Introduction

Many blinding diseases result from the dysfunction and/or death of rod and cone photoreceptors that generate neural signals in response to light, and thus enable photosensitivity of the retina. Following the loss of photoreceptor function, the nonphotoreceptor cells of the retina often remain largely intact and potentially capable of function. However, the absence of functional photoreceptors leaves these cells without light-generated input signals. Multiple groups are working to develop new therapies for photoreceptor degenerative diseases by making the remaining retinal cells directly sensitive to light. In one of these approaches, termed “optogenetics,” investigators introduce the gene for a light-sensitive protein into the plasma membrane (i.e., surface membrane) of light-insensitive cells (Boyden, Zhang, Bamberg, Nagel, & Deisseroth, 2005; Nagel et al., 2003). The expressed protein acts either as a light-sensitive ion channel or a light-sensitive pump, and thereby produces a membrane current (i.e., an electrical signal) in the cell. The most commonly used optogenetic proteins are members of the channelrhodopsin family (Nagel et al., 2002; Nagel et al., 2003), which are ion channels that cause cell depolarization when activated; and members of the halorhodopsin family (Bamberg, Tittor, & Oesterhelt, 1993; Han & Boyden, 2007; Schobert & Lanyi, 1982; Zhang et al., 2007), which are ion pumps that cause hyperpolarization. In a second approach, referred to as “photopharmacology” or “optopharmacology,” a light-sensitive small molecule, termed a photoswitch, is interfaced with native ion channels in the plasma membrane. Here, the absorption of light by the small molecule alters the structure of the ion channel to which it is bound, causing the channel to generate an electrical signal. Photoswitches developed to date include diethylamine-azobenzene-quaternary ammonium (DENAQ), which interfaces with hyperpolarization-activated cation channels (Ih) (Tochitsky et al., 2014), and (E)-N-(2-Aminoethyl)-4-((4-(4-(4-hydroxy-3,5-diiisopropylphenyl)butanamido)methyl)phenyl)diazeynlfibenamide (MPC088), which interfaces with a class of receptors (GABA_A) that are activated by gamma-aminobutyric acid (GABA) (Yue et al., 2012). The chemical structures of both DENAQ and MPC088 incorporate a derivative of azobenzene, a chemical that undergoes cis/trans photoisomerization and mediates the light sensitivity of these photoswitches. Photoswitch technology has also been used in combination with genetic engineering to generate cysteine-substituted variants of native ion channels. Upon the delivery of a photoswitch containing a thiol-reactive group (maleimide), these channels covalently bind the photoswitch to the substituted cysteine residue, enabling photoregulation of the channel’s activity (Banghart, Borges, Isacoff, Trauner, & Kramer, 2004; Caporale et al., 2011; Yue et al., 2012). Both the optogenetic and photopharmacological approaches for vision restoration are aimed, in essence, at bypassing the dysfunctional photoreceptors and engineering a light-responsiveness to remaining healthy retinal cells. Common to both approaches is the delivery of the needed reagents into the eye by intravitreal or subretinal injection. Intravitreal injection is a well-established procedure already in wide use by ophthalmologists for delivering therapeutic drugs to the retina. Subretinal injection is a more delicate procedure, requiring highly trained surgeons.
What Do We Need From a Light-Sensing Molecule?

The success of optogenetic and photopharmacologic therapies will depend on the ability of the introduced light-sensing protein or photoswitch to stimulate adequately their target cells. This leads to the seemingly straightforward question of what qualities are needed from the light-sensing molecule to achieve meaningful stimulation. Clearly important are a sufficiently high concentration and photosensitivity of the introduced molecule and sufficiently fast kinetics of the induced electrical response to light. However, there are caveats that govern the choice of ideal values for these properties. For example, a higher level of expression of an optogenetic protein or a higher concentration of an introduced photoswitch will produce a larger response of the cell to light, but increasing the level of either type of photosensor increases the likelihood of causing an immune response or other type of cellular toxicity. A further potential pitfall must be considered when the light-sensitive molecule is targeted to ganglion cells, the axonal processes of which extend over relatively large distances from the cell body. That is, a high-light sensor concentration in the axons of a given ganglion cell, by generating a response of the cell to light falling anywhere over the large distance covered by its axon, could reduce the spatial resolution of the cell’s light response. A possible optogenetic solution to circumvent this problem is to promote the localization of the expressed photo-protein (say, channelrhodopsin) to a desired region of the ganglion cell (in the present case, the cell body rather than the axonal region). This can be achieved by identifying the amino acid segment (the “motif”) of a native protein that mediates targeting of the protein to sites within the cell body, and then incorporating, as an appendage to the channelrhodopsin gene to be delivered, the nucleotide sequence that encodes this protein motif (Greenberg, Pham, & Werblin, 2011; Wu et al., 2013). A possible solution to circumvent this problem is to use subcellular motifs to reduce the axonal expression in retinal ganglion cells (Greenberg et al., 2011; Wu et al., 2013).

