biomicroscopy picture from a patient at the first postoperative month. Stem cell presence is confirmed at the level of the surgical plane with cells showing a more rounded shape (green arrows).

into the corneal pocket. ADASCs suspended in 1 mL saline were injected into the pocket through a 25-G cannula. No corneal suturing was required in any cases, and the surgery was completed with the administration of topical steroids and antibiotics (Tobradex, Alcon). The postoperative care and assessment schedule is summarized in Figure 3.

So what did we find? Of the five patients enrolled, one was lost to follow-up after one month and was excluded from our analyses. No complications occurred during surgery – or throughout the six-month follow-up (the patient that dropped out had experienced no complications by one month, and later indicated no subjective negative findings or outcomes when contacted directly about this), and full corneal transparency was achieved within 24 hours in all cases (Figure 4). All patients' visual function improved: both uncorrected visual acuity (UVA) and corrected distance visual acuity (CDVA) improved by an average of one line, and by two lines of distance rigid contact lens visual acuity (CLVA) – although this should, in theory, be attributed to the surgical procedure and not the stem cells as the improvements were rapid – and the stem cells had not differentiated into adult keratocytes at this early point. Manifest and topographic keratometry remained stable, and anterior-segment OCT showed not only new collagen production in the stromal pocket (Figure 5), but also a mean improvement in corneal thickness of 16.56 µm. One important question to answer was if the implanted stem cells survived – is their effect likely to be in the short term, or over a more prolonged period? Encouragingly, confocal biomicroscopy (Figure 6) performed at three months confirmed that they survived at the surgical plane, and by six months these cells had adopted a fusiform shape and did not appear different to cells in other stromal planes. Finally, IOP and endothelial cell density remained stable.

So what does this mean for the future treatment of corneal disorders? One has to bear in mind that this was a small, uncontrolled, unmasked pilot study with only a six-month follow up-period – and that any future studies would need to improve on these aspects. But despite these provisos, the clinical corneal stromal implantation of autologous ADASCs appears to: i) be non-immunogenic and without adverse event, ii) result in the production of a (low) amount of new collagen. And the cells appear to survive in vivo. The procedure might provide an alternative to corneal transplantation in patients who have been diagnosed with keratoconus that is too advanced to treat with corneal collagen cross-linking (and might also avoid many of the risks inherent with this form of surgery, principally graft rejection). It would also be interesting to speculate what impact intrastromal autologous ADASC transplantation might have on the natural course of mild or moderate keratoconus. A new door has opened for the clinical treatment of corneal disorders – the next few years should be exciting times.

Jorge Alió is Professor and Chair of Ophthalmology, Miguel Hernández University of Alicante, and founder of VISSUM Corporation. Jorge Alió del Barrio is a cornea, cataract and refractive surgeon at VISSUM Corporation, and an honorary Professor at Miguel Hernández University.

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Resurrecting the Cornea

Can the cornea be "revived" with cadaveric allograft material?

By Sheraz Daya

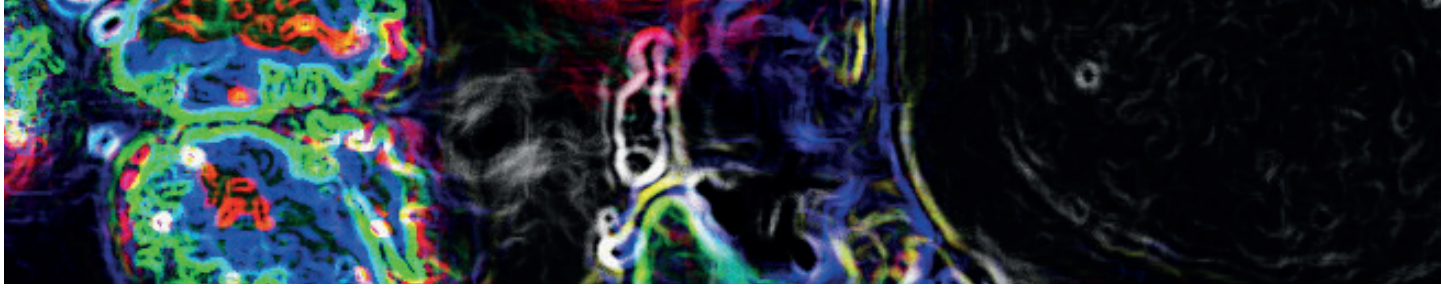
Eye injuries that damage the limbus may result in limbal stem cell deficiency (LSCD) and failure of corneal regeneration. Stem cell transfer procedures can be curative, but have been hindered by the scarcity and immunogenicity of allograft material. Research indicates that allografts can trigger repopulation of the host stem cell niche with autologous cells (1), and this in turn suggests that cadaver limbus could be used as a universally-applicable graft material, in virtually unlimited quantities. Could cadaveric cells eliminate the need for autografts and 'living donor' allografts?

Limbal stem cells are key to regeneration of the cornea after injury… but if the limbus also is damaged, natural corneal recovery may be compromised by LSCD, resulting in problems including dry eye, chronic inflammation, and loss of vision. Hence, external insults, such as physical, chemical or thermal injury, or diseases such as cancer, chronic limbitis or Stevens-Johnson syndrome, may lead to chronic visual defects.

The clinical treatment options for LSCD-based problems are limited, as traditional corneal graft procedures prove ineffective, and penetrating keratoplasty (PK) is contraindicated in these patients. Stem cell transplantation remains the best approach for severe cases, and various options are available to the surgeon according to tissue type and tissue provenance (Table 1).

Source	*Tissue*		
	Conjunctival	**Limbal**	**Keratolimbal**
Autograft	CAU	CLAU	KLAU
Allograft, cadaveric	c-CAL	c-CLAL	KLAL
Allograft, living-related	Lr-CAL	Lr-CLAL	-
Allograft, living non-related	Lnr-CAL	Lnr-CLAL	-

Table 1. Spectrum of graft material used to treat LSCD



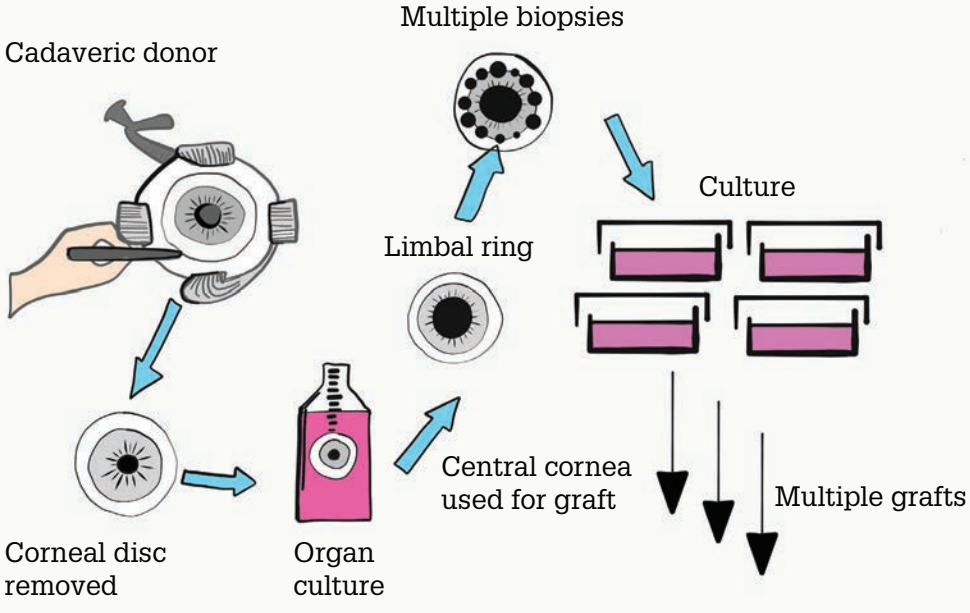


Figure 1. One cadaveric donor provides sufficient material for multiple grafts

To immunosuppress, or not?

