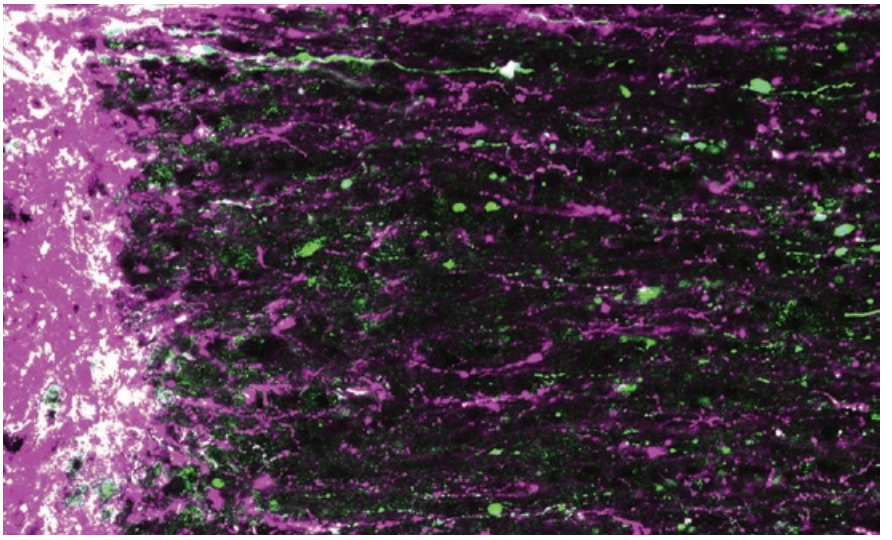
News in Review

COMMENTARY AND PERSPECTIVE

Progress in Axon Regeneration



AXON ACTION. *Retinal axons regenerating in the optic nerve (green and magenta), after damage and treatment with gene therapy and visual stimulation.*

Albert Lim

WITH GENE THERAPY PLUS VISUAL stimulation, scientists have coaxed retinal ganglion cells (RGCs) to grow long-distance, target-specific axons that restored partial functional vision in mice[1]—an unprecedented feat that the researchers hope eventually might pave the way to fruitful clinical studies.

Methods and results in mice. The scientists injected a recombinant adeno-associated virus, modified to promote production of mTOR, a peptide that regulates RGC growth, into the eyes of mice with crush injuries to the optic nerve.

The peptide molecules alone stimulated a small amount of axon growth, the investigators found. But when the treated mice also spent 21 days exposed to high-contrast vertical lines on TV monitors, the axons grew past the optic chiasm and found their correct subcortical targets. In monocular tests of tasks related to visual function, these mice regained some ability to track a moving grating and to respond to a simulated predator overhead.[1]

"We were absolutely surprised but delighted that the retinal ganglion cells in adult eyes are capable of regenerating long distances back into the brain given the appropriate stimuli, and that without any additional help they are able to renavigate these tortuous paths back to their correct location in the brain, form synapses, and reestablish some degree of visual perception behavior," said coauthor Andrew D. Huberman, PhD, associate professor of neurobiology at Stanford University.

Hopes tempered by "unknowns." "This is really encouraging for future clinical prospects, because it suggests that if we can get human neurons to regenerate, they're going to know where to go, as opposed to wiring up willy-nilly," Dr. Huberman said.

Over the next several years, the many unknowns about this apparently synergistic combination of gene therapy and RGC "training" must be addressed before the approach can proceed to clinical trials, Dr. Huberman said. "We know now that regenerating neurons is not entirely science fiction, but there are important steps that need to take place first," he said. Among the outstanding issues:

- Axons did not regenerate completely in all of the eyes' RGCs. Perhaps this could be improved by adding recombinant genes to block molecules that otherwise inhibit RGC growth, Dr. Huberman said.
- The study involved only 2 of the approximately 30 types of RGCs in mammalian eyes, and the remaining cell types must be studied, he said.
- What types of visual stimuli should be used, first in mice, then in humans? "You need the RGCs to be firing a lot, and for that they need high-contrast and high-frequency stimulation. But we don't know what patterns and forms are best," he said.

Seeking to learn more. Since publication of the results, Dr. Huberman said, glaucoma patients have swamped him with requests for guidance about using high-contrast, high-frequency visual stimulation to possibly boost their RGC health—and he plans to begin studies of this soon.

