

News in Review

COMMENTARY AND PERSPECTIVE

GLAUCOMA

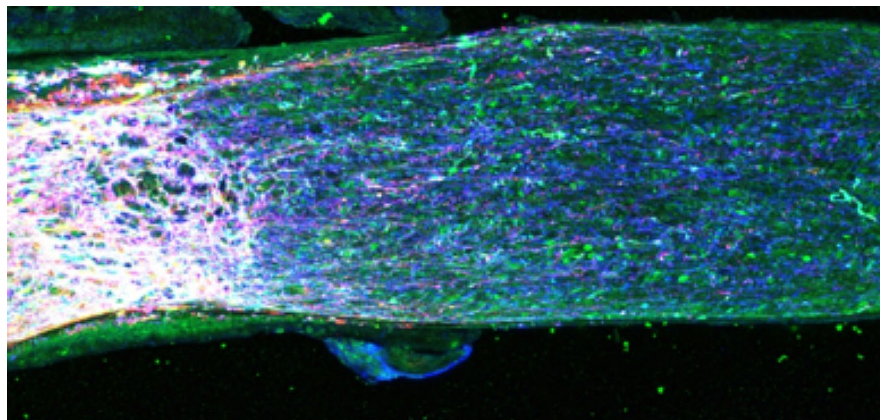
Protein Promotes Optic Nerve Regeneration

NEW INSIGHT INTO AXON REGENERATION could help develop new glaucoma therapies. University of Cambridge researchers have found that protrudin—an important endoplasmic reticulum protein—strongly promotes axon regeneration and neuroprotection in the retina and optic nerve of rodents.¹

“Adult mature nerve cells don’t normally regrow after injury,” said lead author Veselina Petrova, PhD—and successful regeneration of the central nervous system has proved to be an elusive research goal. But the U.K. team discovered that the overexpression of protrudin in cultured rat cortical neurons enhanced axon regeneration after optic nerve crush with a laser.

According to Dr. Petrova, this was one of the strongest promoters of axon regeneration that they had seen in a dish, inspiring them to study the protein in the optic nerve.

Regeneration. To assess the protein’s effect in an animal, the researchers intravitreally injected mice with a gene therapy that elevated the level of protrudin expression. Two weeks after the injection, the researchers performed an optic nerve crush procedure—and two weeks after that, they found that 52% of retinal ganglion cells (RGCs) had survived in the animals with active (phosphomimetic) protrudin, com-



RESULTS. Optic nerve regeneration with enhanced protrudin expression two weeks after optic nerve crush (on the left). Green represents protrudin-positive nerve fibers, blue represents newly regenerating axons, and red represents all axons.

pared with 28% of RGCs in control animals. Protrudin also engendered robust optic nerve regeneration: Active protein induced over 630 regenerating axons to extend as far as 3.5 mm from the injury site, compared with 44 axons with limited regeneration in control animals.

The level of regeneration was surprising, Dr. Petrova said. “It basically equaled some of the best treatments in the field and definitely is one of the best we have seen in our lab.”

Neuroprotection. In a second experiment using the rat acute retinal explant model, the researchers found that protrudin may also confer protection. While control retinal explants lost more than half of their RGCs over three days, retinas that received protrudin two weeks earlier lost none. “I think people are really looking for [this] in the field of ophthalmology right now to protect the cells that are normally dying, especially in conditions such as glaucoma,” said Dr. Petrova. “We think that our preclinical model is very relevant to finding neuroprotective therapies for glaucoma.”

Future directions. Current research suggests that protrudin stimulates axon regeneration by shifting endosomes and endoplasmic reticulum into the distal part of injured axons. Moving forward, the Cambridge group will parse the molecular mechanism behind regeneration and neuroprotection, particularly in humans, Dr. Petrova said. They are already studying protrudin in human retinal explants in a collaboration with coauthor Keith Martin, MD, at the Centre for Eye Research Australia and the University of Melbourne.

“Of course, we have to do all the necessary testing for whether our gene therapy actually works in human tissues, whether it is safe, whether it can restore some visual function, what other side effects could there be, and so on,” Dr. Petrova said. “But we think it is a good step forward to have identified a new mechanism that potentially protects retinal neurons from dying as well as helping them to regenerate.”

—Kanaga Rajan, PhD

¹ Petrova V et al. *Nat Commun.* 2020;11(1):5614.
Relevant financial disclosures—Dr. Petrova: None.

Cornea Protected From the Novel Coronavirus

SARS-COV-2 APPARENTLY DOES NOT penetrate the cornea, unlike the herpes simplex virus 1 (HSV-1) and the Zika virus (ZIKV). This finding comes from a study conducted at the Washington University School of Medicine in St. Louis, Missouri.¹

Given the paucity of data regarding airborne or droplet transmission of SARS-CoV-2 through the eye, the new findings are “somewhat reassuring,”

said Rajendra S. Apte, MD, PhD. “We should be comforted that the corneal surface seems to be innately resistant to SARS-CoV-2 viral penetration.” He stressed, however, that further study is needed.