The photosensitivity of the optogenetic protein or photopharmacological molecule is another important consideration. Channels consisting of an optogenetically introduced protein or native channels that are pharmacologically made light-responsive are not highly efficient. That is, activation of the channel, resulting from the absorbance of a photon, produces only a small membrane current. For an optogenetic channel, the amount of current passed by the channel (and thus the size of the electrical response mediated by a single channel) can be increased in two ways: by making the activated channel more permeable to the desired ions, or by lengthening the period that the channel remains open. Currently, many optogenetic proteins have faster kinetics than necessary, and lengthening the channel-open period could increase the photosensitivity (i.e., yield a greater time-integrated passage of ions). Longer channel-open periods can be expected to decrease the temporal resolution of the light-generated response.

Developing optogenetic and/or photopharmacological agents that could respond to infrared (IR) or near-IR light represents a particularly attractive goal, for two reasons. First, even in cases of advanced-stage photoreceptor degeneration, some visual function mediated by native rods and/or cones may remain. Because the retina ordinarily lacks sensitivity to IR light (i.e., because the visual pigments of the rods and cones do not absorb light at IR wavelengths), IR-induced signals in the retina could minimize or avoid cross-talk with residual native visual signaling that persists despite the disease. Second, the fact that IR illumination largely avoids the excitation of native photoreceptors would likely make IR-sensitive optogenetic/photopharmacological agents valuable for testing in primate models, where (by contrast with, e.g., mouse) there currently exist no genetic strains that exhibit dysfunction or loss of the native rods and cones.

Chemical Versus Genetic Approaches

Optogenetic and photopharmacological strategies have distinct advantages and limitations. The use of genetically encoded optogenetic proteins allows for a one-time treatment of the retina with a long-lasting effect (Busskamp et al., 2010; Doroudchi et al., 2011; Ivanova, Hwang, Pan, & Troilo, 2010; Lagali et al., 2008). The genetic approach also allows investigators to use genetic promoters as well as viral tropism to limit the expression of the optogenetic protein to the desired cell type. However, optogenetic treatment is irreversible. Thus, if the treatment causes an immune response or another adverse effect, it cannot be removed and protein expression will continue. Furthermore, in its current form, it is not possible to increase or decrease the dose after administration to the patient, and if another, better treatment is developed later, the patient would likely be ineligible to receive it. By contrast, the effect of photopharmacological molecules (photoswitches) is temporary. The photoswitches will degrade over a course of days, allowing discontinuation of treatment if adverse events occur (Polosukhina et al., 2012). It would also be possible to adjust the dose over time for each patient to find the optimal dosage. However, the temporary nature of the pharmacological approach is a
disadvantage because it requires multiple intravitreal injections, which is not a trivial procedure. It is possible that photoswitches could be packaged in a time-release polymer, thereby lengthening the period between treatments, or perhaps administered as eye drops, entirely removing the need for intra-ocular injections.

