

Washington University School of Medicine

Digital Commons@Becker

Open Access Publications

2020

Sourcing photoreceptor-like cells for treating vision loss

Rajendra S. Apte

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor***Sourcing Photoreceptor-like Cells for Treating Vision Loss**

Rajendra S. Apte, M.D., Ph.D.

The neurosensory retina is a complex ecosystem composed of precisely layered and diverse neurons, multiple vascular plexuses, and glial cells. It is here that visual signals from the environment are processed and conducted through the optic nerve to the visual cortex to create the vivid images that humans see. The relationship of the neurosensory retina to the brain is fascinating because it is the only extension of the central nervous system that can be easily visualized and is readily accessible to interventional therapies. Photoreceptors are specialized neurons in the retina that sense photons of light and initiate their transduction into electrical signals. Diseases that affect the function and survival of photoreceptors can lead to blindness. These include inherited retinal degenerations, acquired retinopathies such as retinal detachments, and diseases of aging such as age-related macular degeneration.¹

The past decade in vision science has been productive: many novel approaches have been developed to prevent vision loss in diverse diseases. Conventional approaches use pharmacotherapy to improve photoreceptor function and vision. Recent efforts have focused on gene therapy for conditions in which mutations within photoreceptors or retinal pigment epithelial (RPE) cells affect photoreceptor function and survival. These efforts culminated in the regulatory approval of a new intraocular gene therapy for biallelic RPE65-associated gene mutations in retinal dystrophies.² A limitation of these approaches is that they must be implemented relatively early in the course of the disease, before substantial photoreceptor damage occurs. The transplantation of embryonic stem cell–derived or induced pluripotent stem cell–derived RPE cells is being examined in early-stage clinical trials involving humans. In addition, the transplantation of photoreceptors or their precursors is in preclinical development.³ Another innovative strategy has

been to bypass photoreceptors and initiate visual transduction by means of optogenetics (a technique that uses genetic engineering to express light-sensitive ion channels in neurons) or by means of implantable electronic devices that circumvent photoreceptors. These strategies have tremendous potential given the regulatory approval of an intraocular, implantable device for patients with severe vision loss.⁴

In an intriguing study conducted by Mahato et al.,⁵ the investigators pharmacologically reprogrammed fibroblasts into rod photoreceptor-like cells that they call chemically induced photoreceptor-like cells (CIPCs). Using small molecules, they found that fibroblasts from mice and humans can be reprogrammed into CIPCs. Reprogrammed CIPCs express photoreceptor markers such as rhodopsin and CRX (a transcription factor that is critical to the development of photoreceptor cells). Moreover, their transcriptomic profiles are enriched in rod-specific genes.

Mahato et al. transplanted CIPCs into the eyes of mice with severe retinal degeneration and found synaptic connections between and activation by these cells of the inner retinal circuitry. Although they observed variability in the number of CIPCs that survived after transplantation, as well as variability in the results of functional tests such as pupillary response, light aversion, modified optokinetic testing, and electroretinography, they also observed generally improved retinal responses after the transplantation of CIPCs.

Molecular mechanisms that have been proposed for the transdifferentiation of fibroblasts into CIPCs involve mitochondrial translocation of AXIN2, which activates mitochondrial reactive oxygen species (ROS). The mitochondrial ROS in turn activate NF- κ B (nuclear factor kappa-light-chain enhancer of activated B cells), which up-regulates the neural transcription factor *Ascl1* (Fig. 1). Further research is needed to determine

