

News in Review

A LOOK AT TODAY'S IDEAS AND TRENDS

Early Detection, Treatment of Wet AMD

Researchers have identified a cellular receptor that, because it occurs only in choroidal neovascularization, might give ophthalmologists a way to simultaneously diagnose and treat

subclinical, wet AMD—long before the disease has stolen any visual acuity.

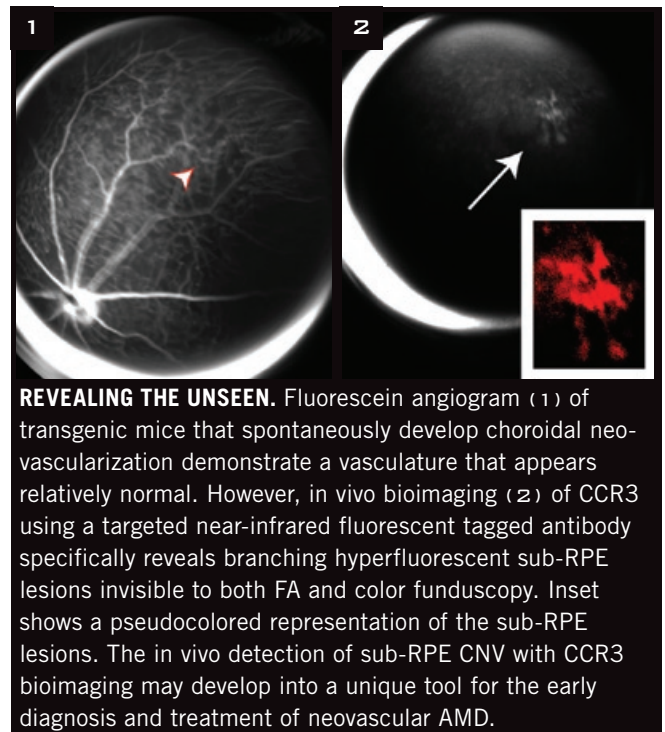
“Detection would be coupled with therapy because the same molecule that is a detection signature is also the therapy,” said the senior coauthor on the paper, Jayakrishna Ambati, MD, professor and vice chairman of ophthalmology, and professor of physiology, at the University of Kentucky, Lexington.

“But the reason we’re

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most excited about this finding is that it would allow ophthalmologists to detect new blood vessels before they become manifest. For the first time, we have a unique signature to the disease.”

Over the last decade, Dr. Ambati’s research team—which now includes collaborators at institutions across the United States and overseas—has produced more than two dozen papers that have helped to build a “higher fidelity model”¹ of the interrelated molecular signals that lead to vision loss from CNV and geographic atrophy.



REVEALING THE UNSEEN. Fluorescein angiogram (1) of transgenic mice that spontaneously develop choroidal neovascularization demonstrate a vasculature that appears relatively normal. However, in vivo bioimaging (2) of CCR3 using a targeted near-infrared fluorescent tagged antibody specifically reveals branching hyperfluorescent sub-RPE lesions invisible to both FA and color funduscopy. Inset shows a pseudocolored representation of the sub-RPE lesions. The in vivo detection of sub-RPE CNV with CCR3 bioimaging may develop into a unique tool for the early diagnosis and treatment of neovascular AMD.

However, the latest paper, published online by *Nature*,² represents a departure from studies that helped scientists to understand the VEGF-mediated inflammatory pathway and to identify exogenous angiogenesis inhibitors such as Genentech’s bevacizumab (Avastin) and ranibizumab (Lucentis).

Working with mice and with choroidal samples

from human tissue bank eyes, the Ambati group found that choroidal endothelial cells begin expressing a completely different type of chemokine receptor at the subclinical phase in the pathogenesis of AMD. This eosinophil/mast cell chemokine receptor, called CCR3 (or CD193), has been studied primarily for its role in allergic dis-

eases such as asthma.

The researchers found CCR3 to be present on the endothelial cells before CNV could be diagnosed with currently available angiography. Furthermore, CCR3 was not present anywhere else in the eye, and this is important because of concerns about neurotoxicity from chronic VEGF inhibition.

