

News in Review

COMMENTARY AND PERSPECTIVE

RETINA

Bioprinted 3D Model Uncovers Drivers of AMD

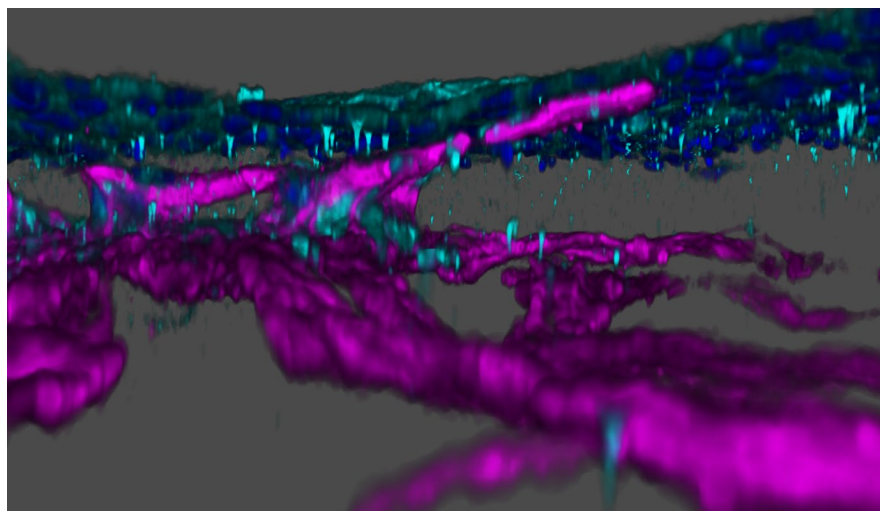
RESEARCHERS FROM THE NEI bioprinted a 3D model of the outer-blood-retina barrier (oBRB) to study the role of the retinal pigment epithelium (RPE) and choriocapillaris in the development of age-related macular degeneration (AMD). They found that complement activation in the oBRB induced dry AMD, whereas hypoxia triggered wet AMD.¹

“We believe that 3D-oBRB is a powerful and physiologically relevant model for the identification of genetic and environmental factors contributing to AMD. Understanding the mechanisms of AMD initiation and progression can help us diagnose and treat AMD at an early stage or prevent the progression of dry AMD to wet AMD,” said Kapil Bharti, PhD, at the NEI.

Bioprinted oBRB also will provide “a unique opportunity to test new drugs and gene therapies directly on human eye tissue, study the role of genetics on treatment response, and develop personalized therapies,” he added.

Study rationale. A key challenge hindering the development of effective therapies for AMD is the limited understanding of the disease owing to the lack of reliable models, said Dr. Bharti. “So far, nobody has been able to replicate true AMD-like macular phenotype in animal models.”

The team developed bioprinted



BIOPRINTED MODEL OF WET AMD. Fluorescence image showing choroidal neovascularization in bioprinted 3D human eye tissue (cyan = RPE cells; dark blue = nuclei of RPE cells; magenta = proliferative choroidal capillaries that have migrated into the sub-RPE space).

oBRB as an in vitro model to study molecular and morphological changes during AMD initiation and progression. They also used human oBRB tissue to study the interaction between RPE and choriocapillaris.

Producing stable tissue. The bioprinting process deposited human endothelial cells, pericytes, and fibroblasts onto a biodegradable scaffold containing an RPE monolayer. Characterization of the bioprinted 3D-oBRB tissue showed that the polarized RPE monolayer supported the formation of fenestrated capillaries and a Bruch membrane-like structure by promoting gene expression alterations in choroid cells. “This native-like oBRB tissue was stable for weeks, allowing us to perform long-term studies,” Dr. Bharti noted.

Triggers of dry and wet AMD. Results of tissue analyses and genetic and functional testing showed that complement activation promoted sub-RPE drusen deposits and significant RPE loss, which are features of dry AMD. In

contrast, stabilization of the transcription factor HIF- α triggered wet AMD and choriocapillaris neovascularization, confirming the role of hypoxia in AMD progression.

Thus far, “people thought that only the endothelial cells and pericytes in the choroid were important in AMD,” Dr. Bharti said. However, the NEI team found, the fibroblasts contributed to a different part of Bruch membrane, suggesting that they are also “important for the formation of a healthy choroid at the back of the eye,” he said.

