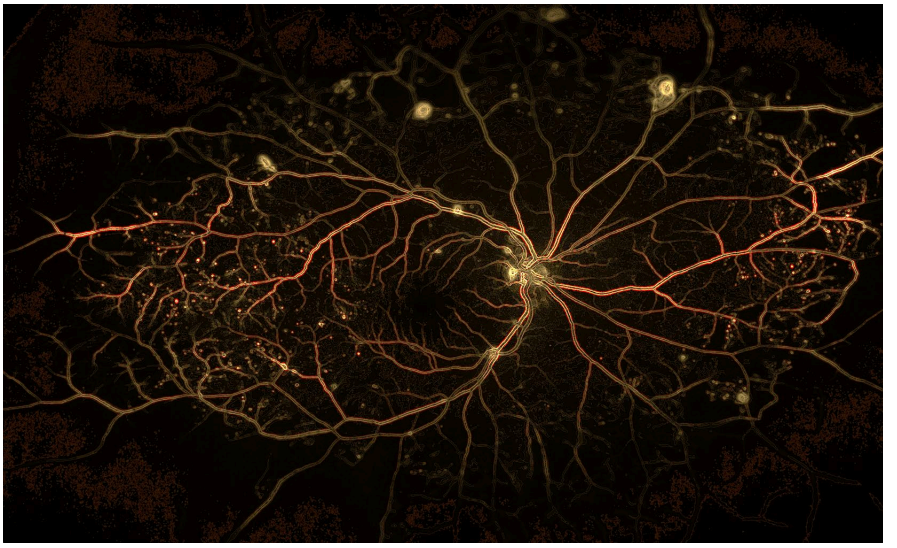


MICROVASCULAR INJURY. *Artistic rendition of a fluorescein angiographic image demonstrating abnormal, leaky retinal blood vessels in a patient with DR. Tight glycemic control, as well as fluctuating serum glucose levels, appear to exacerbate DR.*

Alexander Sodhi, McDonogh School

RETINA

Impact of Glucose Fluctuations on DR Progression

WHY IS TIGHT GLYCEMIC CONTROL— the cornerstone of diabetic management—sometimes linked to worsening of diabetic retinopathy (DR)? A multicenter team of researchers set out to investigate this question in a murine study. Their findings linked low blood sugar levels with a molecular pathway that is turned on in oxygen-starved retinal cells.[1]

Tight glycemic control can involve transient episodes of hypoglycemia, noted Akrit Sodhi, MD, PhD, at Wilmer Eye Institute in Baltimore. And these fluctuating glucose levels "cause an increase in certain retinal cell proteins, which can contribute to the development of abnormal blood vessels and worsening diabetic eye disease," he said. Given the findings, he said, "We believe this study has important implications for optimizing glucose management in patients with diabetes." It also could have implications for diabetic nephropathy and diabetic neuropathy.

"Importantly, this study does not undermine the importance of tight glucose control," Dr. Sodhi added. "But it suggests that transient episodes of low glucose can, by themselves, exacerbate diabetic retinopathy."

Observing a cascade of events. The researchers analyzed protein levels in human and mouse retinal cells and intact mouse retinas cultured in low glucose. They also evaluated mice that had transient hypoglycemia.

They found that in response to low glucose, the retinal cells increased the levels of nuclear hypoxia-inducible factor (HIF)-1α. (HIF-1 plays an essential role in the cellular response to low oxygen.) This increase in HIF-1α activated the cellular machinery—including glucose transporter Glut1 as well as key glycolytic enzymes in retinal Müller glial cells—needed to improve the cells' ability to use available glucose. These responses preserve the limited oxygen available for energy production by retinal neurons.

In the presence of hypoxia, as can occur in patients with DR, this physiologic protective response in Müller cells to low glucose resulted in a synergistic increase in the levels of nuclear HIF-1α and the production of vasoactive mediators such as VEGF and ANGPTL4, which promote the growth of abnormal, leaky blood vessels.

