NEURO-OPHTHALMOLOGY

Using the Visual System to Treat Multiple Sclerosis

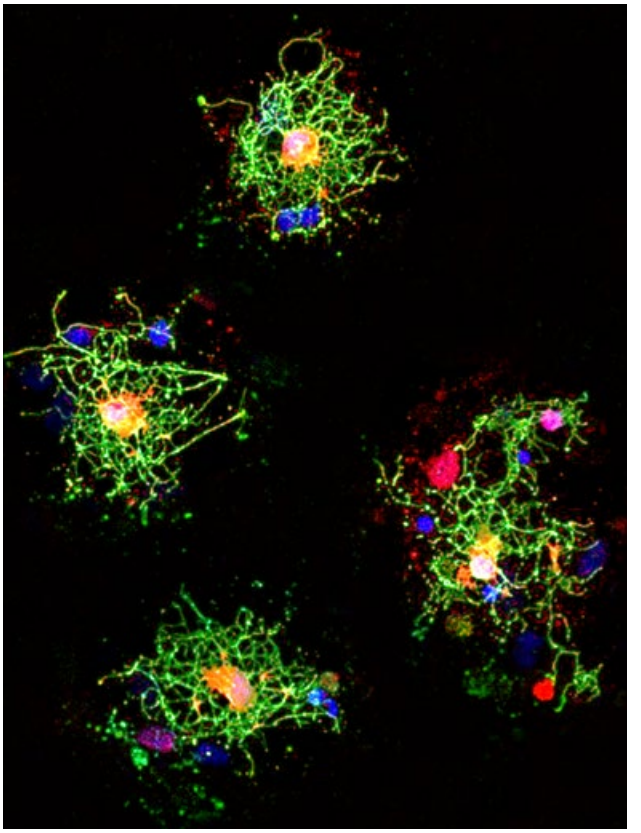
MULTIPLE SCLEROSIS (MS) IS A DE-generative inflammatory disease of the central nervous system (CNS) involving destruction of myelin and progressive neuroaxonal loss. Treatments capable of remyelination are a major unmet need for patients with the disease. However, researchers at the University of California, San Francisco (UCSF), may have taken a step toward filling that need using the visual system and the over-the-counter antihistamine clemastine fumarate (Claritin).[1]

The study. For this double-blind randomized trial, known as ReBUILD, investigators included 50 patients with relapsing MS and chronic demyelinating optic neuropathy. Patients were randomized into 2 groups: The first received oral clemastine fumarate twice daily for 3 months and then placebo for 2 months, while the second received the placebo for 3 months and the active treatment for 2 months.

The primary outcome measure was shortening of P100 latency delay on full-field visual-evoked potentials. "Visual sensory dysfunction is the first symptom in up to 40% of patients with MS, and injury to the optic nerve is extraordinarily common," said Ari J. Green, MD, at the UCSF Multiple Sclerosis Center. "It made sense for us to choose the visual pathway for investigation, especially because of the precision of clinical tests available for assessment."

Possible remyelination? Patients in both groups experienced a reduction in latency delay while on the antihistamine treatment, demonstrating that the drug has a possible remyelinating effect, even after prolonged damage to the CNS.

To Dr. Green, this represents what he termed "a major breakthrough" for drug-induced repair in a chronic neurodegenerative condition. "To our knowledge, this is the first time that a drug has reversed the deficits caused by MS. We aren't saying it's a cure, but this is a step toward that direction."



OLIGODENDROCYTES. *Clemastine fumarate can stimulate differentiation of oligodendrocytes (shown here). From the lab of Jonah R. Chan, PhD.*

Courtesy of Ari J. Green, MD

Importance to ophthalmologists. For Dr. Green, the ReBUILD study demonstrates the value of ophthalmology in treating MS, as there's also preliminary evidence from the trial suggesting that drug-induced remyelination might extend to improved low-contrast letter acuity in patients with MS. But that might only be the beginning.

"We've been taught in the past that the retina and optic nerve are incapable of self-repair; however, we need to develop a more nuanced view acknowledging that there is some capacity for regeneration," he said. Thus, he said, as clinicians wait for other promising treatments, including stem cell therapy, to bear fruit, "we should harness the eye's own natural regenerative abilities, utilizing the processes that biology already provides us and manipulating them via specific medications."