Potential Roles of Light-Projecting Goggles

As presently conceived, signaling processes in the diseased retina initiated by an optogenetic protein or chemical photoswitch will, in multiple ways, differ from those operating in the healthy retina. One key difference relates to the operation, in normally functioning rods and cones, of a cascade of biochemical reactions that amplifies the signal initiated by the photoactivation of visual pigment protein in these cells. Through this phototransduction amplification mechanism, the absorption of light by just a few of the densely packed, large number of visual pigment molecules in the photoreceptor leads to the transient closure of many channels in the photoreceptor plasma membrane and thus, the generation of a highly amplified membrane current response. The inability of optogenetic/photopharmacological therapies to allow a photosensor concentration that approaches the normal abundance of visual pigment (due to toxicity risk; see above), and the overall lower amplification (relative to that achieved by the normal biochemical cascade) achieved by these therapeutic photosensors, emphasize the need for boosting the intensity of light incident on the treated retina. That is, at least for the immediate future, it seems likely that satisfactory vision restoration by optogenetic/photopharmacological approaches will require, in addition to treatment of the retina with the photosensor agents, an intensity enhancement of the visual scene being viewed by the patient. This intensity boost of the visual scene can, in principle, be achieved by a goggle-style electronic device that in real time captures an image of the scene, amplifies the luminous features, and, at wavelengths to which the photosensors respond, projects the enhanced image onto the retina (Goetz et al., 2013).

Although introducing an optogenetic protein or photoswitch into the diseased retina can be anticipated to enable photogeneration of membrane currents by the targeted retinal cells, the nonnative nature of this light-response mechanism, as well as possible abnormalities of signal processing associated with remodeling occurring in the diseased retina, may lead to substantial alterations in the way that the photosensitized cells and other remaining retinal cells process these signals. As a result, the spatial and temporal properties of ganglion cell responses to a given visual scene could differ from the responses produced by the same scene in the normal retina. Thus, an additional likely requirement of the goggle electronic device just referred to will be the capability to transform light of the visual scene into a spatiotemporally altered array of projected intensities that compensates for the altered signal processing in the retina. The goal here is to enable a normally encoded output of the retina to the brain despite abnormal signal processing within the retina. It is important to keep in mind that since the spiking in RGCs is produced in response to changes in the light intensity on photoreceptors, eye movements are an essential component in this signal processing chain. Without eye movements the retina would adapt to a static scene and elicit no response. Therefore, conversion of the video stream into a retinal “code” should include eye tracking.

Yet, a further possible requirement of the goggles may be the need for this device to modify its projected image in response to changes in the eye’s position. In the healthy eye, the fixation point is routinely changed as a visual scene is scanned. Thus, in the absence of an eye-tracking capability by the goggles, if the patient were to change the point of fixation, the goggle-projected, spatially restricted image originally directed at a retinal location that has been made light-sensitive would suddenly be directed to a retinal location where no light-sensitive cells are present. An eye-tracking capability of the goggles could perhaps enable dynamic modification of the relevant “region of interest” of the image, based on the eye’s position, which is projected on the light-sensitive area of the retina. Image processing based on eye tracking can provide location-specific corrections, such as a radial stretch in the fovea (Asher, Segal, Baccus, Yaroslavsky, & Palanker, 2007). Alternatively, the device could perhaps project onto the retina a wide-field image that is larger than the light-sensitive area. In this latter case, however, energy expended by the device to project photons to light-insensitive regions would be wasted.

Which Cells to Target

Another factor to be considered is which cells to target with optogenetic or photopharmacological therapy. There are four main options: (1) a nontargeted approach, in which for simplicity there is no engineering of the delivered gene or vector (optogenetic), or of the delivered chemical photoswitch (photopharmacological), to promote the therapy’s action on
a particular cell type; and the specific targeting of (2) ganglion cells, (3) bipolar cells, or (4) remnant cone photoreceptor cell bodies. Each has distinct advantages and limitations in different states of retinal degeneration (Sahel & Roska, 2013).

Nontargeted optogenetic vision restoration was the first to be used for optogenetic vision restoration in mice (Bi et al., 2006), and nontargeted reagents are also currently used in photopharmacology. The belief is that the natural, sophisticated processing of the retina, with its 20-circuit mosaics each extracting a different feature from the visual, can be sidelinied, and that the plasticity of the brain can allow patients to relearn interpreting the visual scene using the new and simplified language that the resensitized retina provides. This is a radical view, but the plasticity of the brain cannot be underestimated, and likely our brain will extract as much information as possible from any sensory signal provided to it. However, the extent to which this will produce useful vision remains to be tested.

