

# News in Review

A LOOK AT TODAY'S IDEAS AND TRENDS

## SiRNA Holds Promise for Corneal Health

**W**hen activated by a short piece of RNA, the cell-surface receptor associated with macular geographic atrophy also has a second powerful effect, scientists have found: It

prevents both lymph and blood vessels from growing.

University of Kentucky researchers report that non-specific small interfering RNA (siRNA) molecules activated toll-like receptor 3 (TLR3) sites on endothelial cells in mouse corneal and muscle tissue, suppressing formation of both blood and lymph vessels.<sup>1</sup>

This was an extension of the group's earlier work, which found that activation of TLR3 inhibited neovas-

cularization in mouse choroid and skin.<sup>2</sup> Last year, they also reported that activating TLR3 could lead to the dry form of age-related macular degeneration.<sup>3</sup>

This latest discovery about TLR3 represents both good news and bad news for those looking for therapies based on siRNA molecules. Called RNA interference, this approach aims to correct or prevent medical problems by delivering carefully targeted, double-strands of RNA inside cells.

TLR3 is one of at least 13 toll-like receptors, which are sentinels of innate immunity. Each TLR type



**BANISHING CORNEAL NEOVASCULARIZATION.** A plastic wrap-rendering of a flat mount of a mouse cornea invaded by CD31+ cells (red) and LYVE-1+ lymphatic (green) vessels.

recognizes a different class of pathogen through the microorganisms' characteristic molecular patterns, and each initiates a specific intracellular immune mechanism. (TLR3 responds to viral genomes, and it triggers the apoptotic pathway.)

On the positive side, this new knowledge suggests that ophthalmic surgeons

one day might be able to use topical siRNAs to prevent blood and lymph vessels from clouding transplanted corneas, said the senior author on the paper, Jayakrishna Ambati, MD, professor and vice chairman of ophthalmology and visual sciences at the University of Kentucky in Lexington. Eyedrops containing siRNAs

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might preserve corneal clarity after traumatic injury, contact lens overwear and infections, he said.

Likewise, oncologists using siRNAs might be able to increase the effectiveness of cancer treatments by activating TLR3, thus simultaneously limiting the tumor's blood supply and preventing new lymph vessels from transporting cancerous cells elsewhere.

However, the study raises questions about safety, such as scientists inadvertently activating TLR3 by giving

clinical trial patients systemic siRNA therapy. The study found that siRNAs of a certain size (21 base-pairs) activated TLR3, even though the RNA was not specifically targeted to interact with that receptor.

Consequently, siRNAs of this size "may induce undesirable effects in the context of ischemic vascular disease or physiological cyclic angiogenesis. These concerns are particularly salient, given ongoing clinical trials of systemically delivered siRNAs," they write.

The results suggest that one of the fundamental concepts about RNA interference—its specificity to an intended genetic target—might require revision.

"RNA interference was supposed to be this precisely aimed 'surgical tool' where there would be minimal unintended consequences. If that is not how it works, we would probably have to rethink the premise," said Thomas Schluep, ScD, chief scientific officer of Calando Pharmaceuticals, which is testing siRNAs in cancer

patients.

"This is a wake-up call for everyone to show these drugs work through some specific mode of action, and not this nonspecific inhibitory mechanism," Dr. Schluep said. "It raises the bar for every siRNA trial out there." —Linda Roach

1 Cho, G. S. et al. *Proc Natl Acad Sci USA*. Published online April 9, 2009.

2 Kleinman, M. E. et al. *Nature* 2008;452(7187):591–597.

3 Yang, Z. et al. *N Engl J Med* 2008;359(14):1456–1463.

## Refractive Report

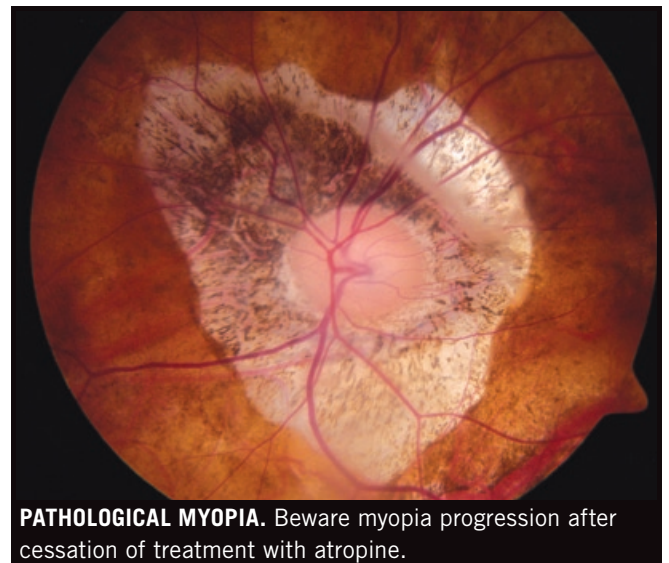
# After Atropine Treatment Ends, Myopia May Progress

Atropine has been used for many years off-label in the treatment of myopia. Recently, a randomized, parallel-group, double-masked atropine study of 400 children aged 6 to 12 years brought to light what may be atropine's weakness—staying power after cessation of treatment.<sup>1</sup>

In a Singaporean study, children with refractive error equivalents of  $-1$  D to  $-6$  D were observed for changes in refraction after having received either 1 percent atropine or vehicle-only eyedrops once nightly for two years. In the year following cessation of treatment, the atropine-treated eyes showed a rapid mean myopia progression of  $-1.14 \pm 0.80$  D, whereas placebo-treated eyes progressed  $-0.38 \pm 0.39$  D. After three

years, however, absolute myopia progression remained significantly less severe in atropine-treated eyes. The spherical equivalent was  $-4.29 \pm 1.67$  D in the atropine group and  $-5.22 \pm 1.38$  D in the placebo group. The axial length in the treated group was also significantly shorter than in the untreated group.