—Mike Mott

1 Green AJ et al. *Lancet.* 2017;390(10111):2481-2489.

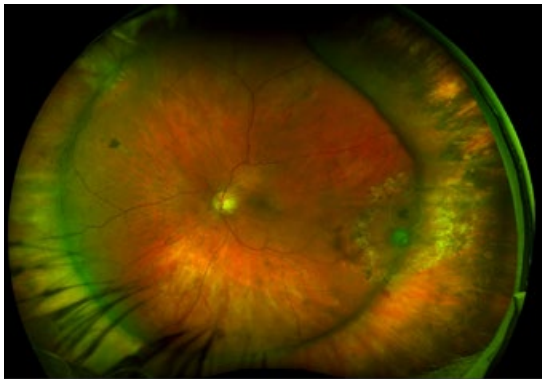
Relevant financial disclosures—Dr. Green: NIH: S; National Multiple Sclerosis Society: S; Rachleff Family: S; UCSF: S.

CATARACT

Assessing Retinal Redetachment Risk After Cataract Surgery

IN PATIENTS WHO HAVE HAD SCLERAL buckling surgery to repair a retinal detachment (RD), the risk of a redetachment remains low for up to 10 years after cataract surgery, a population-based Swedish study has found.

"One could easily think that these patients would have a significant increased risk of redetachment, especially considering that they have had 1 RD already. This study found, in contrast to that, a low risk of redetachment, 2.1%," said Sara Forsell, MD, coauthor of the study.[1]



REASSURANCE. *A previous history of retinal detachment and scleral buckling surgery should not necessarily serve as a contraindication for cataract surgery, the study results indicate.*

Study details. The researchers studied records on all patients who underwent surgery for primary repair of an RD at Norrlands University Hospital in Umeå, Sweden, during a 10-year period (N = 537).

The records showed that 145 of these patients subsequently had phacoemulsification surgery. Up to 10 years after the primary scleral buckling surgery, the cumulative rate of redetachment was 1%. The cumulative rate rose to 5% in the 10 years after cataract surgery, the researchers said. (In eyes with no prior detachment, the incidence of RD after cataract surgery is estimated to range between 0.6% and 1.7% in the first postoperative year, the researchers noted.)

Three redetachments (2.1%) occurred in the study cohort, taking place 2.4 years, 3.9 years, and 6.9 years after the cataract surgery. In all 3 cases, the retinas were successfully reattached with vitrectomy, and the final best-corrected visual acuity was

GLAUCOMA

Gene Editing for POAG Proves Successful in Mice

RESEARCHERS HAVE DEMONSTRATED THE FEASI-bility of directly targeting and editing a gene mutation in the trabecular meshwork to treat the leading genetic cause of primary open-angle glaucoma (POAG).[1] This novel approach delivers a one-two punch that both rescues cell function and prevents further glaucomatous damage—and it has implications for persons with mutations in the myocilin gene (*MYOC*), which have been reported in some 4% of POAG patients, most notably juveniles.

CRISPR to the rescue. "We found that reduction of myocilin gene and protein lowered intraocular pressure [IOP] and prevented vision loss in a mouse model of myocilin glaucoma," said cell biologist Gulab Zode, PhD, at North Texas Eye Research Institute in Fort Worth, who conducted the study in collaboration with Val C. Sheffield, MD, PhD, at the University of Iowa in Iowa City.

The rescue mission deployed CRISPR-Cas9 technology, a biological cut-and-paste method that homes in on a gene defect, makes a double cut in the DNA, and then deletes, replaces, or repairs the damaged gene. For this study, the researchers used CRISPR (which stands for Clustered Regularly Interspaced Short Palindromic Repeats) to delete the *MYOC* gene in mice as well as in cultured trabecular meshwork (TM) cells and human donor eyes.

Building on earlier studies. Previously, the researchers found that mutant myocilin is not secreted into the aqueous humor. Instead, it accumulates in the endoplasmic reticulum (ER) of TM cells. ER stress leads to TM damage, resulting in increased outflow resistance and IOP elevation, Dr. Zode said. "We also found that normal myocilin is not required for regulation of IOP. Therefore, deleting the gene completely works in this case."

Proof of concept. In the murine portion of this study, the researchers injected the *MYOC* gene intravitreally with the virus Ad5-cr*MYOC* to halt expression of the mutant gene. In young asymptomatic mice, gene deletion prevented IOP elevation compared with controls. In older mice with *MYOC* ocular hypertension, treatment lowered pressure.

Treatment also significantly increased outflow facility, demonstrating that disruption of mutant *MYOC* also improves TM cell function in vivo.

