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Review

# Strategies for restoring vision to the blind: current and emerging technologies

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ABSTRACT

This paper reviews the current state of the art in the design of retinal prostheses that hope to restore vision to the blind. The progress and the challenges faced by electronic implants are discussed. Additionally, the emerging technologies in the field are also reviewed. These include optogenetics and chemical interfaces that interface to the neural system. These emerging fields have made tremendous progress in the last few years and offer new hope in the design of retinal prosthetic devices.



**Contents**



## 1. Introduction

Vision is, perhaps, one of the most important sensory modalities that we posses. Loss of visual function is a debilitating condition that afflicts millions around the world and many efforts are underway around the world to restore this lost functionality. Retinal degeneration is the primary cause of vision loss and it is the restoration of visual function due to retinal degeneration that is the primary focus of this review. The two leading causes of retinal degeneration are retinitis pigmentosa and age-related macular degeneration and both diseases result in photoreceptor degeneration, see Fig. 1. Though, there are many efforts that bypass the retina to restore visual function such as cortical and optic nerve based implants [11,24,35], they are not addressed in this review. We will review the current state of the art in techniques to restore visual function, along with some exciting new developments that could potentially lead to new retinal prosthetic devices.

## 2. Electronic retinal implants

Since the discovery of electrically excitable cells the most prevalent method of interfacing with neural tissue is via electrical stimulation. In this approach a stimulating electrode is placed in close proximity to the cell and a return electrode is placed much further away. When a cathodic current is passed between the stimulating and return electrodes, a fraction of the current depolarizes the neural membrane in close proximity to the stimulating electrode resulting in a neural activation.

The first neural prosthesis device that has found great clinical success is the electronic cochlear prosthesis. Even with its modest, 22 electrode system, the current cochlear prosthesis is impressive in its ability to restore hearing. Encouraged by these findings, we, and others around the world, have actively pursued a means of restoring vision to the blind using an electronic prosthesis [14,16,37]. The basic idea of an electronic retinal prosthesis is shown in Fig. 2a. Here the image is wirelessly transmitted to the implanted device. The device stimulates the appropriate electrode to elicit a percept. There has been tremendous progress in the last decade in developing a wireless fully implantable electronic retinal prosthesis, see Fig. 2b [14,16,37]. Recently Zrenner

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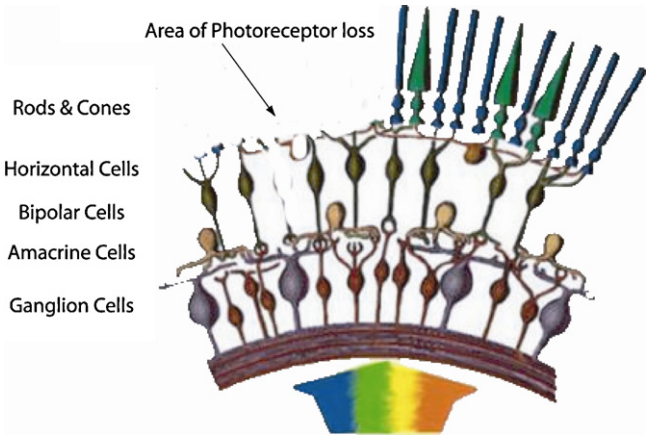


**Fig. 1.** Schematic of retinal degeneration. Photoreceptor degeneration in retinal diseases such as retinitis pigmentosa and age-related macular degeneration.

et al. have implanted a 1600 pixel retinal prosthesis in humans. The results from their clinical trials in patients have shown that subjects are able to distinguish large letters and light objects on a dark-background [37].