Study design. The study researchers pursued two lines of inquiry: 1) to evaluate the three viruses in human and/or animal models and 2) to explore the ability of interferon lambda (IFN- λ) to inhibit viral replication in the eye. This was done by blocking its action to determine whether virus proliferated. (Although IFN- λ and its receptor IFN- λ R1 are known to restrict viral replication in other barrier surfaces, this is the

first study to describe their activity in the human eye.)

Good news with SARS-CoV-2. Results showed that SARS-CoV-2 did not penetrate the human cornea. In addition, the virus was not affected by IFN- λ . Specifically, no evidence was found of SARS-CoV-2 replication in seven donor samples inoculated with the virus in the presence of the anti-IFN- λ antibody.

As the researchers wrote, “. . . blockade of IFN λ R1 did not make the human corneal tissue more permissive to infection with SARS-CoV-2.”¹

Results with ZIKV. Working with genetically modified mice that had been

Toric Versus Toric: Rotational Stability Rates

RESEARCHERS IN CALIFORNIA CONDUCTED A RETROSPECTIVE study to compare the rotational stability of two commonly used toric presbyopia-correcting IOLs and their monofocal toric counterparts.¹ They found that the presbyopia-correcting Tecnis Symfony (Johnson & Johnson) was more likely to rotate and to require surgical repositioning than the ReStor (Alcon)—and that the Tecnis monofocal toric IOL (Johnson & Johnson) was more likely to require surgical repositioning than the AcrySof monofocal toric IOL (Alcon).

Study rationale. Lead author Bryan S. Lee, MD, JD, in private practice in Los Altos, California, explained, “Our previous study demonstrated that the AcrySof toric IOL was significantly less likely to rotate than the Tecnis toric IOL,² but [these two IOLs] had not been compared to their presbyopia-correcting toric counterparts.”

Study methods and design. For this study, the same surgical technique was used by Dr. Lee and his colleague, David F. Chang, MD. Thorough irrigation and aspiration was used to remove all ophthalmic viscoelastic devices (OVDs), including within the capsular fornices and behind the toric IOL optic. The eye was left slightly soft, with an intraocular pressure in upper single digits as estimated by palpation.

Consecutive patients receiving a study IOL were included. All patients had image-guided digital marking to verify toric IOL position at the conclusion of surgery. Postoperative rotation was determined by dilated examination performed later on the day of surgery or the following morning.

Eyes were excluded if digital marking could not be

obtained preoperatively or was not able to be used intraoperatively.

Patients were divided into two cohorts:

- Those who received a presbyopia-correcting toric ReStor (n = 61) or Symfony (n = 779), from September 2016 to January 2019.
- Those who received a monofocal toric AcrySof (n = 2,393) or Tecnis (n = 731), from April 2015 to January 2019.

Results. The toric ReStor was less likely to rotate 5 or more degrees than the toric Symfony (91.8% vs. 79.0%; p = .01). This remained true for rotation of 10 or more degrees (100% vs. 89.5%; p < .003). Mean rotation was 2.3 degrees for the toric ReStor, compared to 4.5 for the toric Symfony (p = .01).

In addition, significantly more toric Symfony eyes required a return to the OR for repositioning (6.9% Symfony vs. 0% ReStor; p < .03), and more eyes that received the Tecnis monofocal toric IOL required surgical repositioning than did those that received the AcrySof (3.5% vs. 1.2%; p < .001).

A matter of the platform? Dr. Lee emphasized that use of digital axis marking (Callisto, Carl Zeiss Meditec) in every case “helped differentiate postoperative rotation from surgical misalignment.” He added, “We believe the consistent rotational results from the previous paper to this one demonstrate that toric IOL stability is an IOL platform effect. Furthermore, the higher surgical repositioning rate for the toric Symfony than the Tecnis [monofocal] toric helps show that toric presbyopia-correcting IOLs are less tolerant of misalignment and residual astigmatism.”

—Arthur Stone

1 Lee BS et al. *J Cataract Refract Surg*. Published online Nov. 11, 2020.

2 Lee BS, Chang DF. *Ophthalmology*. 2018;125(9):1325-1331.

Relevant financial disclosures—Dr. Lee: None.

inoculated with ZIKV, the researchers found ZIKV in the harvested and dissected murine corneas and other organs of the mice. Moreover, once the washed murine donor corneas were transplanted into naïve mice, ZIKV was still evident at low levels in all recipient animals, and one mouse had severe infection in multiple organs.

In human donor samples, ZIKV replicated only once out of three attempts, suggesting that the human cornea is somewhat resistant to ZIKV infection. Histological analysis revealed that ZIKV infected a small number of corneal epithelial cells, but the virus did not substantially penetrate into deeper layers.

