

News in Review

COMMENTARY AND PERSPECTIVE

RESEARCH

In 10 Days: From Skin Cells to Photoreceptors

RESEARCHERS HAVE DEVELOPED A method for transforming fibroblasts into rod photoreceptors that, when implanted into blind mice, enabled the animals to detect light and exhibit visual responses.¹ This novel technique skips the previously necessary step of first converting the fibroblasts into induced pluripotent stem cells (iPSCs), which then can be differentiated into retinal cells. That process takes up to six months to complete, compared to 10 days with the new method.

“Until now, no one has been able to convert fibroblasts directly to photoreceptors,” said study coauthor Anand Swaroop, PhD, at the NEI.

The NEI-funded researchers who developed the new cellular reprogramming technique were led by Sai H. Chavala, MD, at the University of North Texas Health Science Center School of Medicine in Fort Worth. Dr. Swaroop said that his laboratory at the NEI primarily contributed by performing the genetic analyses needed to validate that the new cells were expressing the proper photoreceptor genes.

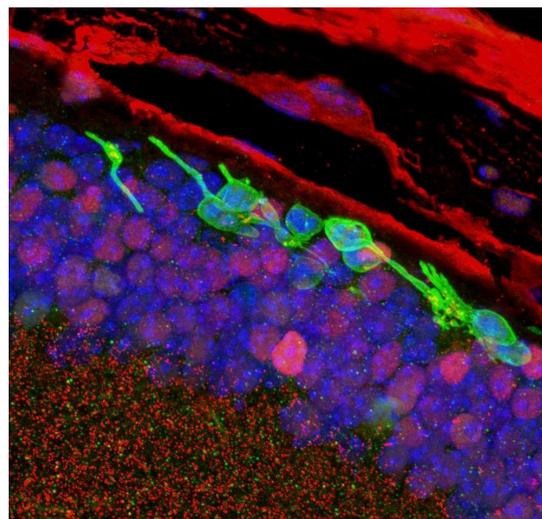
A five-year quest. In a painstaking series of experiments that spanned five years, Dr. Chavala and his colleagues discovered that they could coax both mouse and human fibroblasts to become retinal cells by bathing them

in a chemical cocktail of five small molecular compounds. These compounds were known individually to play a role in rod photoreceptor development.

When the transformed cells were transplanted into the subretinal space of mice that lacked rods, there were signs that the animals could detect light. Six of 14 mice (43%) had robust pupil constriction in low-light conditions, compared to none of the untreated controls. The mice with pupil constriction also were more likely than both the untreated mice and those with no constriction to seek out dark places, which is a natural behavior in sighted mice. Immunofluorescent images taken three months after transplantation showed that the cells were still viable and that their connections to neurons in the inner retina persisted.

What’s next? The University of North Texas has a patent pending on the methods reported in the paper. Dr. Chavala also is with CIRC Therapeutics, a spinoff company founded to conduct clinical trials and commercialize treatments using this cellular reprogramming method.

But Dr. Swaroop noted that much more research will be required in order to address two challenges: 1) how to increase the technique’s yield of functional cells, and 2) how to optimize their location and orientation in the retina, first in mice and eventually in humans.



RESULTS. Three months after transplantation, immunofluorescence studies confirmed the survival of the chemically induced photoreceptor-like cells (green cells). They also show integration of the cells into the layers of the mouse retina.

A related finding. Dr. Swaroop said he also looks forward to learning more about the study’s most intriguing finding: that the chemical cocktail central to this technique activates mitochondria to produce reactive oxygen species (ROS) that are crucial to the cellular reprogramming. That is in contrast to the cell damage that ROS trigger in other ocular settings, he said.

“We don’t have the whole story yet. I think additional combinatorial mechanisms must be there,” he said. “I wonder how the mitochondrial reactive oxygen species activate [the cellular reprogramming processes] but do not go on to cell-damaging pathways. How are those other pathways inhibited? That part is still very intriguing and might have major implications broadly for regenerative medicine.” —Linda Roach

1 Mahato B et al. *Nature*. Published online April 15, 2020.

Relevant financial disclosures—Dr. Swaroop: None.

AI Used to Dx Optic Nerve Abnormalities

AN INTERNATIONAL TEAM OF NEURO-ophthalmologists successfully harnessed artificial intelligence (AI) to detect optic nerve abnormalities from photographs taken with a variety of commercially available digital fundus cameras.¹ Their AI algorithm used deep learning neural networks to distinguish papilledema from other optic neuropathies as well as from normal optic discs.

“This system is intended to help general physicians and nonophthalmic health care providers who need an accurate and immediate assessment of the optic nerve head, in the absence of an ophthalmologist,” said Tien Y. Wong,

MD, PhD, at the Singapore National Eye Centre and Duke-National University of Singapore Medical School. He is a member of the Brain and Optic Nerve Study with Artificial Intelligence (BONSAI) consortium, which created the diagnostic system.

