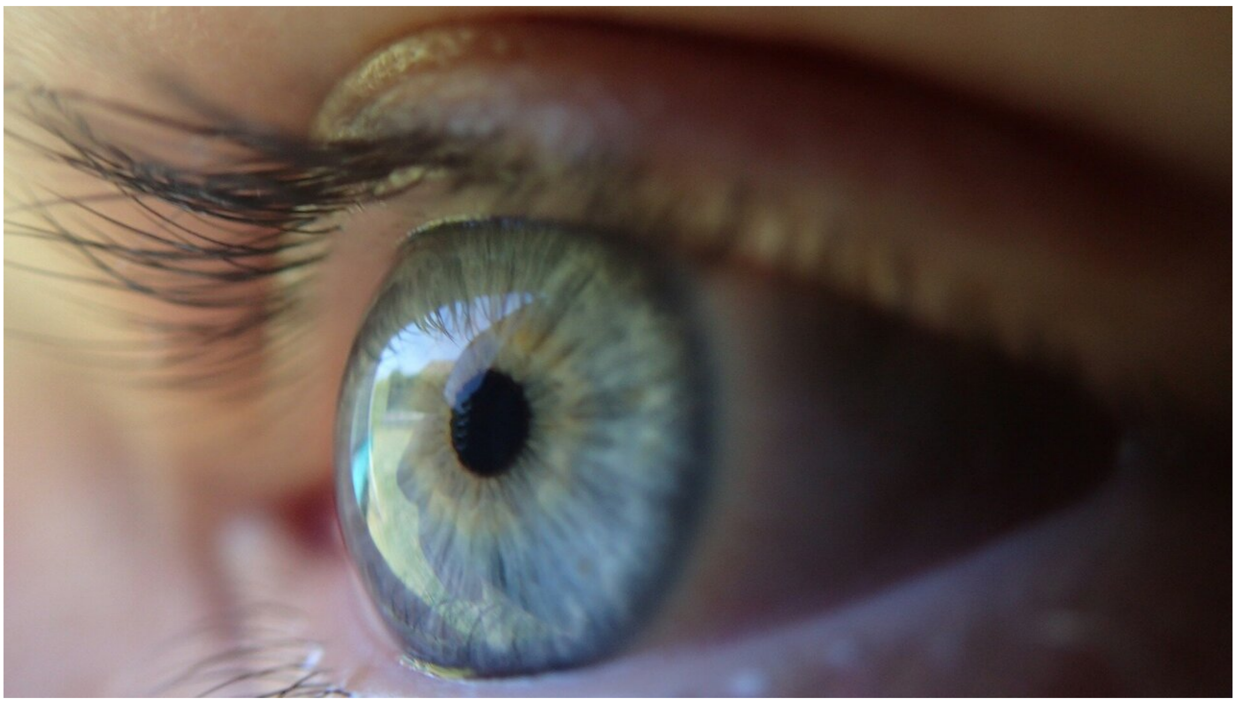
Physician-scientists pioneer new surgical approach to treat progressive blindness

July 21 2020, by Alexandra Demetriou



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Dry age-related macular degeneration (dry AMD) poses a significant clinical challenge. It is one of the leading causes of progressive blindness, robbing millions of people over the age of 65 of their central vision, and it often hinders patients' abilities to read books, drive and discern the faces of their loved ones. Although vitamin-based supplements may slow progression, no treatments currently exist.

A team of physicians and scientists at the USC Dr. Allen and Charlotte Ginsburg Institute for Biomedical Therapeutics (Ginsburg Institute) saw in this situation an opportunity to innovate and pioneer a novel treatment approach for dry AMD patients. Theirs has been a feat of scientific and surgical prowess, and over a decade of their diligence and ingenuity has resulted in what may become the first FDA-approved treatment to transform the prospects of regaining vision for millions of patients.

The Ginsburg Institute team, led by vitreoretinal surgeons Amir Kashani, MD, Ph.D., associate professor of ophthalmology at the Keck School of Medicine, and Mark Humayun, MD, Ph.D., director of the Ginsburg Institute and co-director of the USC Roski Eye Institute, developed a stem cell-based retinal implant and accompanying surgical procedure to help restore vision to dry AMD patients. Their innovative approach and insights from their phase 1/2a clinical trial are described in the latest print issue of the American Academy of Ophthalmology's journal *Ophthalmology Retina*.