Ganglion cells relay visual signals to the brain. There are approximately 20 types of ganglion cells in primates (Dacey, 2004) and in other mammals, and each of these implements a different retinal code that gives rise to 20 neuronal representations of the visual scene (Roska & Meister, 2014). Similar to the nontargeted approach, targeting ganglion cells bypasses all of the retinal processing that takes place in a healthy retina. This limits the ability of the therapy to approximate normal vision. One possible way to overcome this limitation is by recreating the neural code for 1 of the 20 ganglion cell types, using the goggles to transform the light signal into an approximation of normal processing of that type and stimulating the ganglion cells accordingly (Nirenberg & Pandarinath, 2012). Another possibility is to target expression of the optogenetic agent to just one type of ganglion cell that is thought to be the most important. Since the gene expression patterns of retinal cell types are rather different, it is likely that in the future it will be possible to target at least some specific types. Finally, if one could target more than one type, it could become possible to use optogenetic tools with different spectral sensitivities to play back their own neural code. Ganglion cell targeting is especially attractive in late-stage degeneration in those patients where remodeling of the retina may make normal retinal processing impossible (Marc, Jones, Watt, & Strettoi, 2003). Targeting ganglion cells using intravitreal injection is currently problematic, since such injections in primates lead primarily to labeling in the foveal region where ganglion cells are not laid down on a mosaic. However, this is currently a technical limitation and is likely to be solved by new virus capsids or by subretinal injection. So far, only one primate species has been tested; other species may be different.

Targeting bipolar cells would allow more of the retinal processing to be preserved, although some processing would still be lost. Unlike photoreceptors, bipolar cells are preserved even in late-stage degeneration. Bipolar cells provide a compromise between preserving as much of the signal as possible and being applicable to patients in late stage retinal degeneration. However, there are several important limitations. For example, optogenetically transducing a large number of bipolar cells likely requires a subretinal injection. Also, it is possible that late-stage retinal degeneration may cause enough retinal remodelling to distort retinal processing (Marc & Jones, 2003).

Many people with genetic retinal degeneration have a rod–cone dystrophy. That is, the rods degenerate first, followed by a slower cone degeneration. This results in remnant cone cell bodies, where the outer segments have degenerated but the cell is still alive and may survive for many years (Cotter & Noell, 1984). These remnant cones no longer respond to light. Transducing the remnant cones with halorhodopsin can restore light responses to the cones. Targeting cones, by utilizing most of the retinal processing, has the potential to recreate vision with the greatest similarity to normal vision (Busskamp et al., 2010). The remnant cones appear to delay retinal remodeling, preserving the circuitry of the cells below them in the retina (Jones & Marc, 2005). However, this strategy relies on the presence of remnant cones, which are observed only in the fovea at late stages of degeneration (Milam, Li, & Fariss, 1998). Many patients with advanced-stage retinal degeneration will not be eligible for this treatment. Also, it remains unknown whether optogenetic treatment would prevent or slow cone death. If it does not, some of those who are eligible for the treatment may eventually lose the benefit through cone death.

Given the distinct advantages and limitations of targeting three different retinal cell types, it is likely that each approach will be beneficial for different subgroups of patients. Patients who still have a large number of remnant cones would likely benefit most from targeting the photoreceptors. Those who have a more advanced degeneration will likely benefit from targeting bipolar cells, while the most severely affected would require using ganglion cells as the target cell type.

Fovea Versus Periphery

One question that was raised was whether it would be better to target the fovea or the periphery of the retina. Targeting the fovea seems intuitive because that is the area that provides the highest acuity. However, the fovea also has a
different cellular arrangement than the rest of the retina. In most of the retina there is a highly organized mosaic arrangement of cells at every level, and the visual information is sent in a relatively straight line from the photoreceptor to the bipolar cell to the ganglion cell. Because of this mosaic structure, elements of the visual scene “map” in straightforward fashion to (i.e., correspond in simple manner with) locations on the retina. However, in the fovea there are no ganglion cells or bipolar cells directly under the photoreceptors. Rather, these cells are pushed aside to allow light to reach the photoreceptors most efficiently (Kolb, 1995). The cells are arranged in a ring around the fovea, highly organized, but not arranged in a mosaic as they are elsewhere in the retina. If we target the ganglion cells or bipolar cells in the fovea with optogenetic proteins and then project an image onto the retina, the neuronal representation of the image would be distorted. One way to at least partially remedy this problem is to stimulate the foveal ganglion cells with images that have been purposely “predistorted” by a goggles-type device to compensate for the ring-arrangement of the light-sensitive targeted cells. This predistortion capability of the goggles would have to be accompanied by an eye-tracking ability of high spatial precision, to follow changes in fixation (see above). A further challenge related to the positioning of foveal ganglion cells is that their ring arrangement occupies three (not just two) dimensions. Therefore, even predistortion of a two-dimensional image projected onto this three-dimensional array would not in itself enable fully adequate photostimulation of all of the cells.