Training and validation. Neuro-ophthalmologists at 19 sites in 11 countries read 14,341 digital color ocular fundus photographs collected from a multi-ethnic population (Indian, Asian, and non-Asian patients). From the fundus images, they retrospectively diagnosed 9,156 normal discs, 2,148 discs with papilledema, and 3,037 discs with other abnormalities. They then trained the system to do the same.

Next, they externally tested the system’s performance on 1,505 photographs at five additional sites in five countries. The AI system correctly identified 96.4 of every 100 fundus

images with papilledema and 84.7 of every 100 fundus images without papilledema.

Classification errors. The system was not always correct. Of 360 discs with papilledema, 15 (4.2%) were misclassified as “other abnormalities.” However, the system never misread the abnormal discs as normal.

Still investigational. Though the system has been validated in the five external testing cohorts, it must receive regulatory approval in different countries, Dr. Wong said. Moreover, a number of issues need to be resolved, including medicolegal concerns regarding liability for a wrong diagnosis.

To address these and other questions, the group is conducting further prospective, real-life studies in Singapore and elsewhere. “If proven efficient, this system could represent an important step in decision-making processes of

HIGH-RISK PATIENTS

Cataract Surgery Safe in Patients With Heart Failure

THE BENEFITS OF CATARACT SURGERY MAY OUTWEIGH

the risks in some patients with left ventricular assist devices (LVADs). These patients rarely undergo cataract surgery, but under the right conditions, LVADs, the mechanical pumps that provide blood flow and hemodynamic support, need not be a contraindication for cataract surgery, say researchers at Duke Eye Center in Durham, North Carolina.¹

“Our work suggests that careful preoperative planning and intraoperative monitoring with our colleagues in anesthesiology and cardiology can result in successful management of someone who might otherwise be considered at prohibitively high risk for elective surgery,” said Cassandra C. Brooks, MD.

Retrospective evaluation. The Duke researchers reviewed electronic health records of 31 patients (53 eyes) with LVADs who underwent cataract surgery. Most were male (n = 27) and Caucasian (n = 25), and their average age was 69.5 years.

The majority underwent cataract extraction and IOL implantation alone (n = 28). Of note, nearly half of surgeries (47.2%) involved the use of a femtosecond laser, intraoperative aberrometry, and/or a premium IOL.

Most of the patients were lost to follow-up, but for the 18 eyes with complete data, 11 (61.1%) were at ± 0.5 D of their predicted spherical equivalent.

Perioperative planning. While it proved safe and

feasible, cataract surgery in these high-risk patients was not undertaken lightly. Prior to surgery, an LVAD anesthesia team assessed each patient; in addition, an LVAD specialist was present at all surgeries.

In adherence to guidelines regarding anticoagulation for procedures with a low bleeding risk, patients continued anticoagulation therapy prior to surgery.

Safety outcomes. Despite the potential for hemodynamic compromise in patients with advanced heart disease, there were no intraoperative episodes of hemodynamic instability. Two intraoperative events unrelated to the LVAD occurred. All patients were discharged the day of surgery, and no hospitalizations or deaths were attributed to the cataract procedure within the following 30 days.

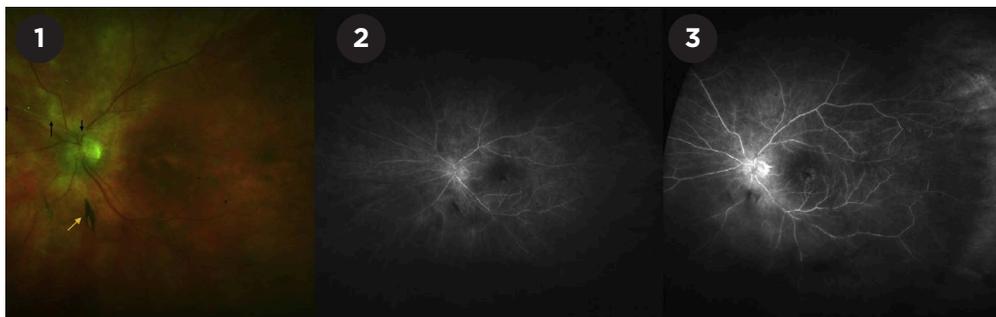
Looking ahead. Future studies will have to determine whether these outcomes can be replicated in the absence of an LVAD team. “Fortunately, none of the patients in our cohort suffered complications,” Dr. Brooks said. “But immediate access to the appropriate specialists would be highly advisable to avoid potentially fatal complications.”