Designing the implant

The team accomplished a remarkable multi-part feat that required inventiveness at every turn, starting with designing the novel retinal implant. Dry AMD causes a single layer of cells in the retina called the retinal pigment epithelium (RPE) to deteriorate. The Ginsburg Institute team decided to utilize stem cells to grow RPE tissue in the lab, with the ultimate goal of implanting those cells in patients' eyes to slow or reverse the damage. Other scientists had attempted to inject stem cell-derived RPE cells into the retina, but had trouble getting the cells to evenly disperse; the Ginsburg Institute scientists instead created a thin membrane made of parylene on which to grow the cells in a single, even layer. Once they had created this RPE layer, the next challenge was to successfully implant it in the eye.

"In practice, being able to get underneath the retina, which is only about a quarter of a millimeter thick, to physically replace the RPE cell layer is a challenging task," explains Kashani, who is lead author of the publication. "Normally we don't operate underneath the retina. It's a place you generally try to avoid during surgery, so that has been a very novel, challenging aspect of delivering these stem cells."

There are very few tools for performing surgery within the subretinal space. Most available tools were designed 30 to 40 years ago, are relatively bulky and are generally meant to remove scar tissue or other lesions rather than insert anything into the subretinal space. The Ginsburg Institute team decided that the most promising option was to start fresh and design a brand-new tool to fit their purpose.

Engineering the tool

This new tool had to fit a number of criteria: it needed to be made of completely non-toxic materials so as not to harm patients, its design had to be easily reproducible, and it had to be small enough—on a scale of millimeters—to perform minimally invasive surgery inside the eye but large enough to prevent crushing the tissue implant it was meant to deliver.

The surgeons worked with materials and design engineers at the Ginsburg Institute to create single-use forceps with an internal compartment to encapsulate the implant and a roller-style thumbwheel to deploy it. The implant itself is shaped much like a champagne bottle, and the forceps grab onto the narrow end. Rolling the implant into the device's compartment causes it to fold into a curved shape, and the surgeon can ultimately release it to lay flat inside the eye.

Pioneering the surgical technique

With the new instrument and implant came an entirely novel surgical approach. Kashani and Humayun needed to figure out how to create space for the implant in the location of geographic atrophy, which is what doctors call the area of tissue degeneration. To do so, the surgeons decided to create an artificial retinal detachment using a technique called bleb formation, in which a small pocket of space is formed under the retina. "Normally we treat retinal detachments, we don't make them. In this particular case, we had to create a very well-controlled retinal detachment within an area of scar tissue that is very adherent to the surroundings," says Kashani. "The challenge was to separate it without damaging the retina."

In pre-clinical models, creating a bleb alone proved insufficient; the surgeons had to innovate again and ultimately used water pressure to dissect one cell layer from another in a process called targeted hydrodissection. To monitor progress during surgery and prevent complications, the team utilized an advanced imaging technique called optical coherence tomography (OCT) to visualize the dissection at the cellular level. "One part of our job was to make this a very doable surgery and I think we have achieved that with this study," Kashani says.

"Without tools like OCT, it would be very difficult to visualize the damage we need to treat," Kashani explains. He emphasizes that in addition to using OCT intraoperatively, he sees a promising role for the technology to be used in earlier-stage AMD patients to monitor the progression of their geographic atrophy. "It's not a standard of practice to use OCT and other diagnostic methods to detect early and subtle disease changes, but that may prove to be really important for classifying disease and treating it in the future."

Kashani adds that one of the most rewarding aspects of the entire clinical trial process has been working with his patients and witnessing their commitment to making this translation from research lab to clinical practice possible. "None of this is happening by magic. Patients are volunteering, and they're taking a chance for the sake of advancing medicine and potentially helping countless other patients down the road. We always appreciate that effort and we thank the patients and their families, too."

More information: Amir H. Kashani et al. Surgical Method for Implantation of a Biosynthetic Retinal Pigment Epithelium Monolayer for Geographic Atrophy: Experience from a Phase 1/2a Study, *Ophthalmology Retina* (2019). DOI: 10.1016/j.oret.2019.09.017

Provided by University of Southern California