Clearly, the only immunologically perfect match for the damaged eye will be autograft tissue (that is, cells taken from the contralateral eye). Historically, this has been the favored approach, as it avoids the need for long-term immunosuppression to avoid graft rejection. The autograft technique, however, is limited to cases where only one eye is damaged and where the patient is willing for the undamaged eye to be used as a stem cell source. And given that the procedure may involve removing two grafts of 90° of limbal arc, there is a small chance that the patient's only healthy eye may be damaged. Understandably, some patients are reluctant to take that risk. The next-best source, from an immunological perspective, is allograft from a relative of the patient – the 'living-related' allograft. Again, the quantity of tissue is limited by the amount of harvesting a healthy eye can sustain. Furthermore, this procedure is only possible where relatives are alive, available and willing to donate corneal tissue.

Finally, tissue may be sourced from non-related individuals, either living or cadaveric. Living non-related donors, however, have the same restrictions as living-related donors with regard to availability, risk to the donor eye and willingness to provide ocular tissue. Cadaveric donors, by contrast, are far less restricted in terms of availability and quantities of tissue that can be harvested per eye. Indeed, in vitro culture of the cadaveric corneal disc followed by multiple explants – each of which is used as a source of cells to expand in culture (Figure 1) – can provide sufficient cells for multiple procedures from a single eye.

So, cadaveric eyes may provide an abundant source of tissue for limbal stem cell transplants and may be especially suitable for patients with bilateral LSCD – or those with unilateral damage who cannot access stem cells from living donors or those who prefer not to undergo an autograft procedure. The problem has always been that cadaveric allograft transplant recipients must suffer a regimen of long-term, systemic immunosuppression if the graft is to survive. Data from our laboratory, however, now challenge this orthodoxy.

Revenant cells

Briefly, our method is as follows.

- Tissue sourcing. We remove the entire corneal disc from the cadaver eye, and maintain it in organ culture medium. When appropriate, we take multiple biopsies

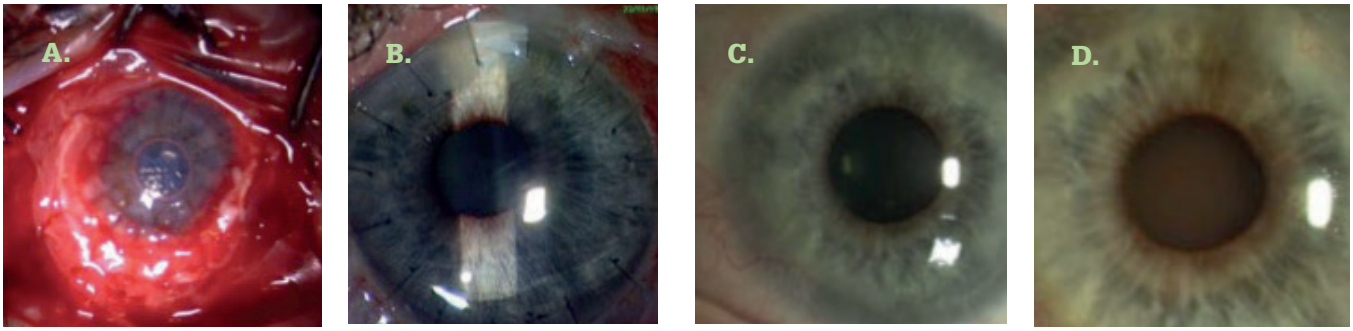


Figure 3. Cultured epithelial sheets derived from cadaveric cells are stable over years. a. ~5 months post-op; b. ~6 months post-op c. 3.5 years post-op; d. ~9.5 years post-op.

from the limbal ring and retrieve viable cells from each.

- Cell population expansion and harvesting. We expand the retrieved cells from each biopsy in separate cultures; this provides material sufficient for multiple graft procedures (Figure 1). Over time, small discrete colonies grow and merge into multilayered epithelial sheets; these are released from the plastic substrate with Dispase II enzyme (2).
- Graft construction and implantation. The cultured epithelial sheet is mounted on a Tegapore dressing, which is used to transport the cultured sheet. The sheet is transferred onto the prepared ocular surface and then covered with amniotic membrane which is sutured to the bulbal conjunctival surface (Online Figure 2).
- Post-operative regimen. Our patients receive intravenous methylprednisolone (1–2 mg/kg/day) until inflammation in the eye has calmed down, plus cyclosporin A (2–3 mg/kg/day); and dexamethasone (0.1%), chloramphenicol and autologous plasma (each, qid).

The above technique produces grafts that appear similar to the limbus by microscopy and molecular marker studies. Thus, the epithelial sheet forms multiple layers with a distinct basement membrane, and markers K19, K3 and enolase are appropriately distributed in the layers of the graft.

Recipients have a number of variables, and the procedure is not perfect: there is a 29 percent failure rate, patients with conjunctival inflammation and lid problems being particularly prone to problems. When successful, ocular surfaces remain stable for periods of nine years or more (Figure 3a-d). Furthermore, the procedure results in marked improvement of symptoms, including decreases in inflammation, conjunctivitis, pigment epithelial detachment, vascularization, photophobia and pain (Figure 4), and improved visual acuity (Figure 5).

Perhaps the most important finding from our work, however, is that allografts not only can be curative in cases of LSCD, but also that they appear to do so by a mechanism involving regeneration of the host limbal stem cell population. The evidence for this is that donor cells do not populate the host limbus – indeed, our DNA analysis shows that they are absent from the host eye by nine months after implantation (1). More recently, others have reported similar findings in keratolimbal allografts (EJ Holland, personal communication). Our conclusion is that the host cells take over stem cell-mediated repair of the eye within a year of implantation, and that the grafted cells are lost during this period.

The death of living donors?

The implications of the findings are immense. Firstly, within ophthalmology, it suggests that there may no longer be a need for autograft or living allograft methods. Indeed, if long-term immunosuppression is no longer required for cadaveric allografts, then living donor methods are left only with comparative disadvantages regarding their availability, the risk to healthy eyes, the discomfort and inconvenience suffered by donors, and the quantity of cells that can be generated from a given eye. Cadaveric eyes have none of these disadvantages.

Secondly – and more broadly – the idea that an unrelated allograft can trigger repopulation of a niche with autologous (host) stem cells is intriguing. Are totipotent or pluripotent stem cells being attracted from elsewhere in the body, such as the bone marrow, and then being triggered to differentiate into limbal stem cells? Or is there a transdifferentiation mechanism at work? Further elucidation of the pathways behind this fascinating observation could have massive implications for repair and regeneration of all types of tissue throughout the body.

Sheraz Daya is the Founder and Medical Director of the Centre for Sight. He was amongst the first in the UK to perform LASIK, and he has pioneered a number of corneal and anterior segment techniques and invented several ophthalmic instruments.

The author reports no relevant disclosures.

