# News in Review

COMMENTARY AND PERSPECTIVE

RETINA

## Imaging Provides Cellular Views of Retinal Layers

**IN A MILESTONE FOR IMAGING THE** retina's deepest layers, NEI researchers have successfully used adaptive optics (AO) combined with indocyanine green (ICG) angiography to visualize the entire photoreceptor/retinal pigment epithelium/choriocapillaris complex in living human eyes.[1]

**Simultaneous visualization.** In the AO-ICG study, simultaneous imaging of the three retinal layers revealed that the dye localized not only to the choroidal vasculature but also to the retinal pigment epithelium (RPE) cells.

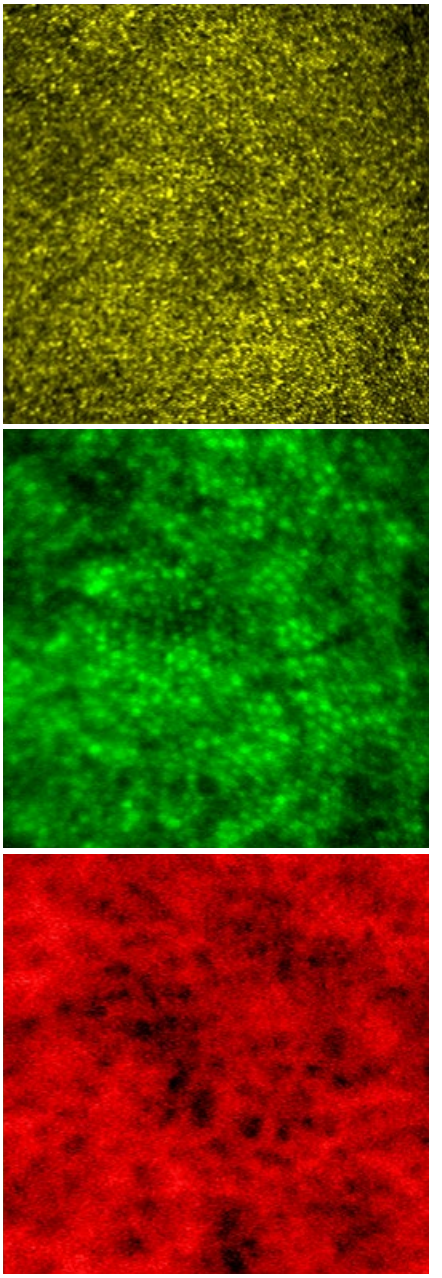
"This is a unique interaction that was unexpected," said senior investigator Johnny Tam, PhD, at the NEI. "Typically, when people think of angiography they think of blood vessels, but this work is interesting because it shows a nonvascular structure, the RPE, that's interacting with the dye."

**Improved resolution.** The addition of adaptive optics, to correct for wavefront aberrations, improved the resolution achievable with ICG and scanning laser ophthalmoscopy to approximately micrometers, sufficient to visualize and even quantify cells in the outer retinal layers, Dr. Tam said.

Moreover, by subtracting the light emitted by the dye in RPE cells, the researchers were able to detect the weaker fluorescent signal emitted by the tiny vessels of the choriocapillaris, he said. "This ability to see the choriocapillaris is not currently possible with conventional ICG," he said.

**Additional findings.** The researchers also reported the following:

- After 23 healthy subjects received an intravenous injection of ICG, the dye was rapidly taken up by the RPE cells, peaking within several seconds. Further exploration of this dynamic process could lead to insights about drug pharmacokinetics in the retina, the researchers wrote.
- A second, smaller peak occurred a mean of 18.31 seconds (SD ± 2.98 seconds) after the first peak, reflecting the dye's recirculation from the systemic circulation. Additional injections did not affect the subjects' individual recirculation times. The researchers suggested that this might eventually allow retinal recirculation times to be used as an individualized biomarker for monitoring systemic vascular perfusion.
- RPE cell spacing and the flow voids in the choriocapillaris averaged 3.1 and 3.7 times larger, respectively, than they were in the tightly packed cone photoreceptor layer. Variations in these ratios over time might eventually enable individualized tracking, at a cellular level, of retinal disease progression, the researchers wrote.
- In a single patient with retinitis pigmentosa, AO-ICG showed intact RPE and choriocapillaris layers underneath areas where photoreceptors had been lost. The borders between areas with healthy and absent photoreceptors were abrupt, rather than gradual. "This data provides a powerful tool for revealing



***VISUALIZATION.*** *Cone photoreceptors (top) appear as tiny, bright punctate spots of varying intensity. Fluorescence shows RPE cells (center) in the initial minute after ICG is injected intravenously. At bottom is the choriocapillaris. All images taken simultaneously at the same location on the retina.*

Johnny Tam, PhD, NEI

the cellular status of disease in the living human eye," they wrote.

**Other applications.** Improved imaging is seen as a major need for the advancement of regenerative therapies for eye disease, according to the NEI, which currently funds five imaging projects through its Audacious Goals Initiative. Adaptive optics is being used to improve other types of advanced retinal imaging, including multiply-scattered light imaging, and angiography using optical coherence tomography. Insights from these and other techniques, such as conventional angiography, will be complementary to AO-ICG, Dr. Tam said.

