

News in Review

COMMENTARY AND PERSPECTIVE

RETINA

Targeting Dry AMD With Lab-Grown RPEs

NEI SCIENTISTS HAVE SUCCESSFULLY demonstrated a method for converting human blood progenitor cells into stem cells that, in turn, differentiate into retinal pigment epithelial (RPE) cells capable of keeping photoreceptors healthy.¹

The ultimate goal is to protect at-risk photoreceptors by transplanting patient-specific sheets of functioning RPE cells into eyes with dry age-related macular degeneration (AMD), said principal investigator Kapil Bharti, PhD, at the NEI.

Animal model. The researchers described a painstaking process for transforming progenitor cells into induced pluripotent stem cells (iPSCs), then inducing differentiation into RPE cells, which are grown in a monolayer atop a biodegradable scaffold.

“We start with the patient’s own blood, isolate the blood progenitor cells, and reprogram them into induced pluripotent stem cells—that is, cells that can make any type of cell in the body,” Dr. Bharti said. “And you can imagine the advantage, then, if you make a tissue out of these cells: It becomes the patient’s own tissue, so the immune system would not reject it.”

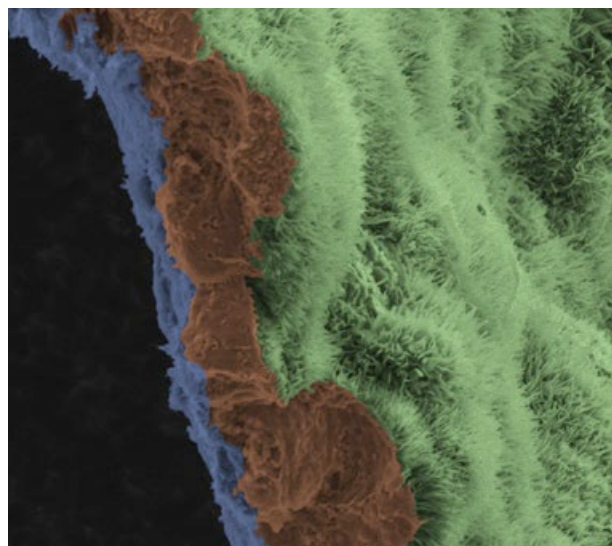
Using a specially designed transplant delivery cannula, the researchers inserted single-source sheets of cells between

the photoreceptors and the dying RPE layer in rodents and pigs. The patch size was 2 mm × 4 mm in the pigs, the same size as a human clinical dose would be, Dr. Bharti said.

Functional results. Imaging, molecular, and electrical studies during up to nine months of follow-up found that the patches of transplanted cells functioned well and without evidence of toxicity. The laboratory-grown RPE cells integrated appropriately into the animals’ retinas as the biopolymer scaffold degraded. They also expressed *RPE65* (the gene that drives regeneration of the ocular photopigment rhodopsin), performed the RPE’s crucial function of pruning photoreceptors through phagocytosis, and facilitated normal electrical responses from the rescued photoreceptors adjacent to the implanted cells.

Because of concerns about possible oncogenic potential in tissue derived from stem cells, the researchers also performed genetic analyses of the iPSCs and found no mutations that are known to be associated with tumor growth, they reported.

Planning for clinical trial. Dr. Bharti said the group’s cellular production processes strictly followed “good manufacturing practice” protocols, in order to facilitate FDA approval of an early



IN THE LAB. A scanning electron micrograph image shows a polarized RPE monolayer on a biodegradable scaffold. The image is colored to highlight the scaffold (blue), three RPE cells (brown), and the apical process of cells in the RPE monolayer (light green).

clinical trial, which the researchers hope will begin this year. Planning is underway for a phase 1/2a trial in patients with geographic atrophy and visual acuity of no better than 20/200, he said.

If this and further clinical studies were to demonstrate safety and efficacy, transplants of this lab-grown RPE tissue could be submitted to the FDA for commercial approval in three to five years, Dr. Bharti estimated.

Dr. Bharti said the researchers are cautiously optimistic about the potential that this individualized approach eventually could have for AMD patients with geographic atrophy. “If implanted in the right place, [these cells] would stop the disease from progressing further—and this is in a disease where there currently is no treatment available.” —Linda Roach

1 Sharma R et al. *Sci Transl Med.* 2019;11(475):eaat5580.

Relevant financial disclosures—Dr. Bharti: None.