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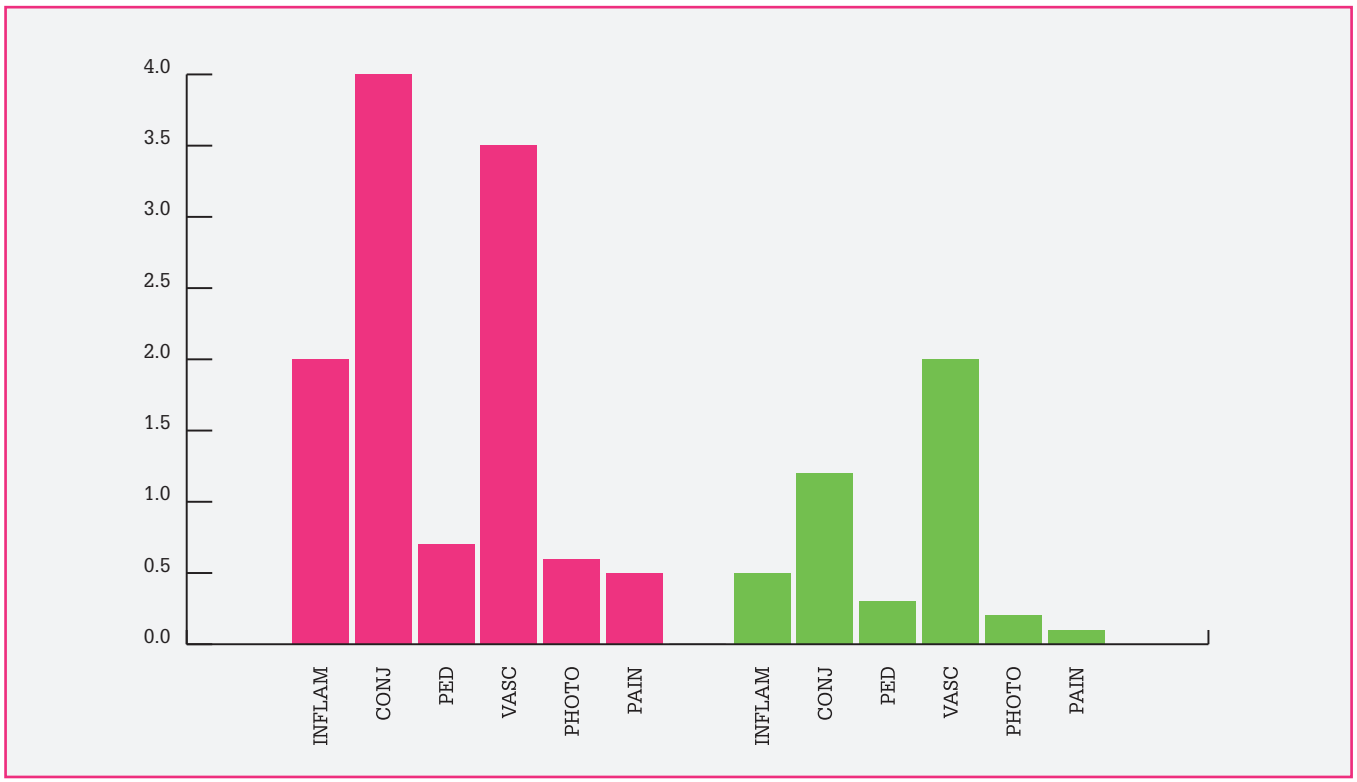


Figure 4. Reduction in symptoms and signs of stem cell deficiency (whole group, excluding failures). PED, pigment epithelial detachment.

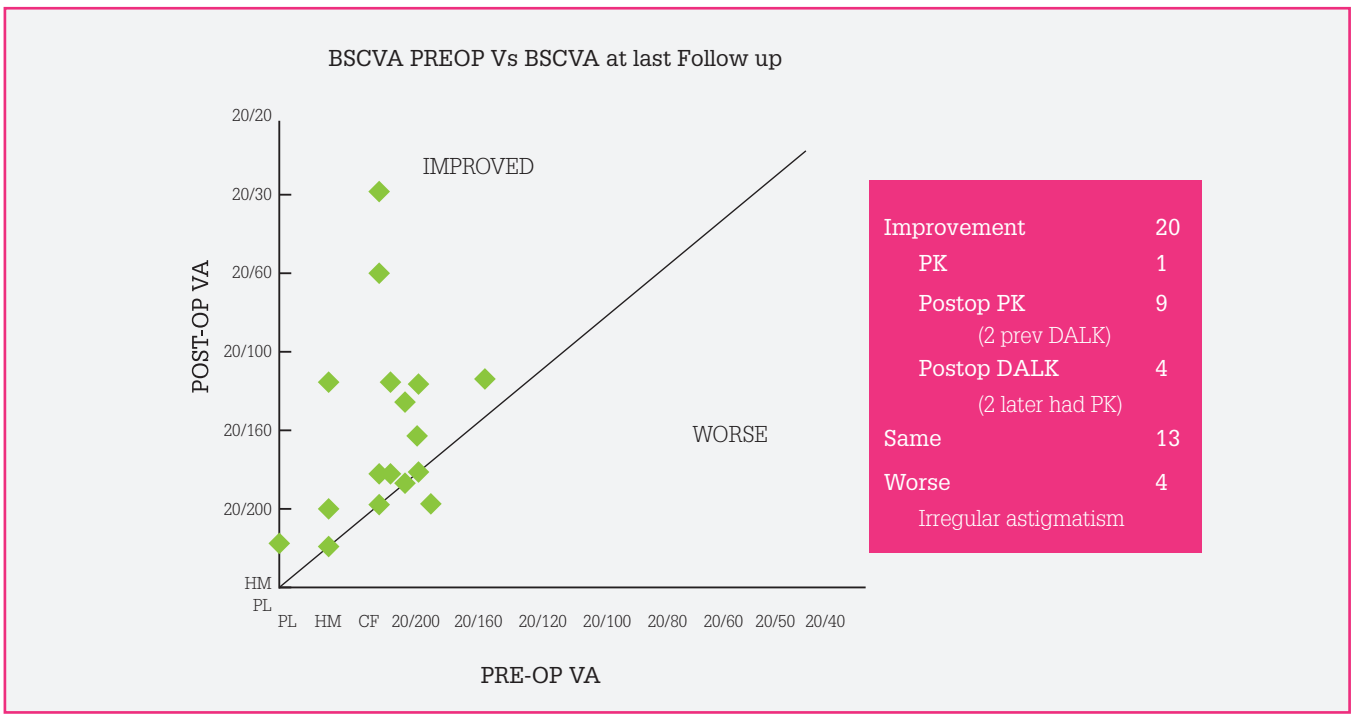
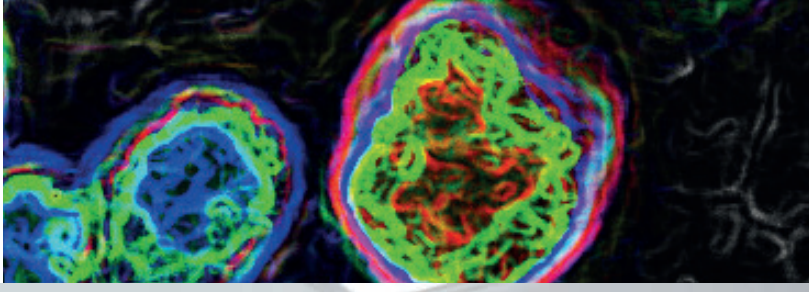


Figure 5. Visual acuity (pre- vs. post-operative BSCVA; 12 eyes with corneal grafts included.




ZEISS

Collaboration of Culture

Monty Montoya and Shigeru Kinoshita share the story of how industry and academia teamed up to bring endothelial cell therapy to patients

Monty Montoya, President and CEO of SightLife Surgical

I first began collaborating with Shigeru in 1997. We met at an ophthalmology meeting and were discussing the need for corneal tissue in Japan. Since then, we've been providing Shigeru with tissue at the Kyoto Prefectural University of Medicine and the other Kyoto institutes where he performs corneal transplantation. Over time, our relationship has grown. When starting his endothelial cell therapy research, Shigeru needed to secure a long-term commitment from an eye bank to provide him with enough research tissue to be eligible for a grant he was seeking. So around 15 years ago we formalized our commitment and we are proud to continue supporting his research.

It was thrilling to announce earlier this year that we are working with Shigeru to bring his groundbreaking endothelial cell therapy to the US. So far, 35 patients in Japan have received injections of cultured donor endothelial cells (See Box – Regenerating the Ocular Surface with Cultivated Endothelial Cell Therapy). Approximately one-third of these received their initial injections over two years ago and have gone on to have fantastic results: no complications, nor instances of graft rejection or infection – all issues that would be considered normal with corneal transplants. It's an incredible achievement and it's been inspiring to see such great results because there are so many patients who are not getting the treatment they need. The math just doesn't add up: across the world, there are more than 10 million individuals with treatable corneal blindness, but only 150,000 corneal transplants are performed per year – partly because there is not enough donor tissue. With cultivated endothelial cell therapy, one donor cornea could reach so many more patients – upwards of 100. It has the potential to reach millions of people who are waiting for a sight-restoring treatment, and my ultimate hope is to one day eliminate all endothelial-related corneal blindness across the globe.

