

# News in Review

COMMENTARY AND PERSPECTIVE

COMPREHENSIVE

## Protective Effects of Diabetes Rx Evaluated

**IN A POPULATION-BASED STUDY,** researchers in the Netherlands found that people who were being treated for their type 2 diabetes were less likely to develop open-angle glaucoma (OAG) and age-related macular degeneration (AMD) than were their untreated counterparts or those without the disease.<sup>1</sup> However, the study results did not show a similar association with the risk of cataract development.

Although this is not the first study to find these protective effects, it drew on more than two decades of follow-up from the Rotterdam Study, allowing a better understanding of exposure time before disease diagnosis. “Our findings accentuate the potential role of diabetes medication in the pathogenesis of OAG and AMD,” said coauthors Eric F. Thee, MD, and Joëlle E. Vergroesen, MSc, at Erasmus University Medical Center in Rotterdam.

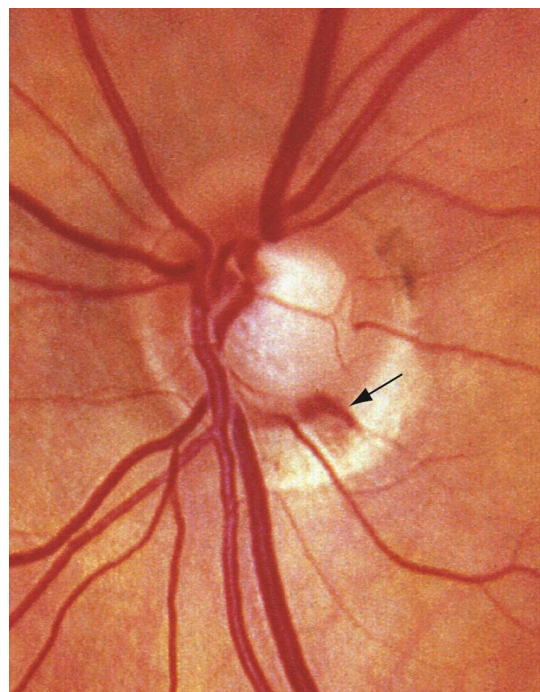
**Study specifics.** The researchers evaluated the records of 11,260 people who participated in the Rotterdam Study from 1990 to 2014. OAG, AMD, and cataract were diagnosed in 4.4%, 17.6%, and 37.3% of the participants, respectively.

Untreated type 2 diabetes was associated with a higher risk of all three diseases: OAG (odds ratio [OR], 1.50), AMD (OR, 1.35), and cataract (OR,

1.63). In contrast, those who received metformin, a first-line treatment for type 2 diabetes, had an 82% lower risk of developing OAG (OR, .18), and those treated with sulfonylureas and insulin (either as monotherapy or in combination) had a 68% lower risk of developing AMD (OR, .32). No protective association was found between diabetes medications and cataract development.

**An unexpected finding.** Moreover, those who were being treated for their diabetes had lower lifetime risks of OAG and AMD than did their nondiabetic counterparts. Specifically, the lifetime risk of OAG was lower for individuals taking metformin than for nondiabetics (1.5% vs. 7.2%), while the lifetime risk of AMD was lower for those taking insulin or sulfonylureas than for nondiabetics (7.05% vs. 33.1%). Dr. Vergroesen described this finding as “most surprising.” He added, “This was unexpected.”

**More than metformin.** To date, studies exploring this topic have highlighted the protective effect of only metformin in OAG and AMD, Dr. Thee said, while associations with other diabetes medications have been overlooked. “These findings suggest that the protective effect [of diabetes medications] found in eye diseases is not per se specific to only one medication.”



**SURPRISE FINDING.** Otherwise healthy patients were more likely to develop OAG (shown here) and AMD during their lifetimes than were those who were being treated for type 2 diabetes. (Arrow = flame-shaped hemorrhage in the left optic nerve head at the 5-o'clock position.)

**Difficult to study.** On one hand, the findings spur interest in the protective effect of metformin and other diabetes medications, the researchers said. On the other, although randomized clinical trials could confirm causality, the research team is not planning an interventional trial at this time. They cited several hurdles to such a trial, including the safety of treating nondiabetics with diabetes medications as well as the ethical concerns of randomizing diabetes patients to a no treatment cohort. —Miriam Karmel

1 Vergroesen JE et al. *JAMA Ophthalmol.* Published online May 19, 2022.

**Relevant financial disclosures**—Drs. Thee and Vergroesen: None.

## CATARACT

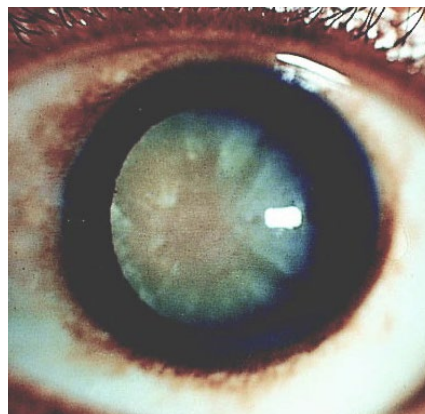
# Topical Cataract Tx: Preclinical Results Offer Promise

