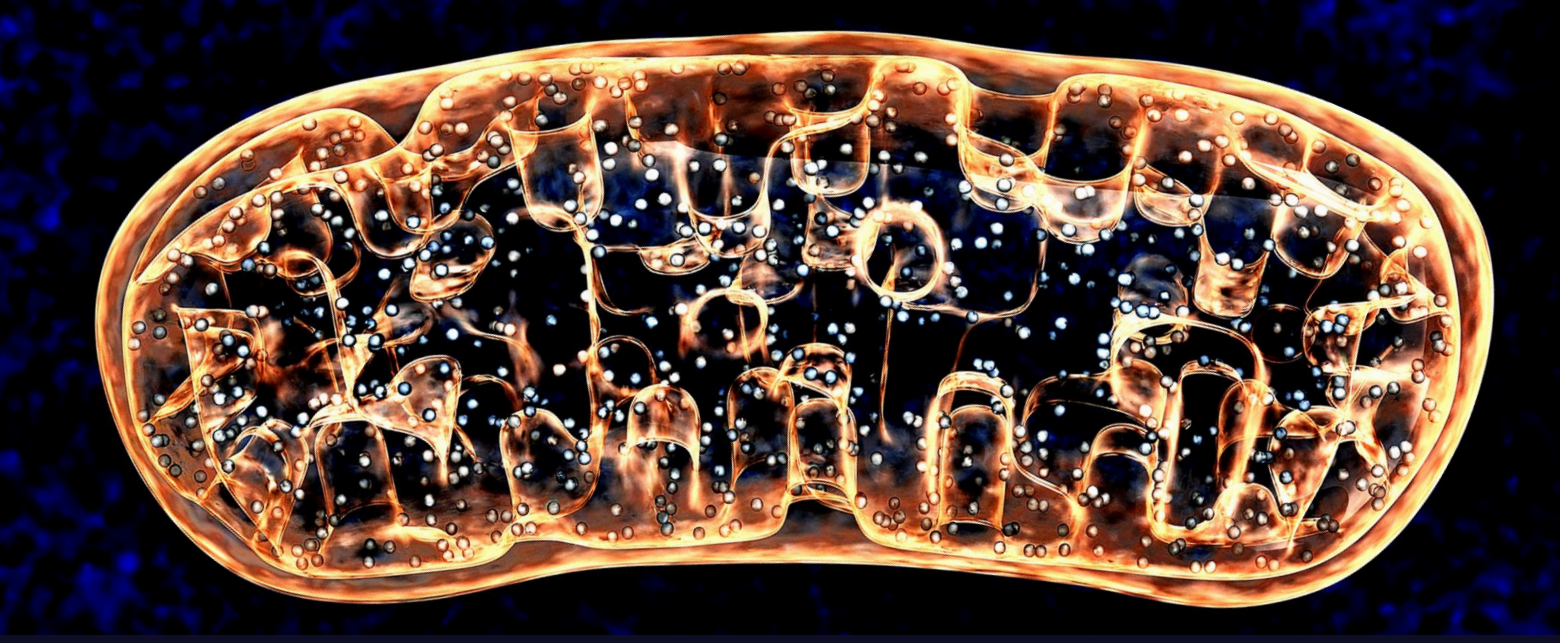
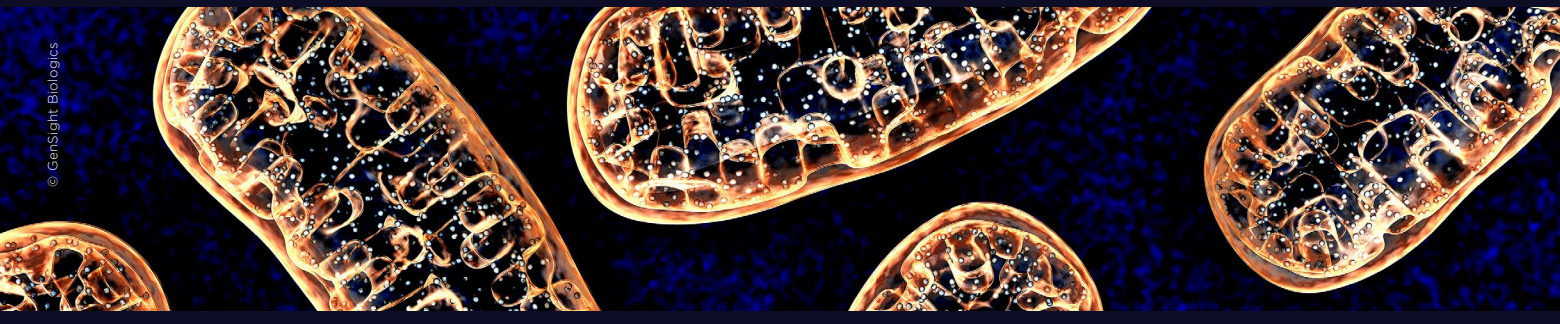