CATARACT

Evaluating Lens and IOL Tilt With SS-OCT Biometry

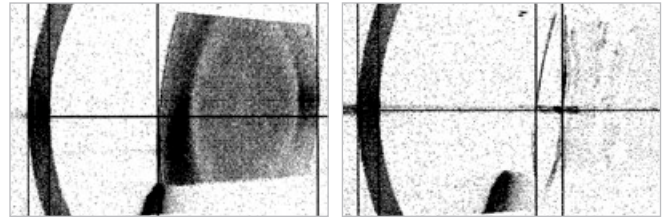
RESEARCHERS HAVE CONDUCTED A retrospective case series study of crystalline lens and IOL tilt using a swept-source optical coherence tomography (SS-OCT) biometer.¹

“We found that we can reproducibly measure crystalline lens tilt—and that this tilt is predictive of postoperative IOL tilt,” said Douglas D. Koch, MD, at the Cullen Eye Institute in Houston. “Knowing this could improve the accuracy of toric IOL calculations.”

Study design. Dr. Koch and his colleagues evaluated 333 patients for:

- repeatability of the lens tilt measurement,
- preoperative crystalline lens and postoperative IOL tilt in the patients’ right eyes (253 phakic, 80 pseudophakic),
- lens tilt mirror symmetry between the patients’ right and left eyes,
- correlation in tilt between preoperative crystalline lens and postoperative IOL, and
- correlation between the magnitude of lens tilt and ocular parameters.

Repeatability of crystalline lens tilt was calculated using participants with preoperative tilt data available for three repeated measurements on the



TILT. Preoperative crystalline lens tilt and postoperative IOL tilt, measured in the same eye.

same day. This was assessed using two parameters: 1) the pooled within-subject standard deviations of repeated measurements, and 2) intraclass correlation coefficient, a measure of the correlation between repeated measurements. Repeatability using the SS-OCT was found to be excellent.

Because of the potential mirror symmetry of lens tilt between right and left eyes, the researchers used the patients’

GLAUCOMA

OCT Illuminates Vision Loss After Glaucoma Surgery

WITH THE HELP OF OPTICAL COHERENCE TOMOGRAPHY (OCT), doctors at the Stein Eye Institute in Los Angeles gained new insight into an infrequent postsurgical complication of glaucoma filtering surgery known as “snuff-out phenomenon.” The clinicians reported two patients who experienced significant, unexplained, and permanent vision loss following placement of a drainage device; in both cases, OCT showed progressive macular thinning after the procedure.¹

It took OCT to demonstrate what had only previously been hypothesized. “This explains one of the mechanisms of vision loss after glaucoma surgery”—that is, ongoing loss of the retinal ganglion cells (RGCs), said Kouros Nouri-Mahdavi, MD, MS, at the Stein Eye Institute. He added that the “fairly rapid RGC loss suggests the possible presence of sick cells that continue to die despite glaucoma surgery.”

Patient profiles. An 89-year-old woman with primary open-angle glaucoma underwent trabeculectomy in her right eye to lower her intraocular pressure (IOP), which was 20 mm Hg on maximal treatment prior to surgery. Pressure remained inadequate after surgery despite escalation of therapy. The patient’s best-corrected visual acuity (BCVA) was 20/50 before surgery. It then fluctuated, in the 20/70 to 20/150 range, and it never recovered to preoperative levels.

At 12 months, the patient received a 250-mm² Baerveldt Glaucoma Implant (Johnson & Johnson). Macular

OCT images taken after device implantation still showed significant thinning of the full retinal thickness, especially in the superior macula.

The second patient, an 85-year-old man, had advanced pseudoexfoliation glaucoma in his right eye. He had previously undergone uncomplicated trabeculectomy and was referred for surgery because of his uncontrolled IOP. Before surgery, his IOP ranged from 28 mm Hg to 32 mm Hg on maximal treatment, and his BCVA was 20/20. He received an Ahmed Glaucoma Valve (New World Medical). One week later, his VA was hand motions, and his IOP was 5 mm Hg.

At nine months, the patient’s BCVA was 20/400. Macular OCT imaging revealed progressive macular thinning deemed to be consistent with progressive and complete central visual field loss.

Can this scenario be avoided? The findings suggest that eyes at high risk of visual loss after surgery are mainly those with advanced glaucoma or extension of the damage to the central field preoperatively, Dr. Nouri-Mahdavi said. But, he added, we need much more data before making clinical recommendations. “One could imagine, though, that a very thin macula observed preoperatively could predict possible worsening of vision after surgery.” For now, he said, doctors might consider preoperative imaging of the macula in eyes at high risk of visual loss after surgery, followed by continued postoperative monitoring. —*Miriam Karmel*

1 Mohammadzadeh V et al. *J Glaucoma*. Published online Jan. 28, 2019.

Relevant financial disclosures—Dr. Nouri-Mahdavi: Heidelberg Engineering; L.S.

right eyes to assess the mean crystalline lens and IOL tilt magnitudes and directions. In 163 phakic patients and 24 pseudophakic patients, there was significant mirror symmetry.