**AN INTERNATIONAL TEAM OF** researchers—using mice that had cataracts associated with crystallin protein mutations—found that a topical oxysterol compound may improve lens transparency and refractive index contours in some lenses, further paving the way toward a topical treatment for cataracts.<sup>1</sup>

In some mice—but not all—the

researchers noted a “dramatic improvement in the eyes that had the compound instilled. This suggests that the compound may be effective for some cataracts but not all,” said coauthor Barbara Pierscionek, PhD, at Anglia Ruskin University in Chelmsford, United Kingdom. She added, “Given that cataracts have a multitude of causes, it is not surprising that different treatments may be needed for different types [of cataracts]. The exciting finding was that, at least for some cataracts, this treatment appears to work.”

The oxysterol compound, VP1-001 (also known as 25-hydroxy-cholester-



**NEXT STEPS.** Studies are needed to clarify method of action and assess effects in humans.

## RETINA

# RPE Subpopulations Discovered and Mapped

**SCIENTISTS AT THE NEI HAVE IDENTIFIED FIVE DISTINCT** retinal pigment epithelial (RPE) subpopulations and created a complete single-cell-resolution morphometric map of their location in the eye.<sup>1</sup> Their discovery demonstrates why different retinal degenerative diseases affect different parts of the eye, and it may lead to targeted therapies.

**Harnessing AI.** The researchers used artificial intelligence (AI)-based software to analyze RPE cell morphometry from nine healthy human cadaver eyes. This analysis produced heatmap images of the entire epithelium. These images visually displayed the quantification of four shape metrics: cell area, aspect ratio, hexagonality, and number of neighbors.

**Creating a map.** The AI-generated cell area maps revealed five RPE subpopulations organized in concentric circles around the fovea:

- P1 roughly corresponds to the fovea and parafovea,
- P2 covers most of the center of the RPE monolayer, including the perifovea,
- P3 consists of a midperipheral ring of RPE cells,
- P4 is a ring of small RPE cells of the periphery of the eye that is similar in cell size to RPE in and around the macula, and
- P5 comprises far-peripheral RPE cells.

**A surprise subpopulation.** With regard to P4, said coauthor Kapil Bharti, PhD, “The presence of a macular-like subpopulation in the far periphery was a surprise.” Lead author Davide Ortolan, PhD, added, “The gene expression profile of this population seems similar to macular cells—and under diseased conditions they behave similarly to macular cells, in that they have higher drusen deposits and higher density of chorio-

capillaris atrophy.” Understanding how those RPE cells in the far periphery interact with photoreceptors may lead to a better understanding of how peripheral vision works, they noted.

**Putting the map to work.** First, the reference map allowed the scientists to analyze RPE from a second set of five cadaver eyes with AMD. In all of these eyes, RPE cells were lost due to disease damage in subpopulation P1 and up to the center of P2. In addition, large areas of geographic atrophy were visible at the far periphery of P4 and P5, often extending into P3.

Second, to test the hypothesis that different types of retinal degeneration (RD) affect specific RPE subpopulations, the researchers analyzed ultra-widefield fundus images of patients with choroideremia (CHM), late-onset RD (L-ORD), and RDs with no identified molecular cause. P1 was relatively spared in these diseases, but midperipheral RPE subpopulations contained areas of RPE atrophy. Overall, P1, P4, and P5 appeared mostly affected in eyes with AMD, while P3 appeared to degenerate before the other subpopulations in patients with L-ORD, CHM, and RD.

**Clinical implications.** These findings may provide a better understanding of AMD pathogenesis and, eventually, pinpoint the location of endogenous RPE stem cells that have been suggested to be present in human eye but not yet confirmed, said Dr. Bharti.

The authors are already using the AI-generated reference map to produce macular- and midperiphery-specific RPE cells. “We are a stem cell-based lab, and we are very good at making RPE cells from human stem cells,” Dr. Bharti said. “Now we will try to make the different RPE subpopulations and then use them to develop disease-specific cell and gene therapies.”

—Miriam Karmel

1 Ortolan D et al. *Proc Natl Acad Sci.* 2022;119(19):e2117553119.

**Relevant financial disclosures**—Drs. Bharti and Ortolan: None.

ol), had been previously suggested as a potential anticataract agent. However, Dr. Pierscionek said, until now, no one had tested whether the compound could restore the optics of the eye.

**Study specifics.** Wild-type and knock-in mutant mice were used in the experiments. Twenty-six mice received topical treatment with VP1-001 (ViewPoint Therapeutics) in one eye and vehicle in the other; nine mice were untreated controls. The researchers used slit-lamp biomicroscopy to analyze the lens and provide apparent cataract grades. X-ray phase tomography measurements were used to calculate refractive index in the lenses of 64 postmortem mouse eyes.