Perspectives on the Profession

BECAUSE THE END OF THE YEAR IS A FITTING TIME TO TAKE STOCK of recent events, *EyeNet* asked a few of its editorial board members to review developments or trends in their areas of expertise and to consider which of these has the greatest potential to shape their subspecialty over the next several years. Kendall E. Donaldson, MD, MS, and Karolinne M. Rocha, MD, PhD, prognosticate on the future of cataract surgery. Prem Subramanian, MD, PhD, looks ahead in neuro-ophthalmology. And Janice C. Law, MD, shares her thoughts on the near future of retina.

Here are their perspectives.



AAV. *The GenSight Biologics gene therapy vector restores energy production in mitochondria, which is vital for vision and is severely impaired by the* ND4 *mutation.*

CATARACT SURGERY

Postoperative Adjustment of IOLs

Dr. Donaldson and Dr. Rocha

For cataract surgeons, success is based on achieving the best outcomes for patients. This is typically judged in two ways: safety and refractive outcomes. Given that cataract surgery is truly the most common *refractive* procedure performed around the world, patients have come to expect outcomes equivalent to or surpassing corneal refractive procedures (such as LASIK or PRK). Patients expect the very highest quality of vision—and more and more frequently they are expecting a quality of vision that allows freedom from glasses.

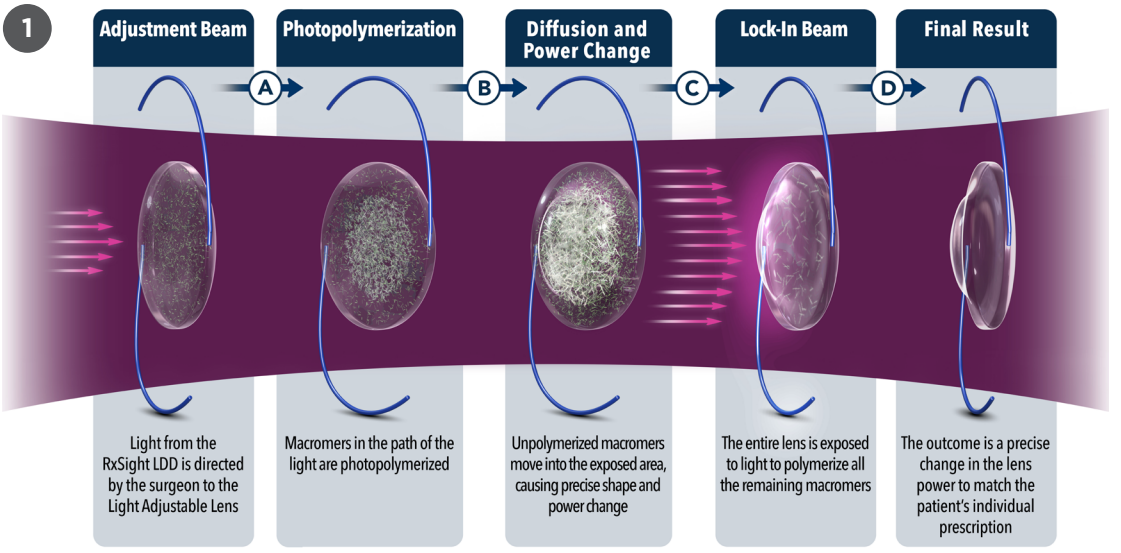
The hallmark of *great* cataract surgery is hitting the intended refractive target. Of course, surgeons know that despite having access to the highest-quality devices to conduct the preoperative assessment, there is some inherent margin of error. In addition, patients may need to accept compromises in quality of vision when light is split, as is the case to achieve the highest degree of spectacle freedom with a multifocal intraocular lens (IOL).