In the 65 eyes with both pre- and postoperative tilt measurements, there was significant correlation between tilt magnitude and tilt direction of preoperative crystalline lens and postoperative IOL. The IOL tilt magnitude increased significantly compared with

the preoperative crystalline lens tilt.

In the 253 phakic right eyes, multiple regression analysis revealed that the magnitude of crystalline lens tilt was negatively correlated with axial length (AL), anterior chamber depth, and lens thickness, and positively correlated with angle α . In the 80 pseudophakic right eyes, the magnitude of IOL tilt was negatively correlated with AL and positively correlated with angle α and angle κ .

The researchers stressed that further studies evaluating incorporation of lens tilt in IOL power calculations in clinical patients are needed. —*Arthur Stone*

1 Wang L et al. *J Cataract Refract Surg.* 2019;45:35-40.

Relevant financial disclosures—Dr. Koch: Carl Zeiss Meditec: C. This study was funded in part by the Sid W. Richardson Foundation and an unrestricted grant from Research to Prevent Blindness.

IMMUNOLOGY

Growing Problem: Ocular Impact From Cancer Rx

OPHTHALMOLOGISTS NEED TO CONTINUE to watch for patients who, after receiving immunotherapy for cancer, develop ocular adverse effects that could prove catastrophic if they go untreated.

In a large retrospective study of patients treated with the immune checkpoint inhibitors ipilimumab (Yervoy, Bristol-Myers-Squibb) and/or nivolumab (Opdivo, Bristol-Myers-Squibb), Yale researchers found that 15 of 1,474 patients (1%) developed ocular adverse events.¹

These side effects included corneal perforation, corneal punctate epithelial erosions, subconjunctival hemorrhage, uveitis, hypotony maculopathy, cystoid macular edema, serous retinal detachment, choroiditis, optic neuritis, and melanoma-associated retinopathy.

Need for suspicion. “These adverse events are uncommon; however, we need to be aware that they can occur in patients undergoing immunotherapy,” said coauthor Renelle Pointdujour-Lim, MD, at Yale University in New Haven, Connecticut. “Even if the patient has vague nonspecific ocular symptoms, the ophthalmologist should have a high suspicion of the possibility of ocular immune-related adverse events.”

Varied presentation. One challenge

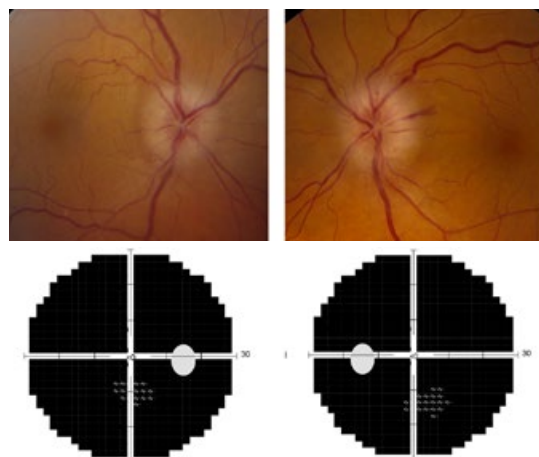
for clinicians is that these side effects can occur days to weeks after the infusion of immunotherapy. Moreover, they can appear mild at first but later become quite serious, Dr. Lim said. For instance:

- One patient complained of floaters that did not go away, and she was later found to have melanoma-associated retinopathy.
- Another patient was having difficulty in the periphery of her [perceived] field of vision, and her initial visual field (VF) showed nonspecific defects, Dr.

Lim said. “A follow-up VF two to three months later showed profound VF loss, and she was found to have antiretinal and anti-optic nerve autoantibodies.” (This case will be published in another report about the clinical spectrum of immunotherapy patients with anti-retinal autoantibodies, she said.)

- A third case began as dry eye and progressed to corneal perforation by the time the patient presented to an ophthalmologist.

Growing problem. Although the incidence of ocular immune-related adverse events from immunotherapy is low, the total number of cases can be expected to increase, Dr. Lim said. “The indications for use of these agents have expanded to include a broader range of malignancies, which means that more and more people will be treated with immunotherapy, and ophthalmologists



VF LOSS. Ocular adverse effects following treatment with immune checkpoint inhibitors included this case of profound VF loss.

need to know that these powerful agents can affect the eye,” she said.

Exam tips. “A complete examination is warranted in patients on immunotherapy, including slit-lamp and fundoscopic examination,” Dr. Lim said. In addition, she said, ancillary testing based on exam findings may be needed, such as optical coherence tomography.

She added, “I would like to stress that most of the ocular adverse effects can be managed locally, with continuation of immunotherapy in select cases. However, if these ocular problems are not caught early and treated appropriately, they can be visually devastating.” —*Linda Roach*

1 Kim JM et al. *Ophthalmology.* Published online Feb. 5, 2019.

Relevant financial disclosures—Dr. Pointdujour-Lim: None.