Though, these are encouraging results there remain many obstacles that must be overcome before functional vision via an electronic retinal prosthesis becomes a reality. One of the major challenges that must be addressed is one of power. In acute human trials performed by us and others [21,28], it has been shown that typically 100s of μA's of stimulation current is required to elicit a perceptual threshold [4,6]. This coupled with the high power supplies (5–10 V) needed due to the large access resistance of electrodes (∼1–10 kΩ) leads to large power dissipation per electrode (500 μW). This is further exacerbated by the limited heat dissipation that is allowed in an in vivo environment. There are strict constraints on the amount of implant's power dissipation due to the close proximity of the electrodes to living tissue. If the cells are exposed to elevated temperatures for extended periods of time, cell death will occur. Temperature increases of more than 3 °C above normal body temperature has been reported to lead to physiological abnormalities such as angiogenesis or necrosis [30]. In guinea pig olfactory cortical slices, aberrant activity began at 2 °C over normal [10]. Temperature increases greater than 1 °C above normal can have long-term effects on the brain tissue in an anesthetized rat [20]. Therefore implants should be designed to limit the chronic heating of surrounding tissue to less than 1 °C. The temperature increase coefficient due to an implant's power dissipation in the brain of anesthetized cat was measured to be 0.0673 °C/mW for in vitro, and 0.05 °C/mW for in vivo conditions. Furthermore, experimental results have also shown that an implanted IC, measuring roughly 6 mm × 6 mm × 2 mm, can safely dissipate approximately 10 mW of power, corresponding to about 0.5 °C of increase in temperature [17]. Given these constraints, the total number of electrodes is limited to about 100.

Cochlear prostheses, containing only 22 electrodes, have shown significant improvements in hearing [38]. However, retinal prostheses with limited number of electrodes (16) have not shown the same level of success. This partly due to the complex spatiotemporal processing that occurs in the retina and the larger number of sensory elements in the eye compared to the ear. Furthermore, the temporal nature of sound enables time-based pulse events that enable the hearing of intermediate tones. Recently, it has been suggested, substantiated by preliminary experimental work, that temporal and spatial based stimulation patterns could produce the sensation of complex patterns beyond those enabled by the spatial positioning of the electrodes [13,14].

The engineering challenges faced are also enormous for retinal implants and they have been steadily overcome over the past decade. From better electrode materials like iridium oxide for higher charge capacity to better strategies for coupling power to the implant, recent electronic prostheses are coming ever closer to delivering the promise of restoring vision to the blind [18]. Additionally, there has been a tremendous effort in the past few years to use non-electronic prostheses to restore vision and these are discussed below.

## 3. Optogenetics: the molecular prosthesis approach

Recently, optogenetics has revolutionized the way in which we study and interact with neural circuitry. Optogenetics refers to the technique where specific host cells are conferred with optical activity via gene delivery and hence can be manipulated by light [7,23]. Moreover optogenetics, unlike other stimulation methods such as electrical, goes beyond mere neural stimulation but offers either gain or loss of specific function due to its cell targeting ability. The most popular optogenetic method is the introduction of a microbial opsin, such as channelrhodopsin (ChR2) a light sensitive cation channel, into neural cells via viral transfection [7]. The biochemical toolbox of optogenetics is constantly expanding at an accelerated pace with the introduction of new opsin variants that offer new functionality [36].

The retina, due to its inherent light accessibility, is probably the most amenable neural system that can be targeted by optogenetics. Bi et al., expressed ChR2 in the degenerated mouse retina of *rd1* mice using a virus-assisted gene delivery technique [1] resulting