Looking ahead. “We are working on further improving our human oBRB model by incorporating macrophages and perfused capillaries to mimic the microenvironment and systemic circulation of the human eye,” Dr. Bharti said. The team also plans to use the oBRB model to study the role of metabolism in AMD progression.

—Christos Evangelou, PhD

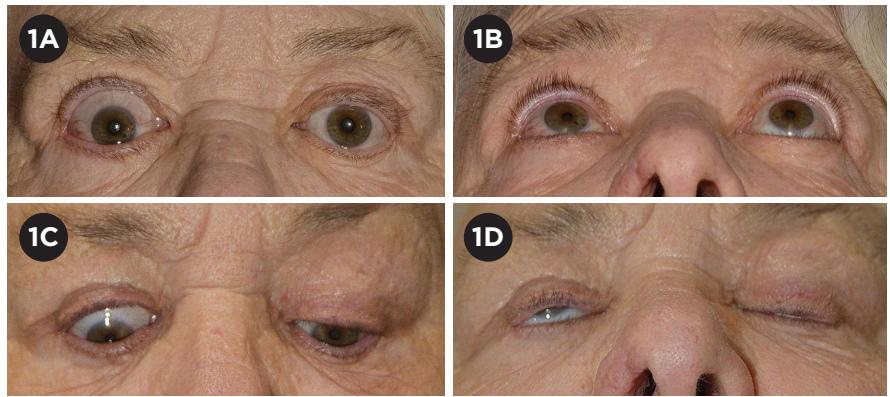
¹ Song MJ et al. *Nat Methods*. 2023;20(1):149-162.
Relevant financial disclosures: Dr. Bharti—None.

Consensus on Treating Thyroid Eye Disease

AN INTERNATIONAL TEAM OF ENDOCRINOLOGISTS and ophthalmologists has issued a consensus statement on the evaluation and management of thyroid eye disease (TED).^{1,2} The statement is intended to serve as a guide for specialists caring for patients with TED.

Support for multidisciplinary approach. The consensus statement emphasizes a multidisciplinary approach to treatment—and it makes the point that ophthalmologists should always be involved in the care of patients with moderate-to-severe TED.

“Thyroid eye disease requires a combined effort from ophthalmologists and endocrinologists in order to ensure adequate assessment of both thyroid and eye manifestations,” said coauthor Mar-



ASYMMETRIC TED. (1A) Right upper eyelid retraction, (1B) left relative exophthalmos, (1C) right upper lid lag with downgaze, and (1D) bilateral lagophthalmos with inferior corneal exposure on the right.

ius N. Stan, MD, at the Mayo Clinic in Rochester, Minnesota.

Rapidly changing therapeutic arena. The need for a consensus statement was driven, in part, by the introduction of teprotumumab (Tepezza) as well as ongoing investigations into other potential agents for treatment of TED, said Dr. Stan.

Lessons for ophthalmology. While the statement targets endocrinologists, it holds lessons for ophthalmologists, said Jeremiah Tao, MD, FACS, at the University of California, Irvine. These include the following:

- TED has differing degrees of severity as well as many phenotypes.
- Smoking cessation can significantly

DRUG DELIVERY

Inkjet Drug Printing Onto Contact Lenses

RESEARCHERS FROM THE UCL SCHOOL OF PHARMACY in London have come up with a novel method of drug delivery: using an adapted commercial inkjet printer to place drugs onto contact lenses.¹ The hope is that such an approach will circumvent problems commonly seen with eyedrops, such as poor patient compliance.

Study focus and design. Study coauthors Thomas D. Pollard, MSc, and Abdul W. Basit, PhD, said they focused on three areas in their study: reliability of drug deposition, level of light transmission through drug-printed lenses, and amount of drug release from the lenses.

The researchers used timolol maleate for this study. An inkjet printer with custom drug-loaded cartridges deposited droplets of timolol on the lens in a circular pattern designed to avoid the pupil area of the contact lens. Two printing patterns were evaluated, with the drug printed on the inside or outside lens face.

The lenses were tested with near-infrared spectrometry, as a nondestructive way of evaluating drug load levels and target dosing amounts. The researchers also used a spectrophotometer to analyze light transmission through the lens as well as a flow rig that mimicked the environment of the eye to observe drug release profiles for the lenses.

More reliable than eyedrops? The researchers found that inkjet drug printing provided significantly more reliable drug loading than eyedrops. While some variation occurred, lenses displayed a tighter range of drug load than did drops. Light transmission of the lens remained unchanged by the drug deposits, suggesting no alterations in vision for the user.

