

News in Review

COMMENTARY AND PERSPECTIVES

HIV Drugs May Fight Geographic Atrophy

Some of the same antiretroviral drugs that brought hope into the lives of HIV-infected patients might now be poised to do the same for a completely new group: people who are slowly going blind

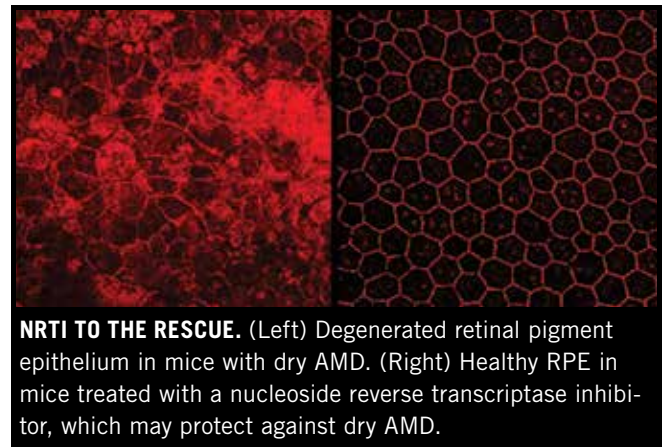
from retinal geographic atrophy (GA).

A multinational research team recently published a report on this intriguing and potentially revolutionary therapeutic approach,¹ and the first clinical trial is expected to begin in 2015.

Importance of the inflammasome. If the trial shows that antiretroviral drugs can protect retinal cells, this would add to the burgeoning recognition that dysregulation of inflammasome protein complexes causes pathology both in the eye and elsewhere in the body, said senior author Jayakrishna Ambati, MD. Dr.

Ambati is professor of physiology and professor and vice chair of ophthalmology and visual sciences at the University of Kentucky, in Lexington.

“The inflammasome now has been shown by a variety of groups, in addition to ours, as being really important in macular degeneration,” Dr. Ambati said. “It also is turning out to be important in a number of cognitive disorders, arthritis, atherosclerosis, and stroke. So the ability to block inflammasome activation with an existing class of antiretroviral drugs could be quite powerful.”



NRTI TO THE RESCUE. (Left) Degenerated retinal pigment epithelium in mice with dry AMD. (Right) Healthy RPE in mice treated with a nucleoside reverse transcriptase inhibitor, which may protect against dry AMD.

Therapeutic possibilities. Dr. Ambati and coauthors carried out their studies in mice and in human retinal cells. Their research demonstrated that nucleoside reverse transcriptase inhibitors (NRTIs) could prevent *Alu* RNA, an overabundant “junk” molecule in the retinal pigment epithelium (RPE), from activating an innate immune mechanism, the NLRP3 inflammasome. Unabated, the process can be toxic to RPE cells, kill photoreceptors, and cause severe GA.

Oral dosing of the AMD-model mice with the NRTI drugs stavudine, zidovu-

dine, lamivudine, and abacavir successfully inhibited the NLRP3 inflammasome, the researchers reported. The anti-HIV drugs also were effective in murine models of choroidal neovascularization, graft-vs.-host disease, and sterile liver inflammation.

Upcoming trials. It's too soon to know how—or whether—repurposed anti-HIV drugs might improve the bleak visual prognosis in patients whose dry AMD is progressing toward end-stage GA, Dr. Ambati said. But he hopes to find some answers by launching two controlled clinical trials.

“This first one will be an oral trial of a drug called lamivudine, which we chose because it is a later-generation NRTI that doesn’t have a lot of the adverse effects that the earlier drugs from this same class had,” he said. “It’s going to be easier to start a trial with an existing

approved medication, and the kinds of doses that we require are already approved for use in people with HIV and hepatitis.”

The second trial will be a corporate-sponsored study that will administer an NRTI drug to at-risk retinas through an ocular implant.

Dr. Ambati said it’s exciting to learn that the inflammasome is a convergent pathway that triggers retinal cell death via multiple insults. “And even more so now that there might be a simple approach of repurposing existing drugs to block it.” —Linda Roach

1 Fowler BJ et al. *Science*. 2014 Nov. 21;346(6212):1000-1003.

Dr. Ambati cofounded and owns equity in iVeena Pharmaceuticals; his university holds patent interests related to his group’s discoveries on GA. He added that he has “an intrinsic financial interest in the success of our work.”