We've completed the first step in our journey, which was to replicate the cell processing and set up a facility in the US. The next step is to demonstrate that we can transfer Shigeru's clinical results from Japan, and we hope to begin clinical studies in 2018. Although we've succeeded in setting up the facility, the process has not been trivial – there have been

Regenerating the Ocular Surface with Cultivated Endothelial Cell Therapy

- Corneal endothelial cells derived from allogeneic donor cornea are multiplied through culturing under specific conditions in a specialized culture medium – the "secret sauce" as Monty puts it.
- Whilst the precise components of the medium are protected by intellectual property, a key ingredient is a proprietary Rho-associated protein kinase (ROCK) inhibitor.
- Work by Shigeru and his team has identified that a specific subpopulation of cultured corneal endothelial cells are the most suitable "effector" cell population for clinical application in the anterior chamber (1). They have also identified that to maximize the proportion of effector cells – for a homogenous population of cultured corneal endothelial cells, the preferred donor age is <29 years and a continuous presence of ROCK inhibitor Y27632 is required (1).
- The cultivated cells are injected into the anterior chamber where they can reconstruct and regenerate the ocular surface.
- The therapy could potentially treat many corneal endothelial disorders such as Fuchs' dystrophy, penetrating bullous keratopathy and post-surgical corneal dysfunction.

many challenges and surprises along the way! One of the main challenges has been the language barrier; all the protocols and instructions were in Japanese and the translations were not always perfect, especially with technical and scientific terminology. We had to work together very closely to verify that our translations were correct. Another was that reading the protocol was not enough. Cell culture is a very precise technical process, so there were techniques that had to be transferred through face-to-face training with Shigeru and his team. Finally, the challenges of taking something from the academic environment and bringing it to a commercial environment, including the preparations for FDA and other regulatory approvals, has been much more complicated than both Shigeru and I anticipated. We thought transitioning the

"We believe that the procedure is extremely effective for cases of more difficult corneal endothelial dysfunction, such as failed grafts."

science would be the hardest part, but right now, transitioning the treatment from academic research to commercialization is equally – if not more – challenging.

Collaboration has been so important, and throughout the whole process we've been in constant communication and have made multiple trips between the US and Japan to ensure that we were all on the same page. Perhaps the most important aspect of our collaboration has been the ability to bring cornea-related academic research from "bench to bedside" – an ability that has been lacking in the cornea ecosystem. There has been a lot of research on the cornea, but the market has never been big enough to try and drive the innovation and commercialization that you see in other fields, such as cataract. But if corneal research performed in academic institutions is not reaching and benefitting patients, it lessens the value of that research. It's why having a bridge between academia and industry is critical; it helps realize the purpose of all the hard work. Shigeru began his research with the vision of providing corneal blind individuals access to a better treatment. Without commercialization of his treatment, that would never happen. And the importance of having a commercial entity such as ours dedicated to the cornea space is highlighted in the ability to develop this treatment for the corneal blind. We're pleased to be part of this vital collaboration to reach the people in need around the world and provide them with a treatment that could safely restore their sight. We simply could not have done this as a nonprofit organization.

Shigeru Kinoshita, Professor and Chair of Kyoto Prefectural University of Medicine, Japan

It is every researcher's dream to see their hard work getting closer to the people it will serve – many research projects never make it to market. I'm fortunate that I've been able to work with such a great team, organizations like SightLife and

Monty Montoya
President and CEO of SightLife Surgical, Seattle, USA

Monty is CEO of SightLife Surgical, and the former CEO of its nonprofit parent company SightLife. He joined SightLife in 1997, and has since been dedicated to transforming the cornea ecosystem by driving innovations in research, products, prevention and policy. He has been honored with prestigious awards for his vision and service, including the Ernst & Young 2014 Entrepreneur of the Year Award in the Pacific Northwest Life Sciences category and the Eye Bank Association of America's coveted Heise Award, which is given to a non-medical individual who has made the greatest contribution to advancing the cause of eye banking.

Shigeru Kinoshita
Professor and Chairman of Ophthalmology at Kyoto Prefectural University of Medicine, Kyoto, Japan

Shigeru Kinoshita established, along with Richard Thoft, the concept of centripetal movement of corneal epithelium. This shed new light on the importance of the limbal epithelium and contributed to the development of corneal stem cell theory. Over the last 30 years, his primary interests have been focused on the research and development of new therapeutic modalities for the cornea. To this end, Kinoshita's group has established systems to transplant cultivated mucosal epithelial stem cells and cultivated corneal endothelium.

now SightLife Surgical, and a community of peer researchers. Without everyone involved, we would not be where we are today.

I got to know Monty in 1997 and I began using SightLife as my exclusive provider of corneas. The real collaboration regarding our research on injectable endothelial cell therapy came together later on. The cultivated endothelium treatment is a very delicate process that has taken over a decade to develop to make it as safe and effective as possible for patients. At a very topline level we cultivate and expand endothelial cells from a donor cornea through several passages in a specialized culture medium. These cultivated cells are then injected into the anterior chamber, and patients lay face down for three hours after the treatment.

We started clinical research with our cell injection procedure in December 2013, and based upon the safety and efficacy data – as well as additional safety data from animal experiments – we received official permission in March 2017 from the Japanese Ministry of Health, Labor and Welfare to perform a clinical trial of this cell injection procedure in Japan. As we are now preparing the cells for injection, we will perform the surgery in a Phase II clinical trial in October and November of this year. What comes next for our research? First, we would like to securely transfer this procedure to the global society. Second, we would like to optimize several aspects related to the cell culture procedure and cell transportation. And third, we would like to develop a novel treatment using an eye drop or injectable material for early corneal dysfunction.

I hope our endothelial cell therapy has a transformative impact on how endothelial dysfunction is treated because it could eliminate the need for corneal transplant – which is a much more intensive treatment. Also I hope it becomes the standard for treating people with endothelial-related corneal blindness, as the treatment eliminates many of the potential complications that come with corneal transplants, including graft failure and infection. It also allows us to treat up to 100 people with a single donor cornea. I believe our therapy would be particularly beneficial in developing countries where access to corneal tissue or health care is limited. Furthermore, we believe that the procedure is extremely effective for cases of more difficult corneal endothelial dysfunction, such as failed grafts.

I'm excited to collaborate with Monty and SightLife Surgical to get this treatment to people around the world. As a researcher there is no guarantee that your work will reach anyone beyond research trials. The collaboration between industry and academic researchers is critical. It is the only way to get new treatments to the people in need.

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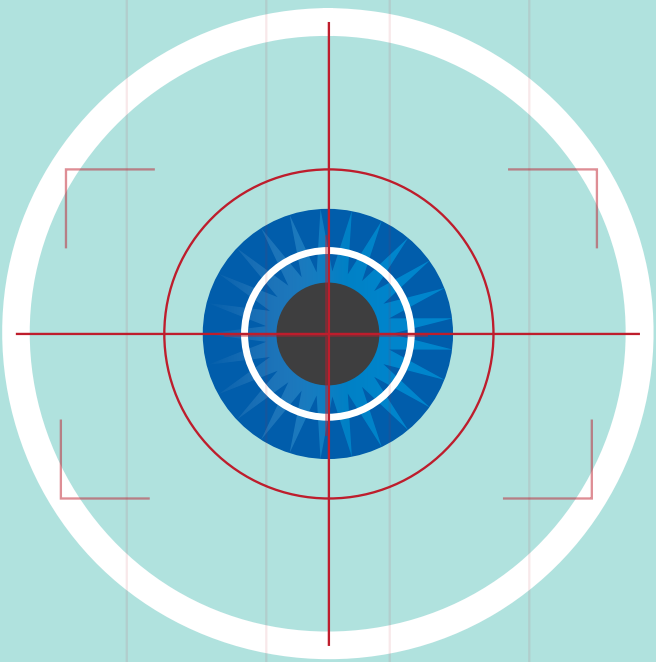