"We see our combined approach as allowing us to start to validate some of the intriguing findings that we see with conventional ICG. We want to go back to existing data and then collect data in new ways and interpret it all in ways that we didn't think about previously," he said.

The ultimate goal would be to apply the cellular-level discoveries from AO-ICG to already familiar imaging modalities, Dr. Tam said.

"Generalizing our results to standard ICG is something we're very interested in. I think that as we start to compare our AO technique with standard ICG, we can take from the concepts that we've learned with AO-ICG and start to apply that toward clinical practice."

*—Linda Roach*

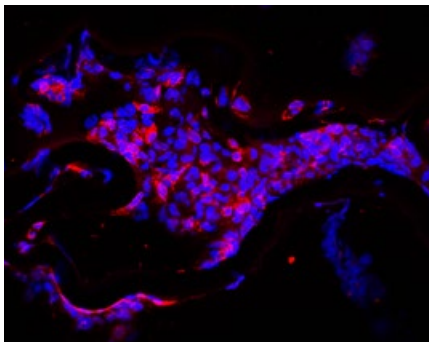
1 Jung H et al. *Commun Biol.* Published online Nov. 14, 2018.

**Relevant financial disclosures**—Dr. Tam: None.

CATARACT

## PCO, Lens Cells, and Inflammation

**RESEARCHERS HAVE COME A BIT** closer to figuring out the primary cause of fibrotic posterior capsular opacification (PCO), an undesirable outcome of cataract surgery. They report a cascade of events triggered by surgical trauma, starting with the transformation of remnant lens epithelial cells (LECs) into signaling centers that promote inflammation.[1]



***INFLAMMATORY CASCADE.*** *Remnant LECs five days following surgery, stained for cyclooxygenase 2 (red), which catalyzes a key step in prostaglandin synthesis. The cell nuclei are stained blue.*

And while the researchers haven't connected all the dots, they speculate that postsurgical inflammation may

TRAUMA

## Amniotic Membrane in Severe Ocular Chemical Injury

**RESEARCHERS HAVE FOUND THAT COMBINED AMNIOTIC** membrane transplantation (AMT) and medical therapy does not accelerate healing in severe ocular chemical injury.[1] However, the data also show that routine medical therapy leads to a quiet, conjunctivalized cornea and deep fornices with minimal complications, making ocular surface reconstructive surgeries—including stem cell transplantation—possible.

**Patients and intervention.** For this randomized study, 60 eyes of 60 patients with Roper-Hall grade IV ocular chemical injury were enrolled in the trial with a minimum follow-up of 12 months. Patients were assigned to two groups: Group 1 (30 eyes) received topical preservative-free lubricating gel and drops, chloramphenicol, betamethasone, homatropine, oral vitamin C, and doxycycline; Group 2 (30 eyes) received AMT on the entire ocular surface in addition to the medical treatment provided in Group 1.

**Outcome measures.** The main outcome measure was the time to complete corneal epithelialization. Secondary outcome measures were best-corrected visual acuity (BCVA) and neovascularization in the central 5 mm of the cornea. Patients were examined on postoperative days 1, 3, 7, 14, and 28; biweekly until three months; monthly until one year; and quarterly thereafter. They were also assessed for the development of complications, such as glaucoma and symblepharon formation.

**Results.** Mean follow-up time was 20.3 ± 2.5 months (13 to 24 months). Corneal epithelial defects healed within 72.6 ± 30.4 days (21 to 180 days) in Group 1, versus 75.8 ± 29.8 days (46 to 170 days) in Group 2. Mean BCVA was 2.06 ± 0.67 logMAR (0.4 to 2.6) versus 2.06 ± 0.57 logMAR (1 to 2.9) in Groups 1 and 2, respectively ($p = .85$). Group 1 developed more central corneal neovascularization (22 eyes; 73.3%) compared to Group 2 (16 eyes; 53.3%). This, however, was not statistically significant ($p = .108$).

**Assessment.** "AMT has been reported as a treatment option in the management of the ocular chemical injury," said coauthor Medi Eslani, MD, at the University of Illinois College of Medicine in Chicago. However, he noted, "Most of the previous studies are nonrandomized with a mixed population. Based on this trial, AMT does not offer any advantage over conventional medical therapy alone in terms of corneal epithelial healing, final visual acuity, and neovascularization in patients with severe ocular chemical injury."

*—Arthur Stone*

1 Eslani M et al. *Am J Ophthalmol.* Published online Nov. 9, 2018.

**Relevant financial disclosures**—Dr. Eslani: None.

Melinda K. Duncan, PhD

play a key role in the onset of PCO, which affects a wide range of adults (25%-70% of patients) and nearly 100% of children 10 years after surgery.

**Starting with mice.** To understand the mechanisms by which ocular trauma results in fibrotic PCO, the researchers surgically removed the lens fiber cells in mice, leaving behind the lens capsule and attached LECs. They then compared the levels of all mRNAs expressed by LECs immediately following surgery and 24 hours later.