Drug release from the lens provided the most intriguing results, said Prof. Basit. “The contact lens slows down drug release, leading to much longer retention times.” Testing results indicated that drug release was not instantaneous—and that dilution appears to begin at the three-hour mark. “This should translate to inkjet printing on contact lenses being a more effective therapy than eyedrops,” Prof. Basit said.

Potential variations. Printing on the inside versus the outside of the lens face led to variations in drug release profiles, with a slower release of timolol observed when it was printed on the inside face. This might open up avenues to modify drug release behavior—and even to personalize ocular therapy, Prof. Basit said.

Mr. Pollard further noted that this technology could potentially allow printing of multiple drugs at once for multidrug therapies. “The opportunities are vast,” he said.

—Patricia Weiser, PharmD

1 Pollard TD et al. *Int J Pharm X*. 2022;5:100150.

Relevant financial disclosures: Prof. Basit and Mr. Pollard—Engineering and Physical Sciences Research Council: S.

improve the disease course.

• Although teprotumumab is considered a promising new option, it is not universally efficacious and is associated with hearing loss and high cost. Other treatment options cited include glucocorticoids and other steroid-sparing agents, radiation, and surgery.

Toward optimal care. Dr. Tao agreed that optimal management of TED is collaborative in nature, spanning many medical disciplines and, within ophthalmology, several subspecialties.

Dr. Stan added, “It is important to keep in mind that TED can precede thyroid abnormalities and, in 5% of cases, the thyroid manifestations may not be present at all, despite clear changes consistent with TED. Monitoring thyroid parameters will be important in these cases, and that is another aspect where collaboration will offer optimal care for these individuals.” —*Miriam Karmel*

1 Burch HB et al. *Thyroid*. 2022;32(1):1439-1470.
2 Burch HB et al. *Eur Thyroid J*. 2022;11(6):e220189.

Relevant financial disclosures: Dr. Stan—Horizon Therapeutics; C; Dr. Tao—None.

EDUCATION

COVID's Impact on the Residency Match Process

DURING THE COVID-19 PANDEMIC, the residency match process switched from in-person to virtual interviews. Going forward, should specialty residency programs offer a fully virtual match process, return to prepandemic ways, or forge a hybrid approach? A recent study on the virtual interview's impact on the residency match, using ophthalmology as a prototype, addressed these questions.¹

Comparing 2021 to earlier years.

The study was a collaboration between the Association of University Professors of Ophthalmology's Match Oversight Committee and researchers at Duke Eye Center in Durham, North Carolina, said

coauthor Pratap Challa, MD, at Duke.

Using data from the AUPO database, the researchers analyzed 3,343 applicants to compare 2021 virtual match outcomes to those that took place between 2016 and 2020.

Hypothesis No. 1. The researchers hypothesized that significantly more applicants would match at their home institutions during the virtual application cycle than in previous years. This hypothesis proved correct; 26.1% of applicants to ophthalmology residency programs matched at their home institution in the virtual match cycle, versus 20.6% of the 2016-2020 matches.

Hypothesis No. 2. Another hypothesis—that applicants would apply to significantly more programs—also held true. The 2021 cohort applied to 78.8 programs, versus 73.1 in the 2016-2020 matches. Furthermore, with an all-time high number of applications, the national match rate for applicants dropped from 81.3% in the 2016-2020 time frame to 76.6% in 2021.

More information is needed. The numbers, however, did not convey how virtual interviews affected outcomes such as rank choices and perceptions of residency programs. In their study, the authors attempted to provide insight, citing small surveys that found applicants to other specialties gave mixed reviews to the virtual match.

In a separate study, which was conducted within ophthalmology, Venincasa et al. found that 126 of 205 applicants (71.2%) and 22 of 37 program directors (78.6%) preferred in-person interviews.²

Dr. Challa noted that, although more feedback is needed from applicants and programs as to their satisfaction with virtual interviews, the process did eliminate some of the travel and financial constraints of the in-person process. “Therefore, I suspect that the virtual trend will continue.” —*Miriam Karmel*

1 Aggarwal S et al. *J Grad Med Educ*. 2022;14(6):674-679.

2 Venincasa MJ et al. *Semin Ophthalmol*. 2022;37(1):36-41.

Relevant financial disclosures: Dr. Challa—None.

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

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