Optogenetics is a technology that uses gene therapy to induce the expression of light-activated ion channels in cells, which renders the cells light-sensitive. When these cells are illuminated with light of the proper wavelength, membrane depolarization (or hyperpolarization) is induced by the light-sensitive ion channels, and if the cells are neurons, synaptic transmission can be initiated (or inhibited). Optogenetics has the potential for minimally invasive neuronal stimulation with high spatial resolution. By proper selection of promoters, the expression of these light-sensitive ion channels can be limited to specific subpopulations of neurons. One might, for example, transfect ganglion cells with light-sensitive ion channels by an intravitreal injection of an adeno-associated virus vector containing a naturally occurring or man-made ion channel coupled to a promoter that limits expression to retinal ganglion cells.

Optogenetics was initially developed as a strategy to study the informational and computational role of neural circuits. It has been repurposed as a therapeutics modality by vision scientists. Transduction of photoreceptors, bipolar cells, or ganglion cells with light-sensitive ion channels, for example, restores vision in preclinical models of retinitis pigmentosa. From a clinical perspective, one advantage to targeting ganglion cells is that they persist in a relatively healthy state even in advanced stages of retinitis pigmentosa. On the other hand, targeting bipolar cells creates an opportunity for signal amplification and processing that might confer greater light sensitivity on the patient, as well as improved visual function. Targeting photoreceptors might seem misguided, as these cells die first in retinitis pigmentosa. Histological studies of postmortem eyes and in vivo studies of human patients using optical coherence tomography and adaptive optics, however, indicate that cone photoreceptors persist in an abnormal state (eg, greatly shortened outer segments) for a relatively long time in patients with retinitis pigmentosa. Restoring light sensitivity to these dysfunctional remnants of cones might be the easiest way to restore useful vision to patients with retinitis pigmentosa, and evidence from preclinical models indicates that this approach might work.

In a recent issue of Translational Vision Science and Technology, Francis et al summarized the proceedings of the First International Optogenetic Therapies for Vision Symposium. The meeting was cohosted by the Massachusetts Eye and Ear Infirmary and the Foundation Fighting Blindness, Inc and was attended by physicians, scientists, members of the US Food and Drug Administration, venture capitalists, philanthropists, and representatives of companies trying to develop this technology for clinical use. Attendees identified a number of issues that must be addressed for optogenetics to be translated into a sight-restoring therapy for human patients. Photoswitches, for example, should be activated at light intensities and wavelengths encountered during activities of daily living. The virus-transgene assembly should not elicit an immune response, particularly if treatment of the fellow eye or re-treatment of a given eye is contemplated. Appropriate efficacy end points must be developed for human trials. If retinal ganglion cells are transfected with light-sensitive ion channels, for example, measuring electroretinogram responses using current protocols would not be an informative endpoint. It also might be beneficial to provide patients with presensitized retinal images so that light signals impinging on the retina are more likely to result in useful visual perceptions. In summary, better technology, better animal models, and better techniques and strategies for clinical assessment will help investigators further improve the therapeutic efficacy of optogenetics.

The history of optogenetics as a sight-restoring therapy illustrates how knowledge of basic chemistry, biology, cell signaling, information processing, molecular biology, and gene therapy can be deployed to create novel treatments for patients with visual impairment. The scientists and clinicians using optogenetics to treat blindness have achieved an incredible amount in a relatively short time, which gives one hope that optogenetics will be developed into a generic treatment for retinal blindness in the near future.


**OPHTHALMIC IMAGES**

### Nevus in a Pterygium

Amir A. Azari, MD; Mozghan Rezaei Kanavi, MD; Pimkwan Jaru-ampornpan, MD; Sherif S. Khedr, MD; Heather D. Potter, MD; Daniel M. Albert, MD; Neal P. Barney, MD

A 23-year-old man presented with a 2-year history of a slow growing lesion in the left eye. The lesion consisted of a vascularized, balloon-like mass straddling the limbus nasally (A). Histopathologic examination demonstrates (B) a conjunctival epithelium with solar elastosis, consistent with a pterygium (left side), and proliferation of melanocytic cells in the stroma and epithelial-stromal interface, consistent with a compound nevus (right side). It is important to note that, except for a small area on the left (black arrowhead) that demonstrates a normal thickness, the remainder of the conjunctiva shows considerable thickening, which measures as high as 6 times the normal value in some areas. This thickening, which gives the lesion its striking clinical appearance, is due to severe reactive fibrosis and solar elastotic changes. Magnification reveals the nevus component in more detail (C [white arrowheads]).