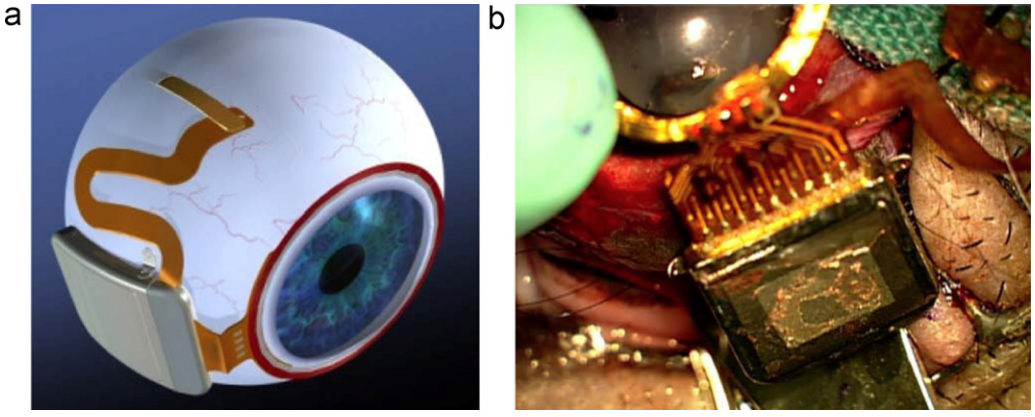


**Fig. 2.** Current electronic retinal prosthesis. (a) Basic ideas behind a retinal prosthesis shown is a schematic version of a minimally invasive approach. (b) Photograph of an implant in the eye of a minipig (figure from [16]).

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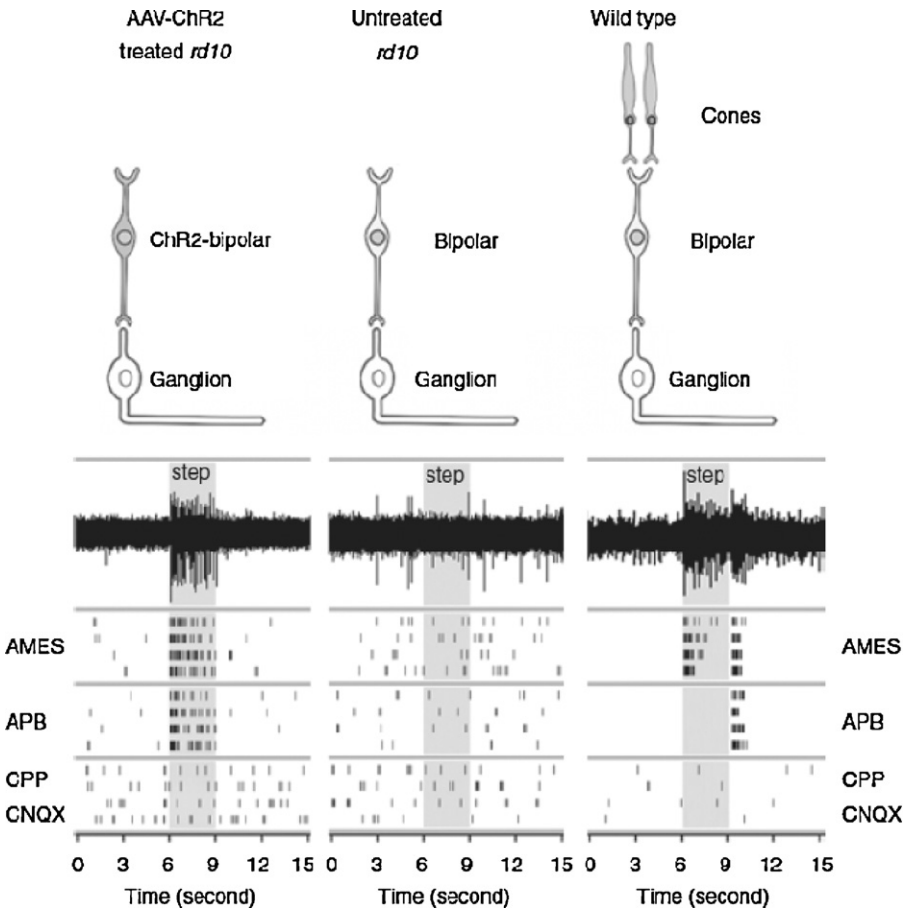