“We were quite concerned during the Zika pandemic that viruses such as these [e.g., flaviviruses] could be transmitted by tissue transplantation,” Dr. Apte said. “It was reassuring to see low rates of transmission [in human tissue], given that transmission of viruses by solid organ transplantation is a major clinical concern.”

The researchers also tested whether IFN- λ protects against infection with ZIKV, using an anti-IFN λ R1 antibody. The results indicate that blockade of IFN- λ enhances replication of ZIKV.

Results with HSV-1. Within 72 hours of infection with HSV-1, viral levels in the human cornea increased approximately 10-fold in the presence of the anti-IFN λ R1 antibody. This blockade of IFN- λ led to more severe HSV-1 infection, suggesting that IFN- λ signaling in the cornea mediates protections against herpesvirus infection. The finding could pave the way for creation of interferon lambda-based therapeutics that can prevent or limit viral infection and any related vision loss, Dr. Apte said.

Making sense of the findings. Although receptors of SARS-CoV-2 are expressed on the corneal and conjunctival surfaces, the coronavirus does not seem to be able to penetrate the cornea and replicate within this tissue, Dr. Apte said. “This result suggests some other resistance factor in the cornea, other than interferon lambda, that prevents

corneal infection from SARS-CoV-2,” he added.

Dr. Apte cautioned that these preliminary data do not definitively prove that the eye is not a route for entry of the virus. “But it is interesting that the cornea does not support SARS-CoV-2 viral infection and replication in the laboratory,” he said. Given the likelihood of future pandemics and epidemics, he added that “understanding how antiviral barrier immunity works will be critically important to our ability to fight these infections.”

—Miriam Karmel

1 Miner JJ et al. *Cell Rep.* 2020;33(5):108339.

Relevant financial disclosures—Dr. Apte: None.

RETINA

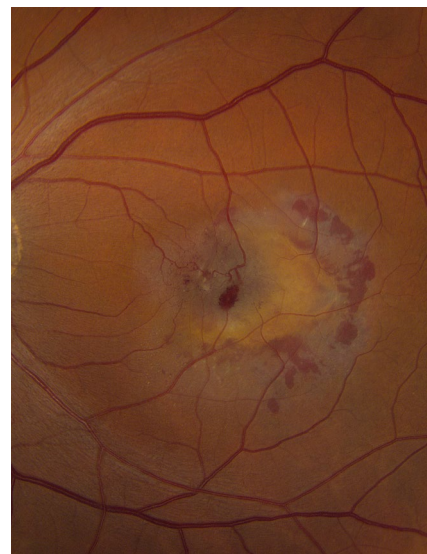
Early Results With VEGF-Grab

A PRECLINICAL TRIAL OF VEGF-Grab suggests that the novel anti-VEGF agent offers significant potential for VEGF suppression.¹

A team of researchers in Korea investigated the safety and efficacy of VEGF-Grab and compared it to aflibercept (Eylea). They found that the in vivo antiangiogenic efficacy of VEGF-Grab was similar to that of aflibercept and that the in vitro anti-VEGF activity of VEGF-Grab was superior to that of aflibercept. The retinal safety profiles were comparable for the two drugs.

Study rationale. Previous investigations have found that VEGF-Grab has a stronger binding affinity to VEGF and placental growth factor than aflibercept, which suggests that it could be a more efficacious anti-VEGF agent than aflibercept.

By extension, VEGF-Grab’s higher binding ability suggests that it may be more effective than ranibizumab and bevacizumab, said Se Joon Woo, MD, PhD, at the Seoul National University Bundang Hospital in South Korea. “VEGF-Grab promises to be efficacious in patients refractory to the current anti-VEGF agents, as well as in treat-



CANDIDATE DRUG. VEGF-Grab shows promise for retinal diseases such as neovascular AMD (shown here) and diabetic retinopathy.

ment-naïve cases,” he said.

In vitro, in vivo. Dr. Woo and his colleagues quantified the effect of aflibercept and VEGF-Grab on VEGF-induced proliferation and migration. In vitro, VEGF-Grab was a better inhibitor of VEGF-induced cell proliferation/migration than aflibercept. Both agents comparably inhibited proliferation in tube formation assays.

In the in vivo animal model studies, both drugs yielded similar results. Their antiangiogenic effects in mice with oxygen-induced retinopathy were comparable. In rats with laser-induced choroidal neovascularization (CNV), VEGF-Grab and aflibercept showed similar CNV inhibition.

In vivo toxicity from injection was evaluated with light and electron microscopy. Neither drug caused adverse events or significant ocular inflammation arising from injection in treated mouse eyes.

Looking ahead. Detailed preclinical experiments are still needed, especially to confirm safety, Dr. Woo said.

—Miriam Karmel

1 Hong HK et al. *Invest Ophthalmol Vis Sci.* 2020;61(13):22.

Relevant financial disclosures—Dr. Woo: None.

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