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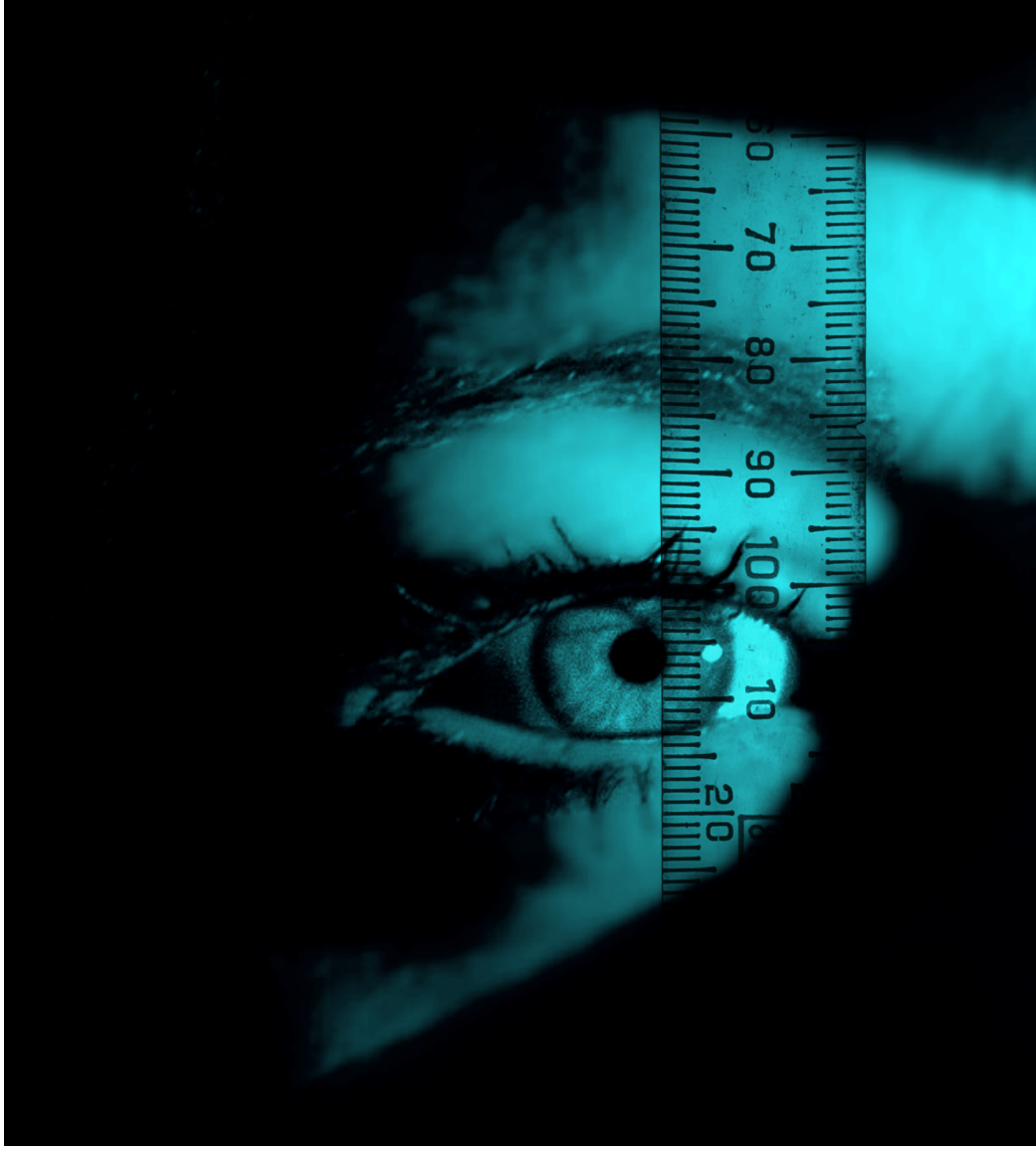
38–41
Don't Be Left in the Dark
Michael Larsen discusses dark adaptation, and how identifying impairments could help diagnose early AMD.

Don't Be Left in the Dark

How measuring dark adaptation could help diagnose AMD earlier

By Michael Larsen, Professor of Clinical Ophthalmology at the Rigshospitalet in Copenhagen and at the University of Copenhagen, Denmark



Age-related macular degeneration (AMD) represents a significant public health burden; over eight percent of the global population live with this chronic condition, and are at risk of progressive central vision loss (1). The disease is typically first diagnosed in its intermediate to advanced stages through fundus examination, and autofluorescence and OCT imaging. However, there is evidence suggesting that very early functional changes can occur – possibly even before structural changes in the fundus can be detected, implying that AMD could be diagnosed much earlier than it is now. Earlier diagnosis could be achieved through functional methods alone or in combination with imaging modalities, and would have important implications for how the disease is managed, as well as patients' prognoses. Because patients with AMD commonly complain of impaired night vision, assessing dark adaption might be one such method.

At a Glance

- *AMD represents a significant public global health burden, but is only typically diagnosed when patients have intermediate to advanced stages of disease*
- *Dark adaptation, the ability of the eye to adjust from light conditions to dark ones, can be impaired in patients with AMD and other retinal conditions*
- *Historically, the use of dark adaptometry to diagnose AMD has been limited thanks to lengthy and burdensome tests – but faster tests are now becoming available*
- *Identifying patients with impaired dark adaption could have a beneficial impact on early AMD diagnosis and management.*

The evolution of dark adaptometry

Dark adaptation refers to the ability of the eye to transition from well-lit or bright environments to dark or dim ones, and is measured through dark adaptometry (See Sidebar – Dark Adaptometry 101). Though the field of medical retina has exploded in terms of volume and sophistication when it comes to diagnostic imaging techniques and treatments, dark adaptometry and assessments to measure and monitor partial night blindness have been 'left in the dark.' In the past, measuring dark adaptation had found few uses in the clinic, as it was considered to be relevant for diseases such as retinitis pigmentosa and vitamin A deficiency – and these can be easily identified by other means. Additionally, traditional dark adaptometers, such as the Goldmann-Weekers device, are manually operated and testing can take 60–120 minutes in a dark room, which can be very tiresome for both the patient and the operator. Consequently, there are few

manual dark adaptometers around and possibly even fewer people who are trained to use them. To address the issue, rapid adaptometers and methods have been proposed, one of which is the AdaptDx (Maculogix) – a dark adaptometer that has been optimized for the assessment of partial night blindness in AMD.

"In the past, measuring dark adaptation has found few uses in the clinic."

Originally developed for use in research settings (such as clinical trials) where optimizing speed, accuracy, and comfort are essential to data acquisition and patient retention, the AdaptDx can perform exams in as little as 6.5 minutes, and can measure rod intercept (RI), an estimate of rod recovery speed that correlates closely with data acquired from traditionally used adaptometer models (2).

Bringing things to light

How can measuring RI help patients with AMD? Studies have shown RI to be a sensitive and specific diagnostic parameter, both in identifying AMD and for predicting future disease. One study assessed both healthy individuals (n=21) and patients with confirmed AMD (n=127), and found that 90.6 percent of patients with AMD had an abnormal RI value – showing high sensitivity ($p<0.001$) – and that 90.5 percent of healthy patients had a normal RI value – showing high specificity ($p<0.027$) (3). When the severity of disease was assessed, the diagnostic sensitivities were 80.5 percent, 94.4 percent, and 100 percent for early, middle, and late AMD, respectively. In a prospective cohort study, RI was measured in 325 patients with normal macula health (both eyes were step 1 on the Age-related Eye Disease Classification system [AREDS]). At the three year follow-up, patients who had an abnormal RI value at baseline were twice as likely to have developed AMD compared with the rest of the study population (4; Figure 1). These findings suggest that impaired dark adaptation might be predictive of AMD before structural lesions have even developed – a finding supported by other studies (3–6). Together, these studies show that dark adaptation is impaired in AMD and suggest that delays in dark adaptation, as measured by the RI value, can predict future AMD and distinguish between early, middle, and late-stage AMD.