These characteristics would make CCR3 an attractive target for a new generation of safer AMD medications that could be used earlier, said J. Fernando Arevalo, MD, a retina specialist and director of the Clinica Oftalmologica Centro Caracas in Venezuela. Because current antiangiogenic

therapy occurs late, only a third of patients gain significant visual acuity, he noted.

“The most interesting aspect of this work is that CCR3 expression is restricted to CNV in human eyes and that this chemokine receptor could be specifically targeted to control CNV in early stages, before it causes vision loss, and without the concerns inherent to current antiangiogenic therapy,” Dr. Arevalo said.

The researchers used a series of experiments in normal and knockout mice, and in human choroidal cells at tissue banks, to show that:

- CCR3 receptors stimulated CNV independent of cellular inflammation, and

independent of eosinophils and mast cells;

- antibodies to CCR3 were more effective at inhibiting laser-induced CNV in mice than antibodies to VEGF-A were (68 ± 3 percent vs. 57 ± 4 percent);
- CCR3 was expressed in CNV tissue (18/18) taken from patients who had not been treated for AMD;
- CCR3 was absent from choroid taken from patients with dry AMD; from age-matched patients without AMD; and from patients with epiretinal fibrotic membranes or choroidal melanoma.

As a next step, Dr. Ambati’s lab is putting CCR3 antibodies into an infrared dye for a human trial of

angiographic detection of subclinical CNV.

The goal is to begin this by the end of 2009, after which efficacy could be evaluated within months, Dr. Ambati said. However, it would take a large clinical trial and several years to evaluate whether CCR3 neutralization can prevent CNV in patients with at-risk eyes.

—Linda Roach

1 Raisler, B. J. et al. *Adv Exp Med Biol* 2008;613:185–192.

2 Takeda, A. et al. *Nature*. Published online June 14, 2009.

Dr. Ambati will receive a portion of any royalties that result from this discovery. The patent is held by the University of Kentucky.

Cornea Update

Contact Lenses May Play a Role in Dry Eye

Dry eye is a common complication and annoyance experienced by contact lens wearers. A group of Japanese researchers hypothesized that meibomian gland loss may play a role. To investigate this possibility, they used a meibographic technique on 121 contact lens wearers and 137 healthy volunteers.

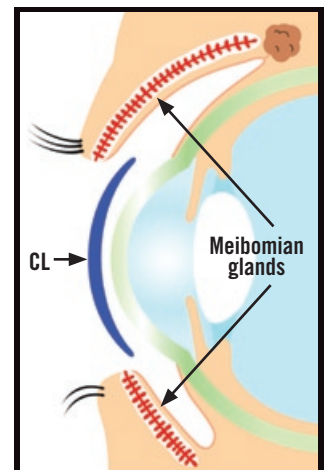
“Our meibography system is composed of a slit lamp equipped with an infrared transmitting filter and an infrared charge-coupled device video camera,” said lead author Reiko Arita, MD, PhD, director of the dry eye service at Itoh

Clinic, University of Tokyo. “The infrared transmitting filter is included as one of the rotating filters of the slit lamp. The examiner can perform meibography with the same slit lamp used for routine examinations.”

Results showed that contact lens wearers had a significantly greater degree of meibomian gland loss than nonwearers, and the decrease was proportional to the duration of contact lens wear, suggesting meibomian gland loss may be one of the mechanisms underlying dry eye associated with contact lens wear. No significant differences were found be-

tween the wearers of soft, disposable and rigid contact lenses. “We think the chronic irritation of meibomian glands by contact lenses through the conjunctiva is a major causative mechanism for meibomian gland loss in contact lens wearers because the clusters of the meibomian glands were similarly shortened from the distal side in most of the contact lens wearers with meibomian gland changes,” Dr. Arita said. “This hypothesis seems to be consistent with the observation that loss of meibomian glands depends on the duration of contact lens wear but not the contact lens materials.”