Neuro News

Evaluating Papilledema With SD-OCT

The Frisén scale, a photographic grading based upon descriptive features, has previously been the accepted method for diagnosing and monitoring papilledema. In a substudy of the NEI-funded Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), researchers explored whether spectral-domain optical coherence tomography (SD-OCT) could provide a more precise, continuous measure for evaluating the disease.

A two-part study. The substudy findings were reported in two parts.¹ Part I confirms that SD-OCT, using 3-D segmentation analysis, can reliably measure structural changes in the optic nerve head and peripapillary retina.

“OCT gave us a lot more information about the pathophysiological processes and changes with therapy than you would get just from a photo,” said lead author Mark K. Kupersmith, MD, professor of ophthalmology, neurology, and neurosurgery

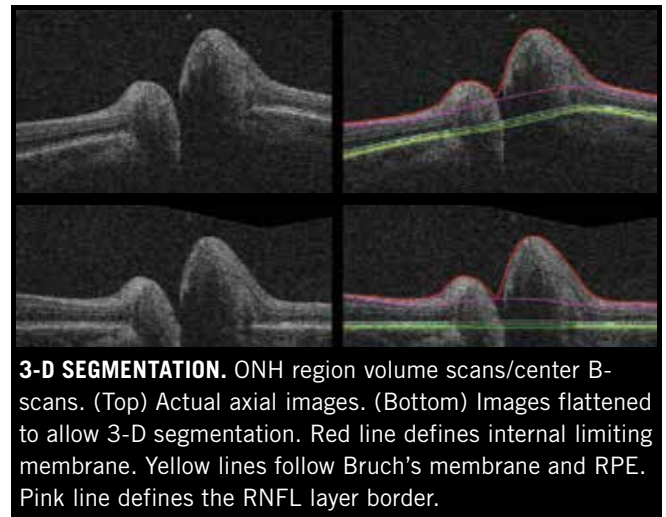
at the Icahn School of Medicine at Mount Sinai in New York City.

Part II focuses on correlating OCT findings with the clinical features of IIH.

Substudy methods. Using the Cirrus SD-OCT at 24 study sites, the researchers performed optic disc and macular scans in 126 subjects with mild visual field loss. They used both proprietary commercial and custom 3-D segmentation algorithms to calculate retinal nerve fiber layer and total retinal thickness, optic nerve head (ONH) volume, and retinal ganglion cell layer (GCL) thickness.

Analysis and artifacts. Standard SD-OCT imaging and software methods have limitations in measuring ONH swelling like that found in papilledema, said Dr. Kupersmith.

Problems can arise with both analysis and artifacts, the study found; conventional SD-OCT methods weren’t designed to evaluate disc edema when the normal architecture of retinal



3-D SEGMENTATION. ONH region volume scans/center B-scans. (Top) Actual axial images. (Bottom) Images flattened to allow 3-D segmentation. Red line defines internal limiting membrane. Yellow lines follow Bruch’s membrane and RPE. Pink line defines the RNFL layer border.

borders is obscured. Even when SD-OCTs acquire data correctly, the algorithms fail once swelling in the retina, ONH, or GCL passes a critical threshold.

A more reliable alternative. However, the 3-D segmentation algorithm, which incorporates contextual information, proved more reliable in evaluating retinal thickness, he said.

Correlations to clinical features. In Part II, the researchers studied the links between the imaging data and clinical features, such as acuity, visual fields, and low-contrast vision. As expected, they found a greater degree of swelling in patients with higher intracranial pressures. Further, all swelling parameters correlated well with the Frisén scale at baseline—though

the correlation weakened as the disease progressed.

“Although early ganglion cell loss does correlate with a reduction in low-contrast vision,” he said, “we found few other correlations in this group of subjects with mild vision loss.” Nevertheless, this study validates the use of an alternative method to obtain credible data in papilledema. —Annie Stuart

1 Kupersmith MK; OCT Sub-Study Committee for the NOR-DIC Idiopathic Intracranial Hypertension Study Group. *Invest Ophthalmol Vis Sci*. Published online Nov. 4, 2014. Part I, doi:10.1167/iops.14-14960; Part II, doi:10.1167/iops.14-14961.

Dr. Kupersmith reports no related financial interests. The study received support from the National Eye Institute.