Implications for clinical practice

Like many other retinal degenerations, AMD initially causes death of rod photoreceptors, ultimately leading to cone degeneration and loss of vision that greatly affect the ability of the patient to lead an independent life. If rod degeneration could be prevented, perhaps cone-based vision could be saved as well. Detecting the presence of disease earlier – or a patient's potential to develop it – would, therefore, be preferable. Dark adaptation is an important aspect of retinal function that could aid earlier treatment intervention, as well as earlier monitoring of disease progression for research purposes and clinical practice alike. And that's why dark adaptometry

Dark Adaptometry 101

Dark adaptometry measures the absolute thresholds of cone and rod sensitivity. In the traditional testing format, the patient (under dark conditions) is presented with flashes of light that cause photobleaching and eliminate all or some of the patient's dark adaptation. The patient's rate of dark adaptation is measured by measuring their response to a dynamic stimulus – after the flash, the dark adaptometer measures the lowest intensity of light that the patient can see (the threshold light intensity) as a function of time and shows it as a dark adaptation curve (Figure 1). The intensity of illumination needed for a flash of light to be just visible decreases with time in a biphasic pattern if the patient has normal vision. The initial phase of adaptation is mediated by the cone photoreceptors, which are responsible for daylight vision, after which follows a phase of adaptation mediated by the rod photoreceptors, which enable night vision.

Traditional dark adaptometers include the Goldmann-Weekers, Roland, Metro-vision and YAK-II devices. The rapid dark adaptometry device, AdaptDx, is a short-duration dark adaptation protocol that induces photobleaching through a short, intense flash, followed by immediate measurements of patient sensitivity to light stimulus. Patients are asked to indicate when a fixation light is visible to them, and with each response, the fixation light decreases in intensity. RI represents when recovery of visual sensitivity and dark adaptation is completely mediated by rod photoreceptors.

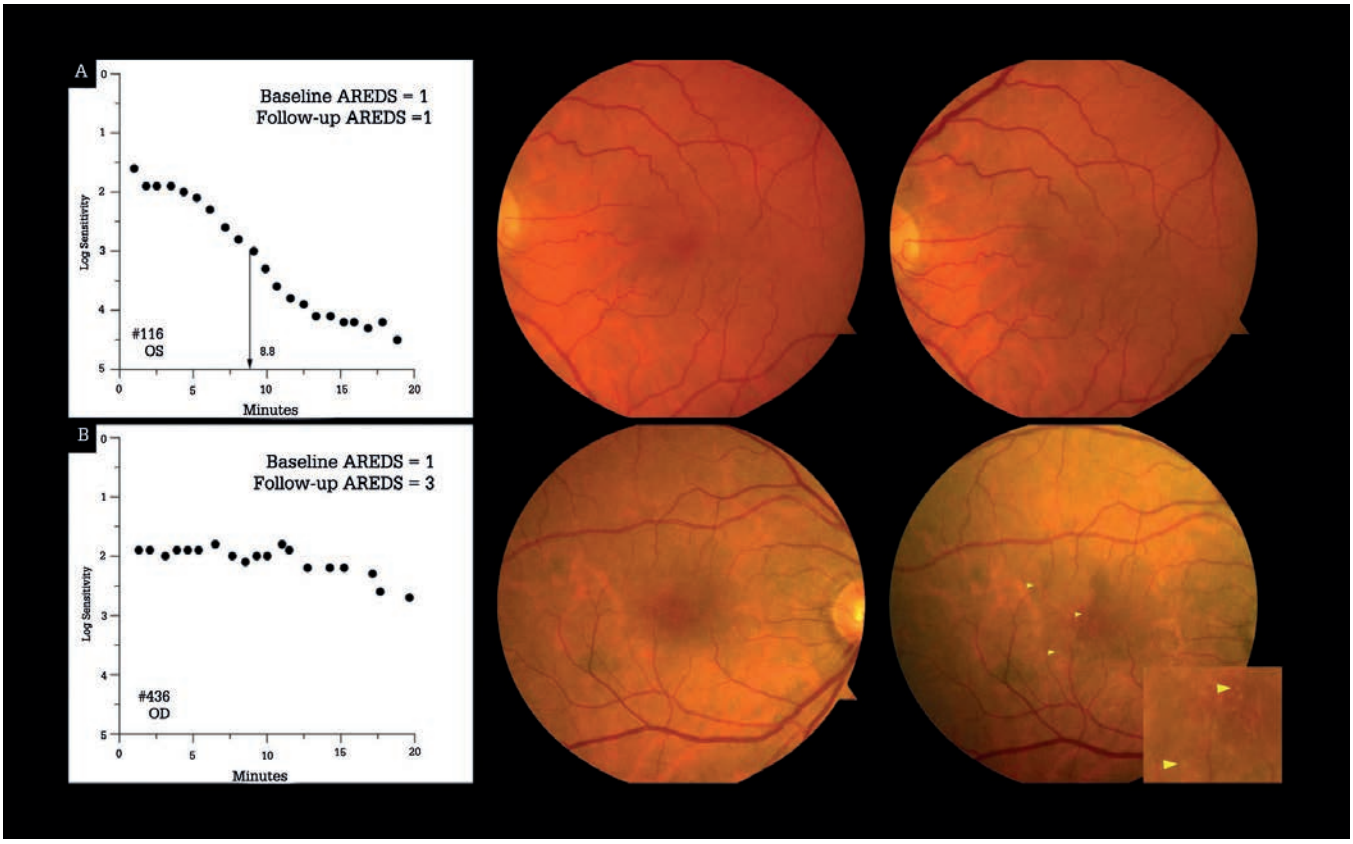


Figure 1. Predictive value of dark adaptometry. A full-length (20-minute) dark adaptation protocol was performed on patients. A patient with a normal fundus at baseline (AREDS = 1, top left fundus photograph) had normal dark adaptation (a) and a normal fundus both at baseline and three years later (top right). Another patient had a normal fundus (bottom left), but poor dark adaptation at baseline (b). Three years later, this patient had developed drusen characteristic of AMD (bottom right). Adapted from (4).

is now transitioning from the research setting into routine clinical care to diagnose and monitor AMD (7), as well as other conditions that can impair dark adaptation, such as congenital stationary night blindness, retinitis pigmentosa and vitamin A deficiency.

Measuring dark adaptation as a functional test of retinal health (in combination with fundus photography and OCT) to assess a patient's risk for developing AMD could also improve how ophthalmologists approach the condition. For example, if a seemingly healthy patient shows impaired dark adaptation but no other eye disease has been identified, the physician could encourage the patient to take preventive measures against AMD: stopping smoking and making dietary and behavioral changes, specifically, eating more vegetables, losing weight (if necessary), and doing more regular aerobic exercise. The fear of going blind has been found to be on a par with the fear of developing cancer or Alzheimer's disease in patients in the US (8), so a predictive indicator of AMD could provide the impetus patients need to make lifestyle changes that prevent or delay the onset and progression of AMD. In my experience, patients are particularly motivated by personalized counseling from a health professional who can confirm and clarify the many recommendations aimed at the general public from sources that are not always reliable.

The bigger picture

Just like high blood pressure and cholesterol are warning signs that motivate patients to discontinue bad habits and make lifestyle changes, impaired dark adaptation could be used as a tool to encourage patients to make overarching improvements in their life, not just for their ocular health, but for their overall wellbeing. By reinforcing this message, ophthalmologists can do more to contribute to general health,

which will reduce the public health burden of not only AMD, but countless other diseases as well.

Michael Larsen is Professor of Clinical Ophthalmology at the Rigshospitalet in Copenhagen and at the University of Copenhagen.

Financial disclosures: Larsen reports that he has no financial interests in MacuLogix Inc.

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How one organization and a flagship aircraft are changing the lives of millions across the globe

By Ruth Steer and Roisin McGuigan

Back in March 2017, we hit the road before dawn to make a 200-mile journey to Stansted Airport. But we weren't jetting off on some far-flung expedition, we were there to see Orbis' new Flying Eye Hospital – an MD-10 aircraft that functions as a state-of-the-art ophthalmic surgery and treatment center, as well as a training facility.