**Results.** All told, 61% of the mice of all genotypes showed an improvement in refractive index profiles following treatment. This was supported by a reduction in apparent lens opacity grade by 1.0 in 46% of the mice.

**Next steps.** Additional studies will seek to clarify the oxysterol's mechanism of action, and clinical trials are needed to determine if the results can be replicated in humans, Dr. Pierscionek said. "Ultimately, if this treatment works, we could revolutionize the way in which cataracts are treated and may be able to reduce the need for surgery." The findings also may aid in treating conditions that have secondary manifestations in the lens, such as diabetes. —Patricia Weiser, *PharmD*

1 Wang K et al. *Invest Ophthalmol Vis Sci*. 2022; 63(5):15.

Relevant financial disclosures—Dr. Pierscionek: National Natural Science Foundation of China: S; NIH: S; SPring-8 Synchrotron: S.

## CORNEA

# Tissue-Resident T Cells Protect Eyes From Infection

**DESPITE EVIDENCE THAT EFFECTOR** T cells are recruited to the cornea in response to infections, it is unclear whether memory immune cells are

formed to confer long-lasting immunological protection against reinfection.

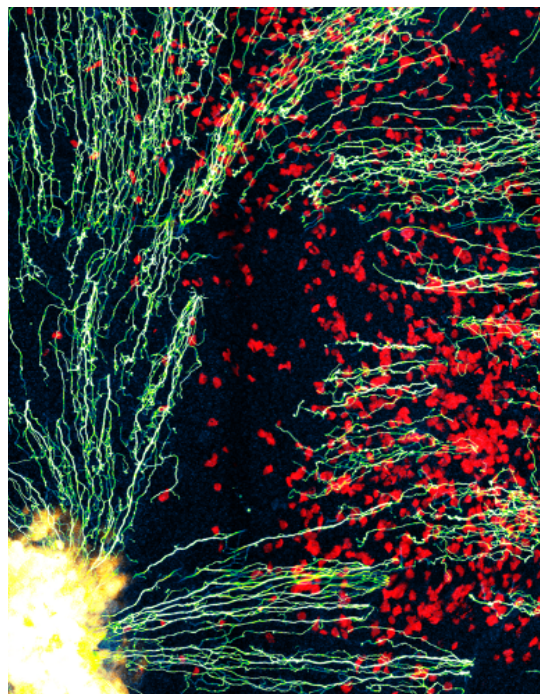
In a recent study, researchers from the Peter Doherty Institute for Infection and Immunity in Melbourne, Australia, used in vivo microscopy to image T cell responses in the cornea in mice. They found that tissue-resident memory (TRM) T cells were present in the cornea after ocular infection and that corneal TRM cells were activated upon reinfection of the eye.<sup>1</sup> In vivo imaging in humans confirmed the presence of TRM-like immune cells in the cornea.

"We found that T cells come into the eye and stay in the cornea for long periods, constantly patrolling in search of pathogens. These T cells can protect the eye from repeated infections," said Scott Mueller, PhD, at the University of Melbourne. He added, "Our findings improved our understanding of ocular infections and how to treat them."

**Approach.** The team used two-photon microscopy to visualize immune cells in a mouse model of ocular herpes simplex virus (HSV) infection. They also used in vivo confocal microscopy in healthy people to visualize the immune cells in the cornea.

**Corneal T cell responses.** HSV-specific T cells entered the mouse corneas by day 5 after infection and persisted for at least four weeks—and the cells were dynamic and motile. Using in vivo confocal microscopy, the researchers observed similar motile immune cells in the corneas of healthy volunteers.

"Although the eye is considered an immune-privileged organ, advanced imaging enabled us to visualize corneal immune cells in mice and humans. The discovery that healthy people have motile immune cells in their cornea was surprising and exciting," Dr. Mueller noted.



**VISUALIZING CORNEAL T CELLS.** Representative fluorescence microscopy image of a mouse cornea after HSV infection (T cells = red, corneal nerves = green, and virus-infected cells = yellow).

## Protection against reinfection.

Characterization of T cells persisting four weeks after HSV infection demonstrated that these cells expressed markers of TRM cells. The development of TRM cells required the cytokine TGF- $\beta$  and local antigen recognition. Notably, TRM cells from previously infected mice responded rapidly to in vitro challenge with HSV, suggesting that these cells may protect against reinfection.

**Future steps.** "The presence of T cells in the cornea could be used diagnostically. However, we first need to understand the conditions under which corneal T cells are protective and whether T cells can contribute to disease, such as dry eye or corneal transplantation rejection," said Dr. Mueller. The team aims to further characterize the immune cells present in the cornea of healthy people to define their roles in health and disease.

—Christos Evangelou, *PhD*

1 Loi JK et al. *Cell Rep*. 2022;39(8):110852.

Relevant financial disclosures—Dr. Mueller: None.

See the financial disclosure key, page 8. For full disclosures, including category descriptions, view this News in Review at [aao.org/eyenet](http://aao.org/eyenet).