"This is a completely noninvasive approach; and while it's true that in our study the visual stimulation by itself was not sufficient to get the axons to grow all the way back to the brain, we were using pretty severe, complete lesions of the optic nerve," he said. "So we are embarking on some clinical studies, setting up virtual reality environments to stimulate RGCs in patients, as a way

to try and preserve their health through electrical activity and presumably maintenance or regeneration of fibers."

He said he initially envisions monitoring effectiveness with visual field testing. But he is working with the Glaucoma Research Foundation to find ways to track the outcomes by developing advanced imaging technology to count RGCs in the living eye.

—Linda Roach

1 Lim JA et al. *Nat Neurosci.* Published online July 11, 2016.

Relevant financial disclosures—Dr. Huberman: None.

GLAUCOMA RESEARCH

Possible New Role for Bupropion?

COULD A DRUG THAT IS PRESCRIBED to treat depression and to aid in smoking cessation also prevent the retinal ganglion cell (RCG) damage that is a hallmark of glaucoma?

This question recently began appearing on research scientists' radar, thanks to 2 large, population-based studies that identified an association between prolonged bupropion use and the risk of developing open-angle glaucoma (OAG).[1,2]

Data from 2 studies. The most recent, a cross-sectional study by researchers at the University of California, San Francisco, and Stanford University, used data from the National Health and Nutrition Examination Survey (NHANES). It found that participants who reported using bupropion for more than 1 year had decreased odds of self-reported diagnosis of glaucoma compared with those who did not use bupropion (adjusted odds ratio, 0.10; 95% CI, 0.01-0.81; p = .028).[1]

In the earlier study, researchers who examined a decade of data from a large managed care network reported that each additional month of bupropion use was associated with a 0.6% reduced risk of open-angle glaucoma (hazard ratio [HR], 0.994; 95% CI, 0.989-0.998; p = .007). Compared with nonusers, those patients who took bupropion for 24 to 48 months were 21% less likely to develop OAG (HR = 0.79, CI: 0.65-0.94, p = .0099).[2]

If bupropion does eventually prove to protect RGCs, the mechanism would likely be by blocking production of an apoptotic molecule, tumor necrosis factor, said Marissé Masís, MD, a UCSF glaucoma research fellow and lead author of the recent NHANES-based study. But further basic and clinical studies are needed, she added.

Opening a door to research. The authors emphasized that the study showed only association, not causation. "It is too early to think of this as a possible treatment to prevent progression, but it opens the possibility in the future," Dr. Masís said.

CATARACT COMPLICATIONS

PCR Boosts Risk of Early Retinal Detachment

Pseudophakic retinal detachment (RD) can occur with or without the surgical complication of posterior capsule rupture (PCR). But PCR during cataract surgery significantly alters both the risk and the time course of RD, according to a report from the United Kingdom National Ophthalmology Database Study of Cataract Surgery.[1] The study included data on 61,907 cataract surgeries (46,824 patients) performed from 2006 to 2010.

Shedding light on risk and timing. PCR, which occurred in 1,100 of those surgeries, substantially raises the risk of RD. During the 4-year study period, the RD rate was 0.16% for eyes without PCR and 3.27% for those with PCR.

Another striking difference is in the time course. Overall, RD risk increased linearly over the 4-year study. In contrast, however, "Over half of the retinal detachments following cataract surgery complicated by posterior capsule rupture occurred within 2 months," said lead author Alexander C. Day, PhD, FRCOphth, at Moorfields Eye Hospital. The median time to RD surgery was 44 days for eyes with PCR and 6.3 months for eyes without PCR.

Effect of the surgeon. Surgical experience was an independent risk factor for PCR. "Trainee surgeons are more likely to have surgical complications such as PCR," Dr. Day said. Further, in surgeries performed by trainees, there was a tendency for RD to occur earlier in eyes with or without PCR.

It's possible, said Dr. Day, that junior surgeons lack the skills possessed by senior surgeons in "tidying up" after PCR and ensuring that no strands of vitreous remain in the corneal wound or around the IOL. Vitreous remnants could increase the risk of tractional retinal tears during posterior vitreous detachment (PVD), which is the main causative event for retinal tears and subsequent retinal detachments.

Recommendations. Given the high risk of retinal detachment following cataract surgery with PCR, the authors recommend close follow-up with dilated funduscopy in the first 2 months after surgery. They also urge surgeons to explain the nature of retinal detachment and PVD symptoms to patients who experienced PCR. "They should be advised to contact their ophthalmologist promptly if they notice any new floaters, flashing lights, or shadows in their vision," said Dr. Day.