Cornea Caveat

DSAEK Rebubbling & IOL Opacification

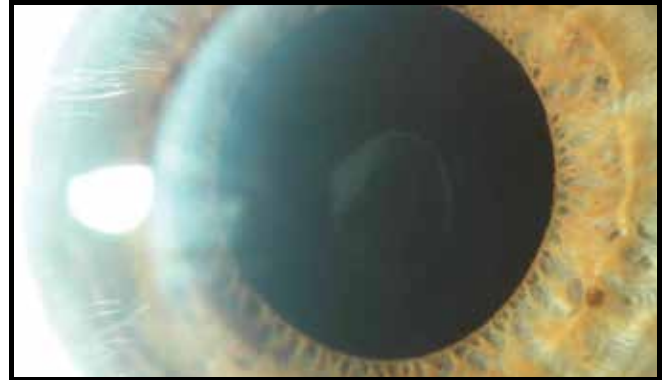
The air bubble used to hold a corneal graft in place may contribute to intraocular lens (IOL) opacification, according to a case review of eyes that underwent Descemet's stripping automated endothelial keratoplasty (DSAEK) at Bristol Eye Hospital in the United Kingdom.¹

"Repeated prolonged intracameral injections of air, along with the presence of hydrophilic acrylic lenses, seem to be the major risk factors for IOL opacification," said Muhammad A. Ahad, MBBS, FRCS, PhD, lead author of the review of DSAEK surgeries he and

colleagues performed between 2008 and 2012.

The authors reviewed eyes of 137 patients. All eyes were already pseudophakic or had cataract surgery performed at the time of DSAEK. Nearly 10 percent of eyes experienced IOL clouding, observed at a median of 17 months after DSAEK. Rebubbling, the only significant risk factor for opacification, had been performed in 62.5 percent of opacification cases, versus 23 percent with no clouding.

Suspecting that opacification was the result of prolonged high-pressure air tamponade in the ante-



CLOUDED LENS. The opacification seen near the center of this IOL is associated with DSAEK rebubbling.

rior chamber, the surgeons reduced the length of tamponade from 40 minutes to 10. Subsequently, the rate of graft dislocation and rebubbling has fallen, and so have cases of opacification, Dr. Ahad said.

Data were not available on the IOL type in patients who had prior cataract surgery, but Dr. Ahad said there's evidence that almost all affected lenses were hydrophilic acrylic. Thus, he

now uses hydrophobic lenses more frequently, especially in younger patients with Fuchs dystrophy. "Now that we know the risk factors and our techniques have evolved, this complication has become very rare."

—Miriam Karmel

1 Ahad MA et al. *Cornea*. 2014; 33(12):1307-1311.

Dr. Ahad reports no related financial interests.

Pediatric Outcomes

Retinoblastoma Survivors Fare Well in Adulthood

The insult of early-in-life treatment for childhood retinoblastoma does not follow survivors into adulthood, according to researchers at St. Jude Children's Research Hospital in Memphis, Tenn. Some three decades after diagnosis, the 69 survivors who participated in the study fell within the norm on measures of neurocognitive function and social attainment.¹ Early diagnosis

was the strongest indicator of success.

Neurocognitive and social outcomes. While survivors were within normal limits on most measures, they scored above average in certain tasks, including nonverbal reasoning. But compared with similar-aged adults, they reported more problems with working memory and fine-motor dexterity needed for tasks like handwriting.

Factors in adult findings.

- Bilateral disease survivors did better on memory measures than those with unilateral disease, though this had little overall impact on adult functioning.
- Age at diagnosis emerged as a powerful predictor of adult cognitive functioning, even offsetting the harmful effect of unilateral cranial radiation. Unilateral disease survivors diagnosed before their first birthday performed more than two-thirds of a standard deviation better on measures of verbal reasoning and memory than those diagnosed after one year.

Senior author Kevin R. Krull, PhD, stressed the importance of early diagnosis.

Dr. Krull is on the faculty of the Department of Epidemiology and Cancer Control at St. Jude Children's Research Hospital. He said that the benefit is "likely due to more plasticity of the brain at that young age. Children who experience focal lateralized brain injury at a young age may recover better than those with a similar pattern of injury at an older age." —Miriam Karmel

1 Brinkman TM et al. *Cancer*. Published online Nov. 24, 2014. doi:10.1002/cncr.28924.

Dr. Krull reports no related financial interests. The study was supported by a Cancer Center (CORE) grant from the National Cancer Institute and by ALSAC.