Now, the advent of postoperative adjustment allows us to hit our target nearly every time and is gaining popularity as we move forward. Several mechanisms allow for IOL power or IOL optics to be adjusted postoperatively. Below is a brief discussion of those that we find most promising in the near term.

Light Adjustable Lens. The only FDA-approved IOL that can be adjusted postoperatively is the Light Adjustable Lens (RxSight). It allows surgeons to fine-tune the final IOL power in the first few weeks following surgery (Fig. 1). It is currently available in a monofocal format; however, future directions include application of this technology to a multifocal variant of this lens. The Light Adjustable Lens works on the principle of polymerization of a photosensitive silicone macromer. The power of the lens may be increased when the unpolymerized macromers migrate to the central portion of the lens causing central thickening of the IOL.

Component devices. In addition to light as a mechanism to alter IOL power, component lenses and devices are on the horizon. These will allow us to change between a monofocal and a multifocal lens and to alter the power of a lens during the postoperative period. The Gemini Refractive Capsule (Omega Ophthalmics) is an example of this type of enabling technology. It is a hollow capsular expansion ring that allows technology of all sorts—lenses, drug delivery, biometric sensors—to be implanted, modified, or exchanged throughout a patient's life (Fig. 2). The device is an open access platform that can essentially hold any C-haptic IOL, while leveraging the device's extra volume for future technology (e.g., augmented reality, electronic devices). Additionally, recent studies have found that keeping the capsular bag open helps to prevent the development of capsular bag fibrosis, which can inhibit devices from working or being exchanged inside the eye. The versatility of this type of device has great potential,[1] but it requires an additional surgical procedure for each modifi-

LAL. *The only FDA-approved adjustable IOL works via polymerization of macromers, allowing unpolymerized macromers to diffuse in specific patterns. (LDD = light delivery device.)*



RxSight

GEMINI CAPSULE. *The circular device keeps the capsular bag open. Lenses and other technologies can be added to the Gemini capsule, or removed, as needed.*

cation of the lens or implantation of other technology.

Refractive index shaping. A third mechanism by which an IOL can be adjusted postoperatively is with a femtosecond laser. This is known as Refractive Index Shaping (RIS, Perfect Lens). A femtosecond laser may be used to alter the hydrophilicity of targeted areas within an IOL, giving the surgeon the ability to change the refractive index of an existing IOL. The femtosecond laser energy applied is well below the threshold for photoablation. Although this technology is in development, it offers a promising method by which postoperative, noninvasive IOL power adjustments can be obtained. This technology allows for in vivo adjustment of asphericity, toricity, and power to correct for any residual postoperative refractive error and create extended depth of focus.[1,2]

In addition, it can create multifocality (refractive and diffractive) in a monofocal lens, and it can be used to customize—and even to reverse—multifocality. Many of these treatments can be performed sequentially and be repeated, as needed, during the postoperative course.

LIRIC. Another emerging technology is known as Laser Induced Refractive Index Change (LIRIC, Clerio Vision). It is a femtosecond laser corneal procedure that can correct refractive error without causing tissue damage. Similar to RIS, LIRIC uses low-pulse energy, operating below the tissue damage threshold. The femtosecond laser produces focal refractive index changes by generating ultrastructural alterations in corneal collagen fibers (denaturation of stromal collagen fibrils).[3] Focal adjustments of the refractive index of the corneal stroma can generate optical corrections of sphere (–3.00 to +1.50 D) and cylinder (up to –1.50 D) as described by Zheleznyak and colleagues.[4,5] The LIRIC technology has also been used to generate a diffractive multifocal pattern in contact lenses.

Conclusions

Ultimately, postoperative minimally invasive adjustments of residual refractive error will provide a mechanism by which cataract surgeons can feel more confident in reaching our refractive target. It will also give us more confidence when placing a presbyopia-correcting IOL because it will allow us to gauge whether a patient may tolerate any optical compromises associated with the light splitting that characterizes multifocal lenses. This flexibility is important for patients who may feel overwhelmed by the IOL options provided to them prior to cataract surgery or who have regrets about their choice of lens.