—Miriam Karmel

1 Day AC et al. *Ophthalmology*. Published online June 21, 2016.

Relevant financial disclosures—Dr. Day: None.

Currently, a large prospective clinical trial is being planned to examine the possible neuroprotective effect of statins in glaucoma patients, and that might eventually occur for bupropion, too, she said. "Whatever we can find to help combat glaucoma, other than lowering IOP, will be a big step," she said.

—Linda Roach

1 Masís M et al. *Br J Ophthalmol.* Published online June 28, 2016.
2 Stein JD et al. *PLoS One.* 2015;10(4):e0123682.

Relevant financial disclosures—Dr. Masís: None.

INTERNATIONAL FOCUS

Africa: Sight-Threatening DR on the Rise

ALTHOUGH THE INTERNATIONAL Diabetes Foundation estimates that the number of adults diagnosed with diabetes in Africa will increase from 12.1 million in 2010 to 23.9 million in 2030, there is a paucity of evidence on diabetic eye disease in that continent. Recently, however, the first prospective longitudinal study of diabetic retinopathy (DR) from sub-Saharan Africa has been published by researchers with the Malawi Diabetic Retinopathy Study (MDRS) to characterize the incidence, progression, and factors associated with DR in patients at 2 diabetes clinics in southern Malawi.[1]

Striking difference in DR progression. According to lead author Philip I. Burgess, MRCS(Ed), PhD, a retina specialist with the Malawi-Liverpool-Wellcome Trust Clinical Research Programme, the most important finding is the high rate of progression to sight-threatening diabetic retinopathy seen in the MDRS patients—the rate is approximately 3 times that reported in recent European studies.

Multiple factors contribute to this disparity, Dr. Burgess said: "The agenda is dominated at a national level by poorly resourced health services and at a community level by poverty. A major challenge is lack of patient knowledge of the disease and the logistics of accessing care on a regular basis. Throughout sub-Saharan Africa, referral pathways between diabetes clinics and ophthalmic services are underdeveloped and poorly organized."

Reasons for hope. Despite these troubling findings, Dr. Burgess noted that a number of DR detection and treatment programs have recently been developed in African countries. He cited the Kilimanjaro Diabetic Programme in northern Tanzania as an example of an integrated, clinic-based, mobile photographic retinal screening service. Another important development is the Commonwealth Diabetic Retinopathy Network, in which U.K. eye units partner with centers in low- and middle-income countries.

Although DR screening and care delivery models from industrialized countries are unlikely to be adopted in resource-poor settings, he said, "New technologies including portable fundus cameras and automated grading of retinal images will help deliver cost-effective services in African countries."

The MDRS progression data can be an important aid in planning the introduction of programs for prevention, early detection, and management of DR in the region, said Dr. Burgess. "Our findings represent a baseline against which the efficacy and cost-effectiveness of such interventions can be judged."

A surprising finding. The most unexpected finding in the study, said Dr. Burgess, was a negative association between HIV infection and DR progression. "HIV infection and antiretroviral agents are associated with macro- and microvascular pathology. We therefore expected those subjects with HIV and diabetes to demonstrate increased rates of DR progression." A possible confounder is that people with HIV receiving antiretroviral drugs already have contact with health services, so their diabetes might have been diagnosed earlier. And, more ominously, "In our study, subjects with HIV and diabetes had a very high mortality rate (approximately 18% in 24 months), which may have reduced the observed rate of DR progression in this group," he said.

EYE CARE IN MALAWI. *Clinical officer Owen Mkangadzula taking a retinal photo.*

Ways to help. Ophthalmologists and allied health professionals from high- and middle-income countries have an important role to play in the development of services for diabetes and DR in African countries, said Dr. Burgess, but it must be done in partnership with local clinicians, using a systematic approach to planning for sustainability and accessibility. "Long-term partnerships between institutions are most likely to provide the most benefit for all parties. Provision of subspecialty training to local ophthalmologists either in their country of origin or elsewhere is extremely important" and will facilitate the development "of local clinician-scientists who can provide health policy leadership in the region."

—Peggy Denny

1 Burgess PI et al. *Ophthalmology.* Published online July 9, 2016. doi:10.1016/j.ophtha.2016.05.042.

Relevant financial disclosures—Dr. Burgess: None.

Philip I. Burgess, MRCS(Ed), PhD

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