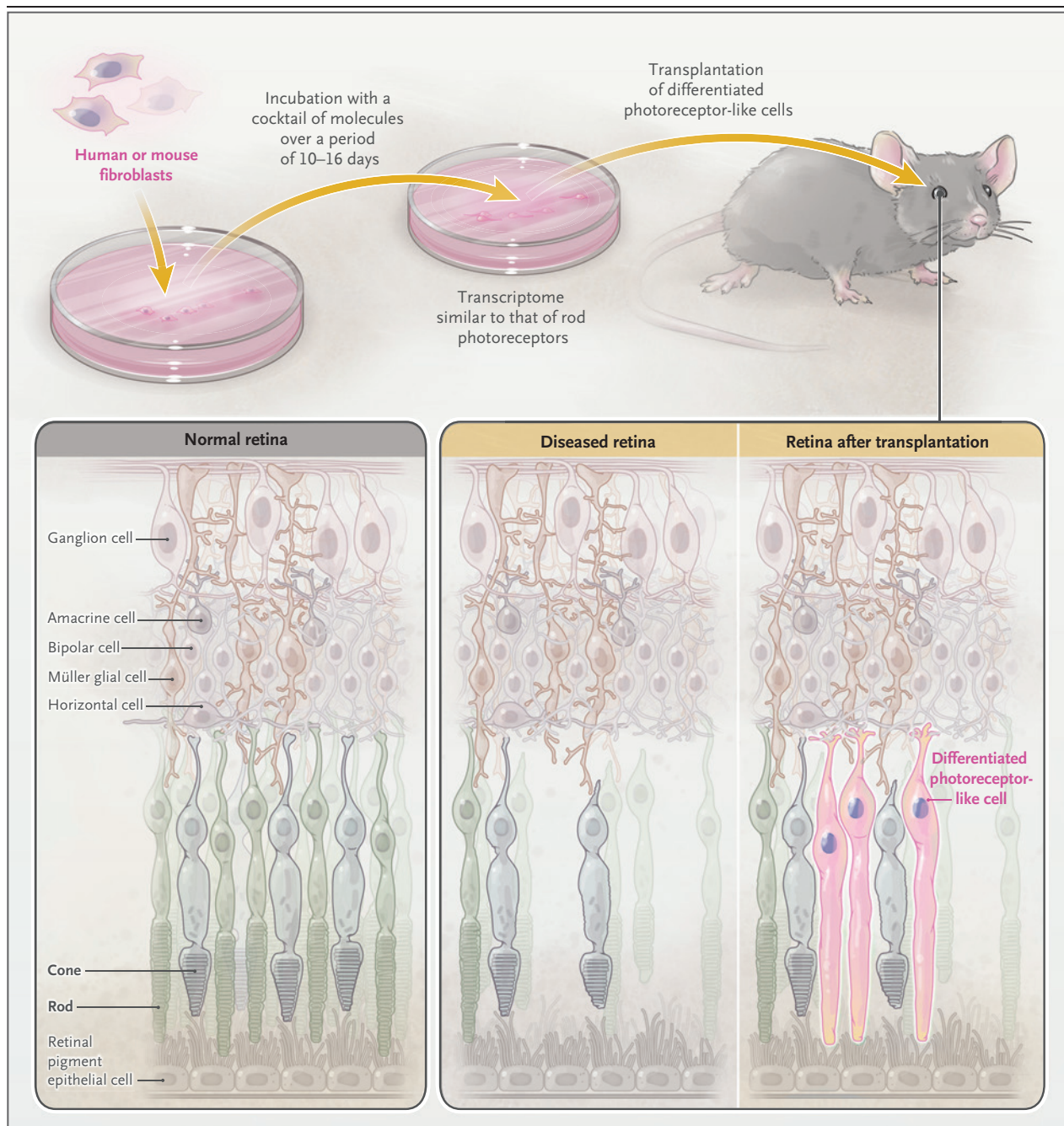


Figure 1. Restoring Retinal Function with Chemically Induced Cells.

In the healthy neurosensory retina, visual transduction begins when light photons reach rod and cone photoreceptors. The information is processed through the layered neuroglial network and conveyed by ganglion-cell axons through the optic nerve to the brain. Vision loss occurs in diseases in which photoreceptors become dysfunctional or die. The transplantation of cells such as chemically induced photoreceptor-like cells into the subretinal space in murine models opens a new avenue for future research to examine the role of cell transplantation in patients with blinding retinal diseases.

the efficiency of reprogramming, the effectiveness and magnitude of synaptic reactivity, and the possibility of material transfer between

donor and host cells that may account for some of the functional effects. Nonetheless, these preliminary findings support a new, albeit tentative,

strategy for the treatment of diverse retinal diseases in which photoreceptor death has caused vision loss and in which pharmacologic and gene-therapy approaches, which require live photoreceptors, would not be appropriate. CIPCs deserve careful examination in additional preclinical studies before clinical development strategies are considered. Additional variables for further evaluation include assessments of long-term survival of CIPCs within the retina, measurements of visual function that are clinically meaningful, and the immunogenicity of transplanted cells. The new and emerging strategies for the rescue, regeneration, and replacement of photoreceptors suggest a bright future in the fight to preserve and restore vision in blinding eye diseases.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Departments of Ophthalmology, Developmental Biology, and Medicine, Washington University in St. Louis School of Medicine, St. Louis.

1. Lin JB, Apte RS. NAD⁺ and sirtuins in retinal degenerative diseases: a look at future therapies. *Prog Retin Eye Res* 2018;67:118-29.
2. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet* 2017;390:849-60.
3. Schwartz SD, Regillo CD, Lam BL, et al. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. *Lancet* 2015;385:509-16.
4. Wood EH, Tang PH, De la Huerta I, et al. Stem cell therapies, gene-based therapies, optogenetics, and retinal prosthetics: current state and implications for the future. *Retina* 2019;39:820-35.
5. Mahato B, Kaya KD, Fan Y, et al. Pharmacologic fibroblast reprogramming into photoreceptors restores vision. *Nature* 2020;581:83-8.

DOI: [10.1056/NEJMcibr2027602](https://doi.org/10.1056/NEJMcibr2027602)

Copyright © 2020 Massachusetts Medical Society.