Beyond mice. Although the study also demonstrated feasibility of human genome editing in cultured human eyes, additional research is needed before the treatment can be taken to the clinic, Dr. Zode said. "We hope that it translates in humans, but the main purpose was to demonstrate that genome editing is possible in vivo—and, especially, that human donor eyes can be used to study genome editing." *—Miriam Karmel*

1 Jain A et al. *PNAS*. 2017;114(42):11199-11204.

Relevant financial disclosures—Dr. Zode: NEI: S.

The American Society of Retina Specialists. For full credit, see this article at aao.org/eyenet.

20/70, 20/25, and 20/30, the researchers reported.

Reassuring cataract surgeons. The study's results should reassure cataract surgeons who are considering surgery in patients with a history of RD and scleral buckling, Dr. Forsell said.

"Now that we know that the risk of redetachment is low, I have changed my view when counseling these patients [and am] more prone to do the cataract surgery earlier," she said. "It is also of value to know that there is no need for extended postoperative care and that the risk of redetachment is not related to the [length of] time after cataract surgery."

Instead, pseudophakic patients who had a previous RD that was repaired with a scleral buckle should be advised to seek prompt medical attention if they experience symptoms of a redetachment, even if several years have passed since the cataract procedure, Dr. Forsell said. *—Linda Roach*

1 Forsell S, Mönestam E. *Ophthalmol Retina.* 2018;2(1):5-10.

Relevant financial disclosures—Dr. Forsell: None.

ONCOLOGY

First U.S. Guidelines for Retinoblastoma Screening

A PANEL OF OPHTHALMIC ONCOLO-gists, pathologists, and geneticists has published the first set of U.S. screening guidelines for children at risk for retinoblastoma—the most common eye tumor affecting children.[1]

The goal. The team from the American Association of Ophthalmic Oncologists and Pathologists met over the course of 2 years to identify the key problems and clinical discrepancies in approaching "at-risk" patients—that is, children with a family history of retinoblastoma in a parent, sibling, or first- or second-degree relative. The published consensus report is a consolidation of how to proceed in different scenarios to initially identify and stratify disease risk and then follow up with these patients.

"The ultimate goal is that all children at risk for retinoblastoma are diagnosed as early as possible and followed up appropriately to treat tumors when they are very small and manageable with local therapies," said coauthor Patricia Chévez-Barrios, MD, at Houston Methodist. "The treatment itself will vary depending on tumor size and location and other features in the eye, and it's at the discretion of the treating team to decide which approach is indicated once the diagnosis is made."

The recommendations. Highlights of the report include the following:

- All children with a family history of retinoblastoma should receive counseling and testing to clarify disease risk.
- The frequency of dilated fundus examination should be stratified on the basis of age and risk. Newborns at high risk, for example, require more frequent examination, every 2 to 4 weeks during their first 2 months of life. Newborns at intermediate or low risk should undergo monthly examination.
- Exam frequency declines as the child grows older, but screening for all at-risk patients should occur up to age 7. For asymptomatic children, no further screening is recommended after this time unless they are known to carry an *RB1* mutation. These individuals should be followed indefinitely, every 1 to 2 years.
- All decisions regarding examination method should be discussed with the child's family. Anesthesia is strongly recommended for any child unable to participate in a thorough in-office exam.
- Examiners should also be aware that tumor location can be age-specific. Newborns may present with tumors in the posterior pole; however, in children who are older at the time of disease development, the tumor may present peripherally.

Multispecialty support. The report has been endorsed by the Academy's Quality of Care Secretariat as well as several medical organizations. *—Mike Mott*

1 Skalet AH et al. *Ophthalmology.* Published online Oct. 18, 2017.

Relevant financial disclosures—Dr. Chévez-Barrios: None.

Management Guidelines for Childhood Screening for Retinoblastoma Families

Risk Category	% risk	Eye examination schedule based upon age of unaffected child							
		Birth to 8 weeks*	> 8 to 12 weeks	> 3 to 12 months	> 12 to 24 months	> 24 to 36 months	> 36 to 48 months	> 48 to 60 months	5-7 years
High Risk	> 7.5	Every 2-4 weeks	Monthly		Every 2 months	Every 3 months	Every 4 months	Every 6 months	Every 6 months
Intermediate Risk	1 - 7.5	Monthly		Every 2 months	Every 3 months		Every 4-6 months		Every 6 months
Low Risk	< 1	Monthly		Every 3 months	Every 4 months	Every 6 months		Annually	
General Population	0.007	Screening with pediatrician							

Nonsedated office examination preferred by most centers

Examination under anesthesia preferred by most centers

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