**Fig. 3.** Neural responses from optogenetic targeting of bipolar cells. Ganglion neural cell responses from ChR2 treated rd10, untreated rd10 and wild-type mice subjected to light stimulus. The abolition of the neural response when co-perfused with glutamate antagonist (CPP/CNQX) shows that the response is due to presynatic activity to the ganglion cell. The abolition of the ON cell response of the wild-type and no change in the ChR2 treated mice, when co-perfused with APB (a metabotropic glutamate agonist), shows that the response is not due to the photoreceptors (from Ref. [8], reproduced with kind permission from Nature Publishing Group).

in neural spiking of the retinal ganglion cells upon laser excitation. Unfortunately, the expression was not targeted and was expressed throughout the retinal layer and even the lateral geniculate nucleus. Furthermore, the light levels required are rather high, $10^{17}$ photons $cm^{-2}$ $s^{-1}$, raising the concern of phototoxicity. Though this form of optogenetic intervention allows for the stimulation of the remaining healthy retinal neurons, the resulting indiscriminate expression will not result in useful vision. This hypothesis was borne out in an experiment conducted by Thygarajan et al. [34]. To increase ChR2 expression and thereby lower the light intensity needed, transgenic mouse line expressing ChR2 were crossbred with *rd1* mice. Five *rd1* mice and *rd1* mice expressing ChR2 were subjected to visual water tasks, based on a two choice experiment [34]. It was found *rd1* mice and ChR2 expressing *rd1* mice showed no significant differences in performance in behavioral tasks. It was hypothesized that this "cortical blindness" despite retinal spiking was due to the simultaneous stimulation of both ON and OFF ganglion cells in the retina. In a ground-breaking effort, Lagali et al. [19] specifically targeted ON-bipolar cells in rd1 mice in an effort to overcome the indiscriminate stimulation of both ON and OFF pathways. Utilizing the mouse Grm6 gene that encodes the ON-bipolar specific metabotropic glutamate receptor, they successfully expressed ChR2 by employing electroporation for gene-delivery. Though, the expression levels were quite low (7%) requiring high photon fluxes (>$10^{16}$ photons $cm^{-2}$ $s^{-1}$), they proved that by selectively expressing ChR2 in ON-bipolar cells only, the mice were able to perform simple behavioral tasks. Another approach, is to use differential targeting of ganglion cells to obtain a center-surround response, however, this has not been validated in vivo [12].

However, to increase efficiency and allow for future use in human trials, a different and more effective method of gene delivery other than electroporation is required. Recently, in a *tour de force* Doroudchi et al. [8], combining previous techniques of ON-bipolar targeting and capsid modified recombinant adeno-associated virus assisted gene-delivery [27], successfully expressed ChR2 in ON-bipolar cells in the retina of *rd1* mice, see Fig. 3. Furthermore, this studied answered some important issues regarding the safety of

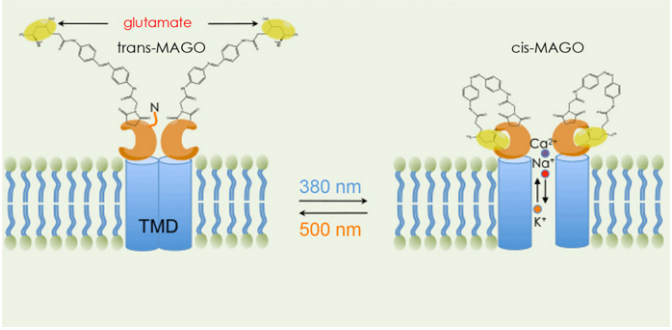


**Fig. 4.** A light activated switch based control of ion flux. A synthetic molecule based gating mechanism for eliciting neural activity. A glutamate tethered azobenzene is used as a photoswitch to either enable binding (cis-configuration) or inhibit binding (trans-configuration), which in turn opens or closes the ion-channel (Adapted and redrawn from Ref. [3]).