Target for new therapeutic treatments. Dr. Sodhi said that several potential therapeutic interventions may help prevent the pathologic consequences of HIF-1α accumulation in response to hypoglycemia. Currently, his lab is investigating signaling pathways that link hypoglycemia to the accumulation of HIF-1α. These pathways could be vulnerable targets for patients newly diagnosed with diabetes, and for patients with diabetes and high glycemic variability. His lab is also trying to develop therapies that directly target HIF-1α.

Dr. Sodhi cited several other potential therapeutic interventions, including preventing episodes of hypoglycemia and directly targeting the HIF-1–regulated gene products that promote DR. In the meantime, he said, "Ophthalmologists should encourage patients to discuss with their endocrinologist strategies to minimize episodes of hypoglycemia." *—Miriam Karmel*

1 Guo C et al. *Cell Reports.* 2023;42(1):111976.

Relevant financial disclosures: Dr. Sodhi—HIF Therapeutics: PS; NIH: S; Research to Prevent Blindness: S; TEDCO: S.

DRUG DELIVERY

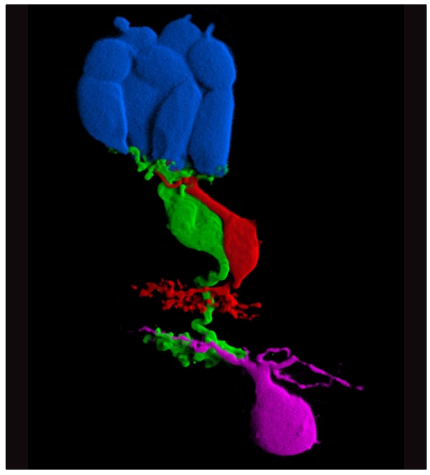
Lipid Nanoparticles Deliver mRNA to Photoreceptors

GENE THERAPY FOR INHERITED RET-inal degeneration took another step forward when Oregon researchers used lipid nanoparticles (LNPs) to deliver messenger RNA (mRNA) to the photoreceptors, retinal pigment epithelium (RPE), and Müller glia in mice and nonhuman primates.[1]

"We have developed LNPs conjugated with peptide ligands that reach the back of the eye and bind to photoreceptors. These LNPs enabled us to deliver mRNA to the neural retina and [they] could be useful in the development of mRNA-based gene therapies for inherited blindness," said Gaurav Sahay, PhD, at Oregon State University and Casey Eye Institute in Portland, Oregon.

Dr. Sahay added, "This is just the beginning. Although there are potential treatments for retinal degeneration, delivering drugs to the right cell type in the eye remains a challenge. We hope this technology will translate into new therapies for inherited diseases through targeted delivery of drugs or genetic material to the cells of interest."

Identifying peptide ligands. LNPs, which are tiny, lab-made balls of fat, are excellent carriers for drugs and genetic material. In the team's previous efforts to develop LNP-based gene therapies for inherited blindness, the LNPs were able to deliver RNA only in the epi-



PROMISE OF NANOTECHNOLOGY. *The eventual goal: confirming the ability of lipid nanoparticles to treat inherited blindness in humans (blue = photoreceptors, green and red = retinal bipolar cells, purple = retinal ganglion cells).*

GLAUCOMA

Real-World Outcomes With Hydrus Stent

IN A REAL-WORLD SETTING, THE HYDRUS MICROSTENT (Ivantis) combined with cataract surgery proved to be a viable option for a variety of glaucoma subtypes and severities.[1] The minimally invasive glaucoma surgery (MIGS) device provided at least medium-term efficacy in reducing both IOP and medication use in patients with mild to severe glaucoma. It also slowed disease progression.

"Ours was the first real-world study to report on Hydrus outcomes beyond 24 months postoperatively, and it reinforced findings from the Horizon study," said Paul Harasymowycz, MD, FRCSC, at the Montreal Glaucoma Institute in Montreal, Canada.