This is an expanding population of patients with specialized needs for ophthalmic surgery. Yet by understanding the patients’ unique risks, and with interdisciplinary collaboration, they can undergo cataract surgery, Dr. Brooks said. “As in all surgical cases, preoperative planning is the key to success.” —*Miriam Karmel*

1 Brooks CC et al. *J Cataract Refract Surg*. Published online April 16, 2020.

Relevant financial disclosures—Dr. Brooks: None.

ordering brain imaging and/or lumbar punctures,” said BONSAI principal investigator Dan Milea, MD, PhD, also at the Singapore Eye Centre and Duke-National University of Singapore Medical School. Moreover, he said, the use of such a system could reduce the incidence of unnecessary or expensive investigations—and spare patients any associated discomfort. —*Miriam Karmel*



PROGRESSION. After bilateral brolicizumab injections, this patient experienced vitritis progressing to vasculitis despite treatment with oral and topical steroids. (1) Vitreous opacity (yellow arrow), optic nerve edema, and superior retinal artery sheathing (black arrow) are evident. (2) Globally sclerotic retinal arteries with peripheral nonperfusion are seen on early fluorescein angiography (FA). (3) Late-phase FA demonstrates hyperfluorescence from the optic nerve and perifoveal region, diffuse vascular staining, and peripheral vascular nonperfusion.

1 Milea D et al. *New Engl J Med.* 2020;382(18):1687-1695.

Relevant financial disclosures—Dr. Milea: None. Dr. Wong: Allergan: C; Bayer: C; Boehringer-Ingelheim: C; Genentech: C; Merck: C; Novartis: C; Oxurion: C; Roche: C; Samsung: C.

RETINA

Real-World Study of Brolicizumab Finds Severe Retinal Vasculitis

THE INTRAOCULAR INFLAMMATION that may occur after intravitreal therapy with brolicizumab (Beovu) can also be accompanied by retinal vasculitis severe enough to cause profound loss of vision, researchers have found.¹

Real-world outcomes. This retrospective analysis of retinal vasculitis in 15 eyes of 12 patients from 10 U.S. centers was the first case series published in a peer-reviewed journal since isolated reports of brolicizumab-associated problems began emerging earlier this year.²⁻⁴

The patients’ mean visual acuity (VA) before treatment with brolicizumab was 20/53. By the time retinal vasculitis was diagnosed, it was 20/191 (range, 20/25 to 20/1,600). And at a mean of 25 days following diagnosis and treatment, it was 20/136. Nine eyes (60%) lost 3 lines or more, and five eyes (33%) had VA of less than 20/200.

The vasculitis and intraocular inflammation noted in these eyes ranged

from “peripheral vasculitis to occlusion of large retinal arteries around the optic nerve or macula with severe vision loss,” the researchers said. All 12 affected patients were women, which suggests that autoimmunity may be a factor, said coauthor Scott D. Walter MD, MSc, at Retina Consultants in Hartford, Connecticut.

Insidious onset. These adverse outcomes occurred in a pattern distinct from anything ever seen with other approved anti-VEGF drugs, said Dr. Walter, also at the University of Connecticut School of Medicine in Farmington. Specifically, the inflammation associated with brolicizumab “tends to be milder in its early stages and more insidious in onset,” he said. “The patient might not become symptomatic for several weeks after the injection, and the inflammation may be mild enough that patient wouldn’t think to call the office.”

In some patients, “the inflammation was picked up when they returned for a scheduled injection,” Dr. Walter noted. In others, he said, “It was overlooked because there was no intense vitritis or hypopyon.” These are typical signs of intraocular inflammation associated with other anti-VEGF drugs, with onset typically in the first week after injection, he said.

Additionally, “There were multiple exposures to the drug in some cases, and a delay of weeks, as opposed to days, before the onset of clinically

apparent intraocular inflammation and retinal vasculitis,” Dr. Walter said. “And if you miss catching this, then it can really get you into trouble.”

If you use brolicizumab. Retina specialists should be alert for inflammation and other events when using brolicizumab, the study authors said. And while researchers try to discover the mechanism behind the problems, Dr. Walter said that he has decided against starting his patients with age-related macular degeneration on brolicizumab, and that he is encouraging those already on it to switch to another anti-VEGF agent.

But for those clinicians who do use the drug, Dr. Walter advises a complete examination of both the anterior and posterior segments to evaluate for subtle signs of inflammation—even for apparently asymptomatic patients—before each subsequent injection. “The most important thing for anyone treating these patients is to not reinject an eye that has active inflammation with brolicizumab or any other anti-VEGF drug.” —*Linda Roach*

1 Bauml CR et al. *Ophthalmology.* Published online April 25, 2020.

2 Haug SJ et al. *Am J Ophthalmol Case Rep.* 2020; 18:100680.

3 Jain A et al. *Am J Ophthalmol Case Rep.* 2020; 18:100687.

4 Roach L. *EyeNet Magazine.* 2020;24(6):30-32.

Relevant financial disclosures—Dr. Walter: Genentech: C.

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