Some questions still remain. For example, Dr. Arita’s group did not examine whether the meibomian glands improve when contact lens use is discontinued. In addition, the impact of refractive surgery on meibo-



DRY EYE IN A BLINK. Chronic irritation of meibomian glands by contact lenses through the conjunctiva during blinking may cause meibomian gland loss.

mian glands is a key question. “We are actually conducting a project looking at meibomian gland changes after refractive surgery but do not have any data to report as of yet,” Dr. Arita said. —Lori Baker Schena

Retina Report

Possible Link Between Glitazones and DME

A study examining the records of some 170,000 diabetes patients at Kaiser Permanente Southern California found that glitazones, a class of oral antidiabetic drugs used in the management of type 2 diabetes, appear to be associated with an increased one-year incidence of diabetic macular edema.¹

Those who took the drug (n = 1,700) were 2.6 times more likely to develop DME than those who did not (n

= 126,000). The results remained statistically significant even after adjusting for age and severity of disease, though the risk was only 1.6 times greater.

But don't make too much of these findings, warned lead author Donald S. Fong, MD. "This is an observational study. It doesn't show a direct cause and effect," he said, explaining that people who have severe diabetes are more likely to be on glitazones and are also more

likely to get DME.

So what does the study tell us? "I want to emphasize that there are many things we give to our bodies to treat disease, and we don't know their impact on the eyes," said Dr. Fong, director of clinical trials research for the Southern California Permanente Medical Group. "That is why I published this work—to show that safety requires a monitoring of large groups of people over long periods of time. This should be done for all therapies."

Though his study confirmed earlier reports linking glitazones and edema, Dr. Fong is shying away from making any bold clinical recommendations. "If someone comes in with

macular edema, think about the association because the drugs could make it worse," he said.

The next step, he said, would be a more in-depth study that better adjusts for severity of disease. Other confounders to consider are duration of diabetes, changes in renal status, hypertension, intravascular fluid overload, anemia, hyperlipidemia, change of medications and race. "We need more studies to fully define the risk," he said.

For now, said Dr. Fong, "The only thing I would take from my study is there appears to be an association." —Miriam Karmel

1 Fong, D. S. et al. *Am J Ophthalmol* 2008;147(4):583–586.

In the Pipeline

One Seafood May Have a Place in the Surgical Tray

Marine mussels and inkjet printers may seem like an odd scientific duo, but they are now being used by researchers for a new-fangled medical adhesive¹—one that is both environmentally and patient-friendly and may have the potential to make eye surgery safer and more precise. The adhesive is created from the natural protein glue that marine mussels use to stick to rocks. Piezoelectric printer technology produces patterns of the adhesive with microscale precision on porcine skin and other surfaces.

The sticky proteins are extracted from mussel feet, placed in solution and applied with inkjet technology to create a customized medical adhesive. Adding iron to the adhesive solution creates structural changes in the protein that make it even stickier, said Roger Narayan, MD, PhD, coauthor of the paper and associate professor in the joint biomedical engineering department of North Carolina State University and the University of North Carolina at Chapel Hill. "It's not quite as sticky as synthetic adhesives—but with more work we could

get there," he said.

Since the new adhesive is less toxic than its synthetic cousins and is biodegradable, it is less likely to cause inflammation and tissue damage when used in surgery, said Dr. Narayan. He added that inkjet printing technology could be used to apply medical adhesives more precisely than conventional tissue-joining techniques, and this may lead to less tissue warping, less inflammation and faster recovery times after surgeries on delicate eye tissues.

He estimates that it could take five years or less for scientists to bring the new adhesive technology into clinical use. While it takes 10,000 mussels to produce just one solid gram of the sticky protein used for the surgical adhesive, only minute amounts would be needed for a typical micro-



SURGICAL ADHESIVE. Proteins from mussels may provide an alternative to suturing for some surgeries.

surgery, and the sticky stuff is in vast supply on mussel farms in the eastern United States.

So consider a future where, in the wake of eye surgery, you'll be reaching not for superglue but for a product that now graces your dinner table.

—Barbara Boughton

1 Doraiswamy, A. et al. *J Biomed Mater Res Part B: Appl Biomater* 2009;89B:28–35.