Targeting the periphery would preserve the map. However, it does not provide the same acuity as the fovea, and it is not the central part of vision, which is the area that is the most useful to patients. It is possible that patients who are treated in the periphery will develop a “pseudo-fovea” similar to patients with age-related macular degeneration, who use a peripheral area of the retina to fixate on images (Schuchard, 2005).

Targeting remnant cone cell bodies in the fovea would bypass the problem of the inner retina’s re-arrangement since the cones are still arranged in a spatial map that correlates with the spatial properties of the image.

Possibility of Immune Response

Another consideration to take into account is the possibility of an immune response to optogenetic proteins or photoswitches, especially when introduced at high levels. Although the eye is normally immune privileged by comparison with other parts of the body, certain eye diseases can compromise the blood–retina barrier (Vinores et al., 1995). The route of administration of an optogenetic protein (intravitreal or subretinal), the specific protein to be expressed, and the specific serotype of the viral vector that is used to target the cells could be important determinants of whether an immune reaction is evoked. More work in primates is needed to characterize the immune response.

Animal Models and Evaluation of Efficacy

There are currently no animal models that allow straightforward evaluation of the clinical feasibility of optogenetic or photoswitch therapies. Each model has limitations in its ability to simulate the human retina well enough for us to draw firm conclusions about the efficacy.

Mice

Mice are widely used as a first model. They breed relatively quickly, have strains with genetic mutations resulting in retinal degeneration of various speeds, and their small size keeps housing costs low compared with larger animal models. However, their eyes are very small compared with those of humans, which results in a proportionally larger area of the retina being transduced by a subretinal and intravitreal treatment. This could cause overestimation of the efficacy of the treatment. Furthermore, mice do not have a fovea, which is a key feature in the human retina. Also, the permeability of the inner limiting membrane is different in mice than in humans or primates. The inner limiting membrane is thinner in mice and lacks the variation in thickness in different parts of the retina that is seen in larger animal models (Dalkara et al., 2009).

Dogs

Dogs have eyes that are more comparable in size to human eyes. Also, there are naturally occurring dog models of blindness. However, dogs, like mice, do not have a true fovea, although they have a fovea-like bouquet of cone receptors that is affected by inherited macular degenerations (Beltran et al., 2014). Also, the inner limiting membrane in dogs differs from the inner limiting membrane in humans, although it is more similar than mouse to the human inner limiting
membrane (Balaratnasingam et al., 2009). Another limitation of the dog model is the amount of time needed for the retina to degenerate. In order to evaluate optogenetic or photopharmacologic treatment, the dog would need to be at a very advanced stage of degeneration, which takes a year or more depending on the specific dog model used (Kijas et al., 2002; Ropstad et al., 2008; Suber et al., 1993).

**Pigs**

There is a transgenic mini-pig model of retinitis pigmentosa that has an autosomal dominant mutation in rhodopsin (Ross et al., 2012; Scott, Fernandez de Castro, Kaplan, & McCall, 2014). This model has many advantages. Pigs have large eyes that are structurally similar to human eyes, and they degenerate relatively quickly (Scott et al., 2014). However, the pig also does not have a true fovea (Beauchemin, 1974). Also, aging the pigs is expensive and time-consuming, and the persistence of robust cones makes degeneration times lengthy, further increasing the costs of using this model (Fernandez de Castro et al., 2014).

**Rabbits**

Rabbits are another large-eye animal in which a transgenic model of RP has been made. Rabbits are smaller and far cheaper than pigs but also do not have a fovea. However, disease progression and retinal rewiring in the rabbit RP model closely parallel autosomal dominant RP in humans (Jones et al., 2011). Another potential disadvantage of rabbits is that much of the retina is avascular, which can result in greater retinal degeneration after subretinal injection as compared with more vascularized retinas.