Many of you will be familiar with the primary mission of Orbis: to prevent and treat avoidable blindness and visual impairment across the world. By flying out to locations across Africa, Asia and Latin America to screen for and treat ophthalmic diseases, they are able to fulfill part of this mission. But the Flying Eye Hospital isn't the full story; the many people who work and volunteer for the organization are the real heroes – and their work goes far beyond the airplane. From the air to the ground, this worldwide outreach program trains health workers, strengthens hospitals, educates local communities, and advocates in addition to treating patients. In this two-part installment, join us on a tour of this flagship airliner, and meet some of the dedicated team members who devote their lives to this worthy cause.

At a Glance

- *Back in 1973, Orbis was founded by a visionary Texan ophthalmologist who wanted to combine eyecare and aviation*
- *By 1982, the Flying Eye Hospital was born, and was transporting volunteers worldwide to provide eyecare and outreach programs to those who needed it most*
- *Now, the Orbis Flying Eye Hospital is in its third-generation, and is expanding its global reach as well as its eyecare and training capabilities*
- *Join us on a visual tour of this state-of-art aircraft, and hear from some of the volunteers involved.*

A Flying Visit

The airplane

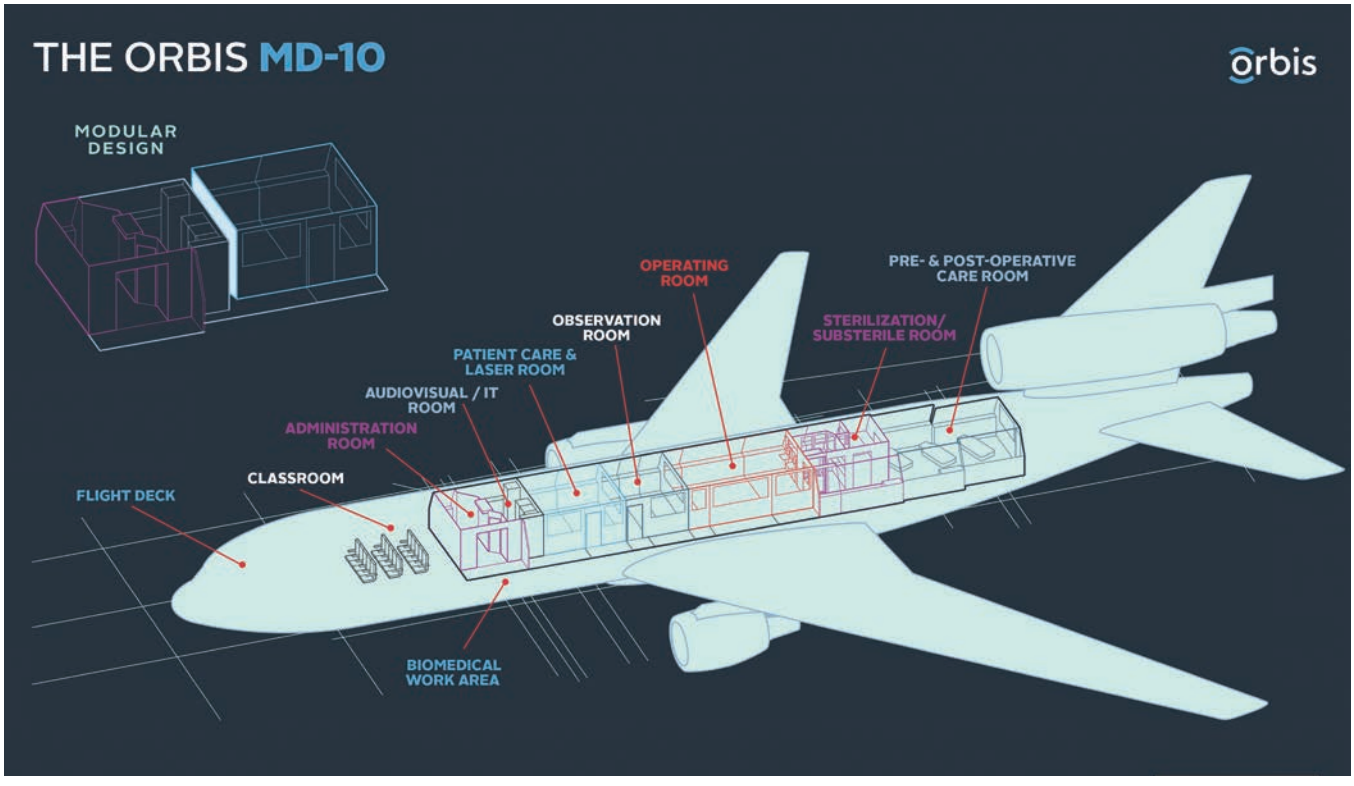
Back in 1982, the first Flying Eye Hospital took off. Now, the iconic aircraft is in its third generation. The newly crafted McDonnell Douglas MD-10, a donation from FedEx, has been converted using a modular design to include an operating theater, an observation room, a 46 seat classroom, and a sterilizing room, as well as a pre- and post-operative care room. The MD-10 has an increased flight range compared with the old DC-10 Flying Eye Hospital (from 4,000 to 6,000 nautical miles), and it only requires a two-person flight crew (pilot and co-pilot) rather than the DC-10's three (pilot, co-pilot and flight engineer).

Heading inside…

With your blue overshoes applied, going through the front door brings you into the classroom – the cockpit, as usual, is to the left. When flying, it hosts the crew, but on location it turns into a lecture theater and cinema. "When we do a training program, we usually work with the local eye hospital and invite their doctors, nurses and anesthetists to come on board," says Celia Yeung, Orbis' Communications Manager. "We have different kinds of training,

The MD-10 ready for painting.

Installing the Modules



"Programs will focus on training across a wide range of sub-specialties, including pediatric oculoplastic, glaucoma and cataract surgery."

including lectures and symposia, and they can watch live surgery from the operating room." The aircraft also has the capability to live-stream footage so that people all over the world can watch surgery in real time. "We also record all the surgeries and give them to the local hospitals for training material," Yeung says.

Into the main arena…

At the rear of the classroom, a door leads to the hospital unit, which comprises an audio-visual/IT room, a patient examination and treatment room, the operating theater, as well as sterilization, pre-operative preparation, and post-operative recovery rooms. The patient examination and treatment room is full of equipment: slit lamp, OCT, optical biometer, and a corneal topographer to name but a few. One key piece of equipment is the VRmagic EyeSi virtual reality surgery simulator, used to train local doctors.

The operating theater is located in the heart (and the most stable part) of the aircraft – in the center of the fuselage, right between the wings. Ian Fleming, volunteer anesthetist, says, "One of the biggest jobs was getting the floor 'rock solid' – it needs to be as stable as possible." Jokingly reassuring the visitors that they do not operate whilst flying, Fleming notes that if you saw the OR in flight, you wouldn't recognize it – everything is strapped down and bolted away. "It takes the crew half a day to set it up when we land," he says, referring to the vast array of surgical equipment in the theater, with the bed and large top of the range 3D microscope forming the centerpiece of the room. Now that the operating theater has gone 3D, visitors in

A Timeline of Orbis and the Flying Eye Hospital

- *1973*
  Project Orbis is born. David Paton, an ophthalmologist from Houston, Texas, has a bold vision: "to use aviation to deliver medical education to the eyes of the world."
- *1982*
  The DC-8 Flying Eye Hospital takes off from Houston, Texas, bound for Panama on its first ever program.
- *1984*
  Orbis is commended by the UN for bringing together Turkish and Greek doctors to deliver training during a trip to the divided island of Cyprus.
- *1987*
  The Flying Eye Hospital makes a historic visit to the Soviet Union, conducting programs in Moscow and Leningrad at the height of the Cold War.
- *1991*
  The plane is invited to Cuba to conduct a three-week program. Fidel Castro himself visits the plane.
- *1993*
  Mother Teresa visits the plane during a trip to Kolkata, India.
- *1994*
  Orbis' DC-8 is formally retired and donated to Datangshan museum near Beijing, China, and the Orbis DC-10 takes to the skies.
- *1994–2011*
  The DC-10 conducts 120 programs in countries including Syria, Kenya and Laos.
- *2011*
  FedEx donates an MD-10 aircraft.
- *2011*
  Actor Daniel Craig visits the Flying Eye Hospital in Mongolia to film a short documentary on Orbis' work.
- *2016*
  After completing a further 19 programs, the DC-10 is retired and donated to Pima Air and Space Museum in Tucson, Arizona, USA. The MD-10, the third-generation Flying Eye Hospital, takes to the skies, landing in Shenyang, China for its first program.