Adjustable lens technology aims to reduce the need for IOL exchange, allowing surgeons to customize the treatment postoperatively, optimizing patients' outcomes. In addition, it will improve accuracy of IOL power in patients with challenging eyes (i.e., post-RK, keratoconus and other forms of irregular astigmatism, long and short eyes).

This new approach will be a game changer in growing the presbyopia IOL market and may dramatically increase both patient and doctor satisfaction in the upcoming years. Postoperative adjustment of IOL power and type will be a powerful tool for increasing accuracy and providing the highest quality of vision with refractive cataract surgery.

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NEURO-OPHTHALMOLOGY

Therapies Are on the Horizon for Previously Untreatable Disorders

Dr. Subramanian

For decades, researchers have been pursuing methods by which optic nerve function may be protected, restored, or even regenerated in the setting of acute or chronic disease. The biologic barriers to achieving these goals have been defined as being both structural and biochemical.

Biochemical. Experiments on both spinal cord and optic nerve injury models have shown that acute neuronal injury (such as crush or even ischemia) leads to creation of a biochemical impediment to axonal regrowth through the area of injury, involving inhibitory proteins that specifically limit axonal extension as well as more general gliotic changes. Injured axons also trigger degeneration and programmed cell death (apoptosis) of the axonal soma even if located far from the injury itself.

Structural. Chronic or degenerative diseases pose a different challenge, with preservation of the neuronal soma being the primary goal and axonal health and continued function following from that.

Recent advances in both areas have demonstrated promising therapeutic strategies, and neuro-ophthalmology seems poised to have new therapies for previously untreatable disorders.

Gene Therapy

The physical proximity of the retinal ganglion cell layer to the vitreous has made it an attractive target for intravitreal injection (IVI) of a gene therapy vehicle, the benefit being that a surgical approach is not needed (unlike the surgery necessary for treatment of Leber congenital amaurosis with voretigene neparvovec-rzyl [Luxterna]). Several animal and human experiments have demonstrated safety and tolerability of an IVI with an adenoviral vector, and three research groups around the world have shown potential clinical efficacy of a gene therapy treatment strategy for patients with Leber hereditary optic neuropathy (LHON).

Clinical trials. In a series of multinational clinical trials, a commercially developed gene therapy vector (GenSight Biologics) targeting the mitochondrial *ND4* gene (see image, page 43) was injected into either one or both eyes of subjects who were within one year of onset of vision loss from LHON associated with the *G11778A* mutation. In the unilateral injection studies (REVERSE and RESCUE), subjects' eyes were randomized to receive drug injection in one eye and a sham injection in the other. In the bilateral study (REFLECT), all subjects were injected in one eye with drug and had the second eye (the study eye) randomized to drug versus placebo injection. The results of all three studies have been released, although full publication in peer-reviewed journals is still underway.

Surprisingly, both the injected and sham eye showed improved best-corrected visual acuity in the unilateral injection trials. Preliminary data from the bilateral injection study show similar findings, with a possible trend toward a greater improvement in subjects who received drug in both eyes. Overall, the outcomes of treated patients appear superior to the natural history of LHON with the *G11778A* mutation.

Lab study. A separate nonhuman primate study provided evidence for transport of the gene therapy vector between the eyes via the optic nerves and chiasm. This finding may lead to new strategies for targeting optic nerve disease and has implications for approaches in which only one eye manifests disease and is injected with a potential therapy. Separate research teams in China and the United States also have shown safety and efficacy for similar, although not identical, treatment approaches.

Further research. Questions remain regarding optimal timing of therapy once vision loss occurs, as the existing data do not show that early treatment is superior within the chosen one-year window. Also, the bigger question of treating asymptomatic or presymptomatic genetic carriers who have not manifested vision loss in either eye remains to be addressed. Nonetheless, the demonstration of apparent success in improving visual function in a population in which spontaneous recovery is otherwise uncommon opens the door for treatment of other inherited optic neuropathies. In addition, the well-tolerated delivery of a genetic vector to the retinal ganglion cells provides an opportunity to treat other optic neuropathies by expressing molecules associated with enhancing cell survival and/or axonal regrowth in patients with acute or chronic optic nerve injury from disease or trauma.