Study specifics. The findings are based on a single-surgeon consecutive case series involving 75 patients (106 eyes). Participants underwent implantation of the Hydrus with phacoemulsification between 2013 and 2021.

Nearly two-thirds of the patients had primary open-angle glaucoma (POAG). Disease severity was fairly evenly distributed between mild (30%), moderate (39%), and severe (31%). Twelve eyes had undergone previous incisional surgery, and 41 eyes had a history of selective laser trabeculoplasty (SLT). Success was defined according to the absence of specific failure criteria: 1) glaucoma reoperation; 2) SLT; and 3) IOP less than 5 mm Hg or greater than 18 mm Hg, or an increase in the number of glaucoma medications, or loss of light perception due to glaucoma.

At three years. Overall, 67% of eyes met all success criteria, with only 14% needing additional surgery. IOP decreased 26.5% following surgery, from 18.9 ± 4.8 mm Hg to 13.9 ± 2.3 mm Hg. Medication use fell by at least one drug in 71% of eyes, while 21% were medication free following Hydrus implantation (vs. 7% preoperatively). Use of carbonic anhydrase inhibitors (CAIs) declined from 18% preoperatively to 3% following surgery.

Adverse events were few and transient. Failure was associated with higher baseline IOP and preoperative use of oral CAIs. "Interestingly, severe disease [for which Hydrus is not FDA-approved] was not linked to a higher rate of failure," Dr. Harasymowycz said. "Most importantly, we showed that this procedure can effectively slow disease progression as demonstrated by the stability of visual fields and retinal nerve fiber layer thickness."

Clinical implications. Dr. Harasymowycz tends to choose the Hydrus over other MIGS devices for patients who have moderate POAG and coexisting cataract, have an IOP in the high teens or low 20s, and take two or three glaucoma medications. An important consideration is the size of the Schlemm canal in the affected eye. In eyes with average or small trabecular meshwork width, he said, "We avoid Hydrus implantation as there is a greater likelihood of the implant cheesewiring into the anterior chamber or the ciliary body."

He is now conducting a multicenter study to assess the five-year real-world Hydrus outcomes. "We hope that the findings are comparable to those of the Horizon study," he said. *—Miriam Karmel*

1 Salimi A et al. *Ophthalmol Glaucoma.* 2023:6(2);137-146.

Relevant financial disclosures: Dr. Harasymowycz—None.

Courtesy of Wei Li Laboratory, NEI

thelial cells of the eye. For this study, the researchers used a peptide screening assay known as phage display to develop LNPs that recognize photoreceptors. "This approach allowed us to identify peptide ligands that target photoreceptors," Dr. Sahay noted. The most promising peptides were identified using in vivo biopanning, an "in vivo version of phage display," he said.

Delivering mRNA to photoreceptors. Peptides injected intravitreally or subretinally into mice showed rapid localization to the photoreceptors at the back of the eye. Moreover, LNPs coated with peptide ligands crossed biological barriers of the eye and successfully delivered mRNA to the animals' photoreceptors, Müller glia, and RPE.

Commenting on the translational potential of this approach, Dr. Sahay noted that, "with lipid nanoparticles, the rate of translation from nonhuman primate to humans is extremely high." Moreover, he said, "having positive nonhuman primate data is the next best thing before a human clinical trial."

Next steps. "Our priority now is to show in multiple animal models that we can treat blindness using peptide-coated LNPs. We also want to study the tolerability of LNPs and perform dose escalation studies in nonhuman primates," said Dr. Sahay.

Following these proof-of-concept studies, the team is planning to perform clinical trials to confirm the ability of LNPs to act as a gene editing tool. If successful, this would allow researchers to sidestep the limitations associated with current AAV (adeno-associated virus) gene editing strategies, the researchers wrote.