**Monkeys**

Macaque monkeys are a very good model for the human eye. Monkey eyes possess a fovea, and the properties of the inner limiting membrane appear to be similar to that of the human retina (Yin et al., 2011). Additionally, monkeys can be trained to perform complex visually based tasks, which allows a better understanding of the level of conscious vision achievable using optogenetics or photoswitch therapy. Unfortunately, there are no well-established models of blindness in which cell deterioration and resulting vision loss closely mimic the disease processes evident in humans. Local retinal degeneration can be induced by subretinal placement of a thin implant, which causes rapid demise of photoreceptors above it due to chronic separation from the retinal pigment epithelium (RPE) (Mandel et al., 2013). Alternatively, photoreceptors can be selectively coagulated over large areas using pattern scanning laser irradiation. However, new, innovative ways of evaluating the efficacy of treatment in the presence of functional photoreceptors, or ways of inducing retinal degeneration in primates, are needed.

Because all animal models have limitations, the only way to truly evaluate the quality of vision obtainable from optogenetics or photopharmacology is through human trials. It will be essential to make sure that the patients enrolled have reasonable expectations of the therapy. A successful therapy would provide useful visual function to patients.

**Future Directions**

Several goals for developing optogenetic and photoswitch therapies were identified:

1. Develop an IR-sensing optogenetic protein or photoswitch. IR stimulation would allow for better efficacy studies and could allow earlier treatment because it would not overlap with normal visual function in the retina.
2. Develop eye drops capable of delivering photopharmacological drugs to the retina. Eye drops would remove the barriers to re-administration of a photoswitch. Without the need for frequent injections, photoswitches would provide an opportunity to validate optogenetics without the risks associated with permanent treatment.
3. Optimize the kinetics of photo-sensor activation and de-activation of optogenetic photo-proteins and photopharmacological reagents. The sensitivity of optogenetic proteins could be increased by increasing the amount of time the channels are open and increasing the permeability of the channels to the desired ions. Maximizing the sensitivity of the proteins or photoswitches will lower the required amount of light for effective stimulation of the retina.
4. Develop viral-mediated targeting of optogenetic sensors to specific inner retinal neurons.
5. Develop better animal models for blindness. The current models of blindness are inadequate to allow us to evaluate efficacy, especially in the fovea. Ideally, we would need a model of blindness in monkeys. Within this overall objective,
there is a need for further development and testing of chemicals/drugs that, when administered systemically or
intravitreally, cause widespread photoreceptor degeneration in animals. For example, pharmaceutical companies have
compounds that have failed in their intended development for clinical application because they cause retinal
degeneration in one or more species. The identification and validation of these compounds could enlarge the toolbox
of compounds available for studies of retinal degeneration in a variety of experimental animals, both large and small.

6. Human trials. There are several optogenetic therapies that are very close to human trials. All of the preclinical data so
far show that optogenetic therapy is safe and is capable of inducing light-driven activity in the degenerated retina.

7. The success of optogenetic or photopharmacological strategies for vision rescue will likely depend on better
understanding of the mechanisms of retinal remodeling, and the incorporation of this knowledge into the design for
therapeutic treatment. Once remodeling and negative plasticity ensue, interventions by these treatments may be co-
opted into plasticity as the remodeling “program” continues. It will thus be important to define windows of
opportunity when optogenetic and photopharmacological interventions will be most successful.

Summary

The paragraphs above summarize research progress toward therapies that seek to restore vision in late-stage
photoreceptor degenerative disease by engineering light sensitivity of the inner retina by genetic or pharmacological
approaches. The proof of concept studies have shown that it is possible to take advantage of the innate retinal circuitry to
restore light sensitivity (Bi et al., 2006; Busskamp et al., 2010; Doroudchi et al., 2011; Lagali et al., 2008; Tochitsky et al.,
2014). Although the first optogenetic proteins were naturally occurring channels isolated from algae and archaea, many
new variants have been developed to optimize their utility in probing the function of neural circuits. Now that
optogenetics has been repurposed as a treatment for blindness, new proteins should be engineered with the specific
requirements for vision in mind. With several groups moving forward to clinical trials, it will be exciting to see the level of
vision that will be obtained.

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