While, as expected, many genes associated with fibrosis are upregulated, the researchers' comparison revealed that LECs robustly activate the innate immune response within hours of cataract surgery.

**An unexpected finding.** "That lens cells have the capability of becoming signaling centers for ocular inflammation was surprising, because the lens is classically thought of as an immune-privileged site," said Melinda K. Duncan, PhD, at the University of Delaware in Newark. "But here, lens cells are making huge amounts of cytokines associated with the innate immune system."

**Two implications to consider.** First, if the remnant LECs prove to be primary drivers of postsurgical inflammation, they could be targeted to directly reduce this side effect of surgery, Dr. Duncan said. "Second, if we can shut down the inflammatory response by lens epithelial cells, we can test the idea that inflammation is a trigger for fibrotic PCO. If that is the case, inhibiting that inflammation could be an approach to reducing fibrotic PCO."

**Up next.** The researchers hope to identify the precise mechanism by which surgery induces this process. Their most recent results have shown the likely upstream trigger is a signaling cascade initiated immediately after surgery, leading to the activation of "immediate early response" transcription factors.

"We anticipate that this trigger will involve a receptor that we could anticipate blocking clinically," Dr. Duncan said. However, she said, researchers are "likely two to five years away" from identifying the relevant pathways. "Our goal is to identify a therapy that could be instilled into the eye during surgery to block this cascade."—*Miriam Karmel*

1 Jiang J et al. *Invest Ophthalmol Vis Sci.* 2018; 59(12):4986-4997.

**Relevant financial disclosures**—Dr. Duncan: None.

DRUG DELIVERY

## Drug Delivery Via Microneedle Patch

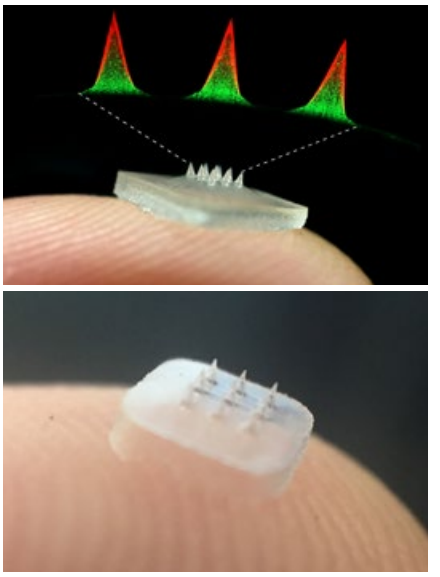
**A TEAM OF BIOMEDICAL ENGINEERS** has demonstrated the effectiveness of an eye-contact patch equipped with double-layered microneedles for both rapid and controlled drug delivery directly into the eye.[1] The patch, intended to overcome the limitations of systemic, topical, and intraocular injection, is as easy to apply as a disposable contact lens. While not yet tested in human eyes, it promises a paradigm shift for long-term treatment, allowing patients to manage their ocular disorders at home.

"Our work provides a new strategy for efficient drug delivery into the eye, with the help of dissolvable tiny microneedles," said Peng Chen, PhD, at Nanyang Technological University in Singapore.

**Building on earlier success.** Dr. Chen and his colleagues recently developed microneedle-based skin patches to manage obesity.[2] Their ease of use and effectiveness in transdermal drug release "inspired us to further explore microneedle applications in eye disease treatment," he said. The researchers tested the eye patch in mice with corneal neovascularization, but it has applications for other ocular diseases, he said.

**A one-two punch.** The patch consists of multiple pyramid-shaped microdrug reservoirs attached to a polymeric contact lens–like substrate. The microneedle tips are thinner than a human hair and a fraction the length of a grain of rice.

Using corneal neovascularization as the disease model, the researchers applied the patch to mouse corneas for a quick burst of an anti-inflammatory compound, followed by sustained release of an antiangiogenic monoclonal antibody. The biphasic release achieved an approximately 90% reduction of neovascular areas with a single 1-gram dose. The result far surpassed human clinical studies that have shown the need for repeated high-dosage topical drugs to treat corneal neovascular disease.[3,4]



***RESERVOIRS.*** *Each needle has two separate reservoirs: The fast-dissolving inner core (green) is covered by a outer layer (red) that provides a slower release of medication.*

**Looking ahead.** Dr. Chen hopes to find clinical collaborators to launch a clinical trial. In the meantime, he said, "We are continuing to work on optimizing the eye patch for better practical use in human eyes." —*Miriam Karmel*

1 Than A et al. *Nat Comm.* 2018;9(1):4433.
2 Than A et al. *Small Methods.* 2017;11(1): 1700269.
3 Ferrari G et al. *Cornea.* 2013;32(7):992-997.
4 Bock F et al. *Graefes Arch Clin Exp Ophthalmol.* 2008;246(2):281-284.

**Relevant financial disclosures**—Dr. Chen: Singapore A*STAR Biomedical Research Council: S; Singapore National Research Foundation: S; Singapore Ministry of Education: S; Singapore Ministry of Health: S.

Than Aung, MBBS, PhD

**See the financial disclosure key,** page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.