Treating Optic Nerve Trauma

Although the time horizon for clinically useful therapeutics may be five to 10 years, better understanding of biochemical signals that allow for axonal extension through an area of injury and early glial scarring has identified promising targets.

The Wnt/beta-catenin signaling pathway, crucial for embryonic targeting and cell guidance, becomes active even in adult neurons after axonal injury. When axons regrow, they must have guidance to end up in the correct location, and upregulation of the Wnt/beta-catenin pathway in rodent models has improved such targeting in model systems. A hurdle still to overcome is to create this activation selectively, as the same cellular proliferation may be stimulated within glial cells and can cause them to proliferate further and erect a structural barrier to axonal extension.

For now, traumatic optic neuropathy from a focal optic nerve injury remains a relatively uncommon cause of vision loss, at least in North America. However, development of these therapeutics may enhance our ability to use axonal survival strategies or even to shape the next generation of treatments that could include neuronal replacement with neurons derived from stem cells, as such cells would need targeting signals to extend axons to the correct locations.

Limitations to Remember

The occurrence of apoptosis after neuronal injury must be prevented to maximize visual function after injury. Blocking apoptosis in patients with nonarteritic anterior ischemic optic neuropathy (NAION) seemed an obvious strategy for preserv-

ing neurons while the acute swelling and local tissue changes of the disease resolve. However, an international clinical trial of IVI within 14 days of NAION onset using an inhibitor of caspase-2 expression versus sham injection was halted after an interim analysis of the data showed that outcomes between the groups were not dissimilar enough to allow the study endpoint to be achieved.

Conclusions

Therapies are in the pipeline to improve visual function in patients with previously untreatable optic neuropathies. The retinal ganglion cells and optic nerve are accessible to potentially durable IVI-based therapeutics. In the next five to 10 years, our patients are set to benefit from these recent advances in the laboratory and clinical trials settings.

RETINA

When Retina Surgeons Become Microtransplant Surgeons

Dr. Law

Dry macular degeneration, wet macular degeneration, macular holes—as retina specialists, this is what we see every day. And over these last few decades, we've become adept at working in the vitreous and on the retinal surface to treat these often precarious but common sight-threatening diseases. However, our current therapies are still limited. My prediction for the future of retina is that the following novel therapies and approaches will revolutionize the way we treat these diseases: Retina surgeons will become microtransplant surgeons.

Dry AMD: Stem Cell Therapy

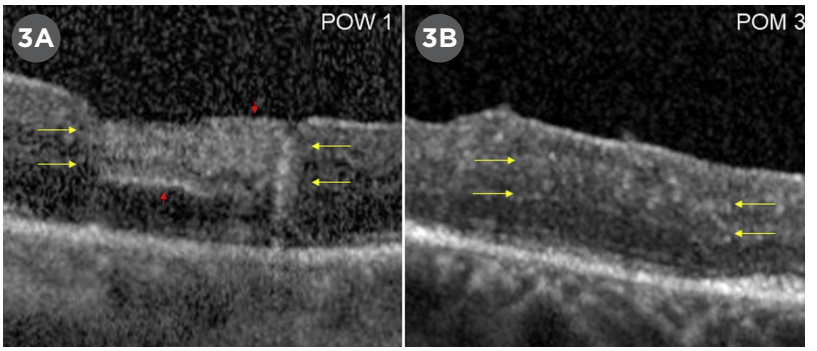
Age-related macular degeneration (AMD) is a condition that we've learned so much about over the last 15 to 20 years. Yet we haven't learned nearly enough. Despite a better understanding of the complement cascade and causes of oxidative stress, we still don't have treatments for dry AMD, only preventative measures—vitamin supplements, quitting smoking, and wearing UV eye protection. Numerous biologic and pharmaceutical companies have attempted to target different parts of the inflammatory pathways, but more research and information are needed about the pathogenesis of dry AMD and the interrelation between genetics and environmental exposure in order to halt the degenerative process.