"There are more than 200 mutations in the photoreceptors that cause retinitis. LNPs are very versatile, and if we show that this technology works for one mutation, we will adapt it to target other blindness-causing mutations," Dr. Sahay added. —*Christos Evangelou, PhD*

1 Herrera-Barrera M et al. *Sci Adv.* 2023;9(2):eadd4623.

Relevant financial disclosures: Dr. Sahay—Enterx Bio: EO.

NEURO-OPHTHALMOLOGY

Using AI to Help Diagnose Optic Neuropathies

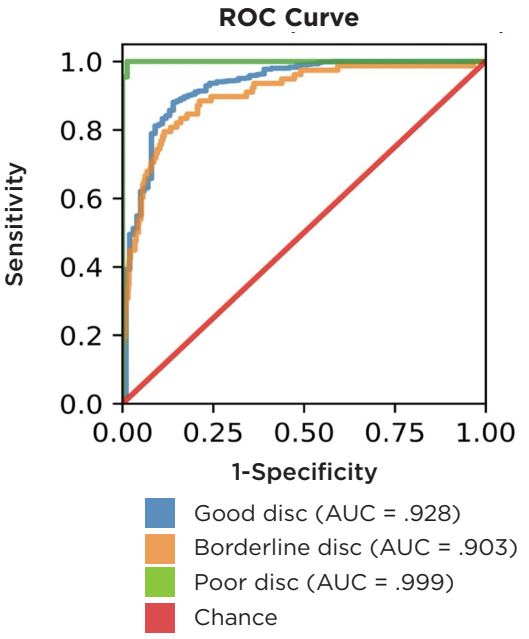
RESEARCHERS FROM THE BRAIN AND Optic Nerve Study With Artificial Intelligence (BONSAI) Consortium and the Singapore Eye Research Institute developed a deep learning (DL) system to automatically identify high-quality images of the optic nerve head (ONH). The system accurately distinguished between poor- and high-quality fundus photographs and may help improve the selection of optimal-quality photographs for diagnosis of optic neuropathies.[1]

"In contrast to our initial assumption that the presence of pathologically blurred discs in otherwise high-quality images would result in interpretation errors and image misclassification as of poor quality, the system was able to accurately determine the quality of retinal images," said Dan Milea, MD, PhD, at the Singapore Eye Research Institute.

Study rationale. Although DL algorithms have been developed to automate the identification of low-quality retinal images with blurred areas used for the diagnosis of diabetic retinopathy or glaucoma, papilledema is "by definition a visually blurred area due to optic disc swelling," Dr. Milea noted. As a result, the team developed an algorithm to evaluate the quality of retinal images irrespective of the presence of blurred discs.

Study specifics. The BONSAI researchers developed, trained, and tested their DL system on "5,015 mydriatic and nonmydriatic ocular photographs from 31 neuro-ophthalmology centers in 20 countries," Dr. Milea said. Disease conditions represented included papilledema and glaucoma; images of eyes without pathology also were included. Three experts independently determined the quality of images as good, borderline, or poor.

For high-quality images, the BONSAI system provided 91.4% (95% CI, 90%-92.9%) accuracy, 93.8% (95% CI, 92.5%-95.2%) sensitivity, and 75.9% (95% CI, 69.7%-82.1%) specificity. High performance was also obtained for fundus photographs of poor and borderline quality. The system's overall accuracy in distinguishing between the three levels of image quality was 90.6% (95% CI, 89.1%-92.1%).



AI RESULTS. *Performance of the DL system in a multiethnic external-testing dataset (AUC = area under the curve, ROC = receiver operating characteristic).*

Potential clinical utility. This DL algorithm could be connected to a fundus camera for real-time quality assessment of an image, Dr. Milea said. "Fundus photographs of high quality could be used to detect papilledema or other optic disc abnormalities, whereas those of poor quality would be marked for reacquisition."

—*Christos Evangelou, PhD*

1 Chan E et al. *Diagnostics.* 2023;13(1):160.

Relevant financial disclosures: Dr. Milea—None.

Dan Milea, MD, PhD

See the financial disclosure key, page 10. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.