Would this favorable result be fully cancelled out over time? Paul J. Rychwalski, MD, pediatric ophthalmologist with Cleveland Clinic's Cole Eye Institute, notes that myopia progression might continue in the atropine group. "You could almost take a pencil and draw a dotted line, extrapolating that if the curves continued in the same direction, the two groups would intersect in another year or



**PATHOLOGICAL MYOPIA.** Beware myopia progression after cessation of treatment with atropine.

so," he said, adding that it's clearly too soon to know. Years four and five will help elucidate whether atropine treatment effects are stable or transient, as the present studies may suggest.

It's also not yet clear whether a different protocol—a different dose or earlier course, for example—would be more efficacious. "Ideally, with genetic testing you could identify the population at highest risk for serious complications and treat them for the shortest length of time necessary," said Dr.

Rychwalski, adding that it doesn't make sense to over-treat a population without a family history of complications, such as choroidal neovascular membrane or retinal detachments because atropine is not a benign treatment. Children in the Singaporean study, for example, experienced side effects such as glare and photophobia, as well as blurred vision from induced cyclopegia.

—Annie Stuart

1 Tong, L. et al. *Ophthalmology* 2009;116:572–579.

## Glaucoma Update

## No Association Between POAG, Mortality

Is primary open-angle glaucoma an ocular condition that's part of an underlying systemic disorder? If so, does that underlying disorder lead to premature death? For decades, researchers have pondered these questions, yielding conflicting evidence to support a connection.

A new meta-analysis pooled data from nine observational studies, and the researchers concluded

that POAG is not a disease consisting of a sick eye in a body predisposed to excess mortality.<sup>1</sup>

The finding did not surprise Sara Akbari, MD, a co-author of the meta-analysis. She said that in the final analysis, none of the studies, except for one, revealed a statistically significant association between POAG and mortality. Dr. Akbari, a resident at the University of Michigan's Kellogg Eye

Center, said, "Further investigation is necessary to better characterize susceptibility factors and clinical pathways involved in the pathogenesis of POAG." She went on to explain that while some ocular conditions are defined by their biochemical processes, POAG is often characterized by its risk factors.

One impetus for the meta-analysis study was to determine whether POAG has an impact on patient survival, said Dr. Akbari, noting that an association could have implications for clinical care and counseling of patients. "Our study suggests that POAG does not affect survival," she said.

Ongoing research is

exploring the possible connection between POAG and other systemic conditions, such as diabetes and body mass index, Dr. Akbari said. Some researchers are looking for genetic markers that might affect disease susceptibility, and whether this will influence individual response to therapy.

"The meta-analysis might set our minds at ease about mortality, but we can't make any assessment of the pathogenesis of POAG," she said. "I hope this paper brings to light the necessity of taking a better look at disease markers."

—Miriam Karmel

<sup>1</sup> *Arch Ophthalmol* 2009;127(2):204–210.

## Publications

## Minimizing Bias in the Peer-Review Process

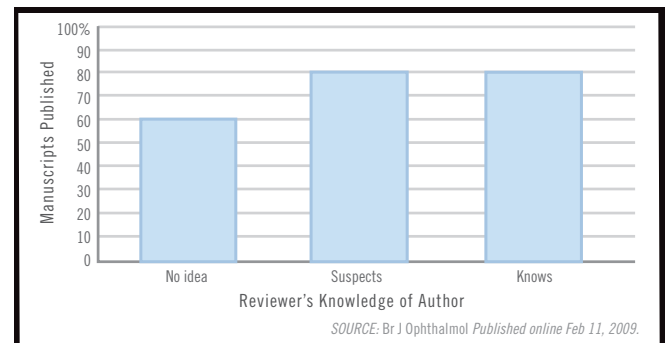
Bias creeps into the peer-review process when the reviewers of submitted papers know—or even suspect—the author's identity, according to an unprecedented analysis of more than 1,000 reviews of manuscripts submitted to a single ophthalmic journal.

"There's a bias within the reviewers, even if it's unconscious," said the lead author of the study, Sherwin J. Isenberg, MD, professor of ophthalmology at the University of California, Los Angeles. "If the reviewer knows, or thinks he or she knows, the author, the paper is more likely to be published."

The study looked at 1,182 reviewers' recommendations on all 531 manuscripts submitted from 2000 to 2005 to the *Journal of AAPOS*, where Dr. Isenberg was editor-in-chief.<sup>1</sup>

The results suggest that medical journals should consider tightening their systems for masking author identity, Dr. Isenberg said. "Most journals don't tell the author who the reviewer is, but the reverse isn't true. I review papers for many journals, and with every one of them I usually know who the author is—one way or another," he said.

The *Journal of AAPOS*



long has had a policy of double-masking, a labor-intensive process for keeping both authors and reviewers anonymous. The study found that double-masking succeeded at hiding the authors' identity 77.7 percent of the time. In those cases, there were lower recommendation scores ( $p \leq 0.004$  for overall shift in accept-revise-reject recommendations).

The study results helped end disagreement on the *Journal of AAPOS* board about the value of double-masking, Dr. Isenberg said.

For maximum effectiveness, it requires the removal of indirect clues to author and institutional identity from each paper before it can be sent out for review. Currently, the journal asks authors to send two versions, one of them with the information redacted.

"Journal editors might not want to do this because it involves a lot more work," Dr. Isenberg said. "But all of us want to minimize bias in peer review." —Linda Roach

<sup>1</sup> *Br J Ophthalmol*. Published online Feb. 11, 2009.