So, if we can't stop it, let's replace the retina cells that are dying off. One group of researchers is taking human retinal pigment epithelial cells derived from an established pluripotent cell line and injecting a suspension of up to 200,000 cells directly into the subretinal space.[1] By transplanting these cells underneath the retina via vitrectomy or suprachoroidal injection, we can, for the first time, replace the lost cells that have degenerated and thinned out. It's still in a phase 1/2 safety and efficacy trial, so we will not see changes in practice patterns right away, but the early results are promising. In fact, during the four years of follow-up, treatment was well-tolerated and demonstrated a partial restoration of the retinal anatomy, with an 8 to 18 letter gain in a cohort of patients.

Wet AMD: Viral Vectors

The standard of care for wet AMD involves monthly anti-VEGF injections, which often yields great results but is accompanied by a treatment burden that is costly and inconvenient. As retina specialists, we try to find that balance of injection frequency and disease control, but we also must manage patient compliance and the cumulative risks of repeated injections. Thus, the treatment is far from perfect. However, one form of gene therapy in particular involves transplantation of sorts and has shown great potential to drastically change treatment protocols for wet AMD.

Gene therapy using viral vectors involves adeno-associated viruses (AAVs) that transport modified functional DNA to a defective cell genome. Essentially, after the AAV binds to the targeted cell membrane, the customized gene is inserted into the cell's nucleus for proper expression. And because there's a degree of immune privilege in the eye, the



ART. *Macular hole (3A) at one week post-op shows that the plexiform and nuclear layers are in seeming alignment (yellow arrows). And again (3B) at three months, the neurosensory layers of both host and donor continue to appear to be in alignment.*

vector does not spread systemically nor is there a larger immune response.

So, what does this mean for wet AMD? After the retina surgeon transplants these AAVs into the subretinal space, the viral vectors encode an antibody fragment to inhibit VEGF. In essence, this approach creates a tiny factory of anti-VEGF in that milieu underneath the retina that will, in the end, reduce or replace the need for repeat office injections of bevacizumab, ranibizumab, aflibercept, and the like. And a number of phase 1/2 trials employing different cohort groups have demonstrated positive safety profiles—with no need for rescue anti-VEGF injections. The studies have also found significant duration of treatment effect, defined as levels of anti-VEGF high enough to reduce the need for additional treatments; in some cases, the reduced need for additional anti-VEGF treatment lasted more than a year.[2-4]

Macular Holes: Autologous Retinal Transplant

The third type of transplantation surgery that is radically changing the retina subspecialty is due in large part to the research of one of my previous mentors, Dr. Tamer H. Mahmoud.

Until recently, retina surgeons' tried-and-true method for repairing macular holes has involved pars plana vitrectomy and internal limiting membrane (ILM) peeling, often along with placement of gas tamponade. Although our closure rates exceed 90%, there are many instances—maybe the hole is exceptionally large or the hole is recurrent or refractory to treatment—where, no matter what you try as a surgeon, the hole does not close, and the patient is left with a central scotoma.

In contrast, Dr. Mahmoud's ART (autologous retinal transplant) work is remedying this gap in treatment. Pun intended. The retina surgeon harvests an autologous neurosensory retinal free flap from a local site in the midperiphery and then places the graft down into the hole, flattening it. The neurosensory layers find each other, reconnect, and line up (Fig. 3). Dr. Mahmoud's research group has found promising results, with hole closure rates of around 90% for challenging cases.[5] Reconstitution of retinal layers was found on imaging, especially the ellipsoid zone, and alignment also predicted improvement in vision. This is significant. In a situation where not much more could be offered, we can now harvest retina graft tissue and use microtransplant surgery to offer new hope.

Teaching a New Generation

If my predictions are correct in the redefining of our retina subspecialty, we will see changes not only in how we practice but also in how we will teach. Vitreoretinal fellowships will need to include graft harvesting and subretinal cell delivery techniques in the operating room—and we might also expect injectable subretinal or suprachoroidal delivery in office scenarios. And so, the next generation of retina specialists will be subretinal specialists, too. As we move forward, our mainstays for treating the most common retinal conditions will take us into a new space altogether.

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MEET THE EXPERTS

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See disclosure key, page 10. For full disclosures, see this article at www.aao.org/eyenet.