the classroom can watch whole surgeries in 3D. Fleming says, "We have five cameras in here, with one through the microscope, so that everything can be filmed and relayed to the classroom." Microphones also allow the surgeon to provide a running commentary as well as field questions from the classroom. Coming out of the operating theater, a small corridor bypasses the sterilization room and leads to the pre-operative and post-operative recovery room, complete with iconic Orbis teddy bears for younger visitors to play with. The separation of the sterilization room is a major improvement in the new MD-10 hospital – patients and staff had to walk through sterilization to get to recovery in the old DC-10.

Back on solid ground…
Shortly after its pit stop at Stansted Airport, the Flying Eye Hospital left for Dubai, then Qatar – with many more destinations planned including Cameroon and Bangladesh for six weeks of additional training programs. With over 10 volunteers already enlisted, these programs will focus on training their peers within the host countries across a wide range of sub-specialties, including pediatric oculoplastic, glaucoma and cataract surgery.

The first and second generation Flying Eye Hospitals – the DC-8 and DC-10, respectively – were each in service for 12 years. There are doubtless many years of service ahead for the MD-10 and its dedicated volunteers – and that means many years of preventing and treating avoidable blindness and visual impairment across the world.

In next month's issue, we'll meet some of the dedicated volunteers from the organization and hear their stories.

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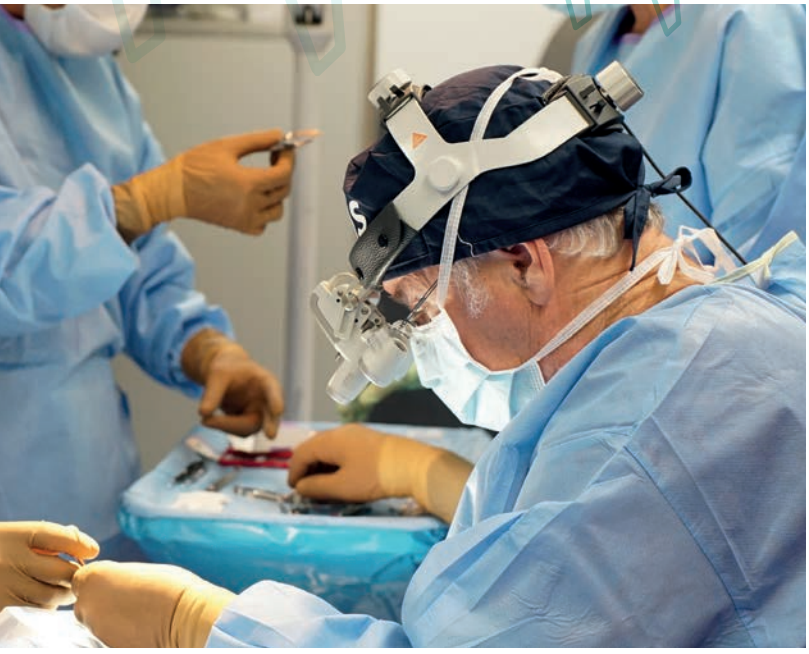

Ophthalmology Chose Me

Sitting Down With… Richard Lindstrom, Chairman and Founder of Minnesota Eye Consultants, Minneapolis, Minnesota, USA

What was the starting point of your career?

I grew up surrounded by the family business, which is a small construction company that provides insurance restoration. I was starting to be indoctrinated into the business around the age of 12 – mostly at the dinner table! The intent for me was to attend college and then join the company. Turns out I was a pretty good student – at the University of Minnesota I was placed in the Honors Division and the Dean of the Medical School ended up as my advisor. To make a long story short, he was very charismatic and it took him about a year to talk me into going into medicine instead of joining the family business. So I'm a little atypical; I wasn't one of those young people who always wanted to be a doctor – medicine chose me. It was fate or serendipity, depending on how you look at the world.

And ophthalmology?

I was interested in surgery so I rotated through all of the specialties in medical school. And, similar to my move into medicine, I was 'chosen' to become an ophthalmologist by the late Donald Doughman – a very talented professor and corneal specialist, who had come to Minnesota from Harvard. I ended up working in his laboratory in my third year of medical school, and within a year, he'd convinced me that I was not only going to become an ophthalmologist, but that I was going to become a cornea specialist and become involved in eye banking and corneal preservation – all things that I have gone on to do.

I always remind my mentees that opportunities roll pretty fast and although you don't always know where they will take you, saying "yes" will likely lead to growth experiences and adventures. Many people question their skills and labor over decisions, and I also had doubts: was I up to the challenge of being a doctor or working in a research laboratory? Could I make a meaningful contribution? But by simply embracing those opportunities, I was rewarded with wonderful educational and growth experiences.

What got you into working with industry?

At 32 years old, as a young Assistant Professor at the University of Minnesota, I got a call from a senior executive from the 3M Corporation – they'd just acquired an eyecare business and wanted to speak to me about it. I became their Chief Medical Officer and it developed into quite a business education! While I was there, we developed the first diffractive multifocal IOL, as well as gas permeable hard contact lenses. I spent the next 15 years working with them until they sold the business; the cataract/multifocal part was acquired by Alcon and that technology led to the ReSTOR multifocal IOL. It was this experience with 3M that got me started working with industry, and ever since I have been excited about innovation and new technology, not only in translating it from the bench to the clinic, but also in teaching people how to use it.

And your drive to set up Minnesota Eye Consultants?

After becoming a full Professor at the University of Minnesota and being awarded the Harold G. Scheie Research Chair, I decided I wanted to try private practice, and founded Minnesota Eye Consultants. My goal was to build an academic private practice, a new concept at the time. Twenty-eight years later we've gone from myself and six employees to being a very strong practice in our region with 26 doctors and over 300 employees: we perform a lot of translational research, consult with industry, and train young ophthalmologists in our area of expertise (primarily cornea, cataract, refractive and glaucoma).

I believe that teaching fellows is one of the greater contributions I have made. I have certainly contributed to ophthalmology in terms of inventions, publications, and educational materials, but when I think about what was most valuable, I would say that it has been training young and talented cornea, cataract, refractive and glaucoma specialists. The impact has been greater than anything else, and I am proud of it.

Did growing up around your family's business influence your own career?

The way the world sometimes works is amazing. I have actually ended up being the Chairman and CEO of the company. When my father was ready to retire at age 70, I bought the company from him. He sat on the board for 10 years after that; working together was exactly what he wanted and in the end we actually got to do it, and now my family members will continue to be part of the business. Isn't it funny how things can sometimes come full circle?

Any plans to retire?

I don't actually plan to retire, but there is a point at which it is wise to step out of the operating room. I'm a planner, and I'm just into the first year of my current five-year plan. In just over four years, I plan to transition into being a medical ophthalmologist, but will still be involved in leadership positions, venture capital, industry and the ophthalmic societies that are such a big part of my life. I plan to be much like Brad Straatsma – very involved in ophthalmology and committed to seeing it succeed years after stepping down from active practice.

I have a wonderful family and many friends, and I could just decide that I want to spend the rest of my days playing tennis and golf, and fishing and hunting. And though I take time to enjoy all of these things, I still continue to be intellectually curious. I have many business friends who are retired but whose profession was just to make a living. My career gives me joy and makes me feel fulfilled, and I want to continue in the field as long as I am able to do so.

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