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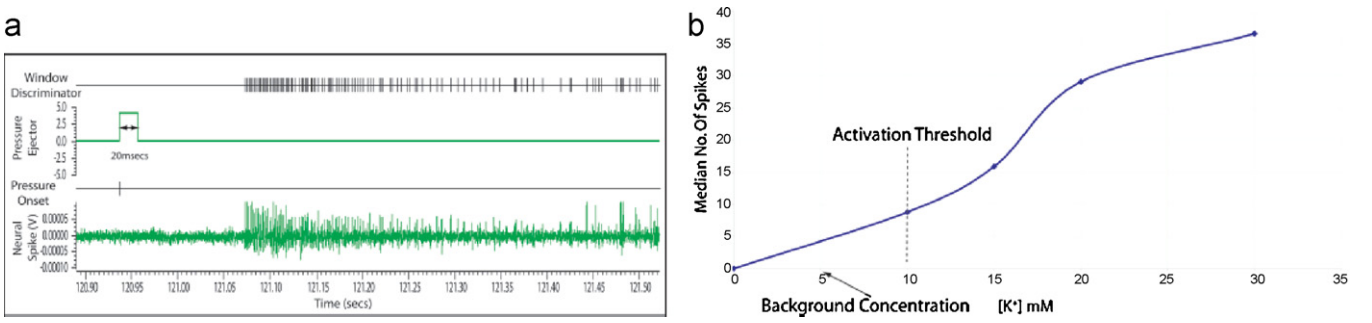


**Fig. 5.** Dose-response of $K^+$-evoked response from retinal ganglion cells. (a) Neural spike recording from a rabbit retinal ganglion cell to a potassium stimulus of 30 mM of duration 20 ms. (b) Potassium evoked response median data. The number of spikes is the median value of recording from a number of cells (10 mM, 20 mM-7 cells, 15 mM-2 cells, 30 mM-5 cells).

virus assisted gene delivery and the use of high-level light stimulation. The study found that mice retina exposed to very bright light levels ($\sim 10^{18}$ photons $cm^{-2}$ $s^{-1}$) did not show any signs of phototoxicity. The study also proved that there was no immune response to the virus assisted delivery.

A closely related approach is the use of synthetic photosensitive molecules that enable the gating of endogenous ion channels [3]. The advantage of using synthetic molecules is that they can be easily tuned and possibly enable a broader dynamic range. Caporale et al. [3] recently use a photoswitch based on azobenzene to enable the photoactivation of retinal ganglion cells in rd1 mice, see Fig. 4. The disadvantage of this method is the use of a synthetic photosensitive molecule that is not available endogenously and therefore must be supplied via periodic intravitreal injections [5].

Though these are very encouraging results and show promise of a clinical relevant molecular therapy for restoring some level of useful vision, many challenges must be overcome [2,5]. First, the dynamic range of opsin based molecular therapies is 2–3 orders of magnitude, far less than the 7 orders of magnitude found in biological vision. So some external light delivery device is needed capable of performing the processing, adaptation and delivery of the required light intensity. Studies have shown the sustained ($\sim$10 months) expression of ChR2 [8], albeit at a slightly lower level. Though, it is unclear if this would persist, and if not, it raises the question whether the animal will tolerate repeated viral injections. Furthermore, the translation of mouse model results to humans needs to be established. The specific targeting ON bipolars using the mGRM6 enhancer sequence, previously used in mice, has not been successful in post-mortem human retina [9]. An associated issue is the occurrence of natural occurring photosensitive molecule melanopsin present in the retinal ganglion cells that causes the pupil to shrink, exacerbating the need for higher light intensities [2]. The last, perhaps crucial, advance that remains to be made is the specific targeting of both ON and OFF cell types, allowing for the close mimicry of the natural visual processing that occurs in the retina. Though, this is an issue in electronic implants as well.

## 4. Chemical neural interfaces

Nature uses neurotransmitters for neural signaling, so it must be possible, at least in principle, to design a retinal prosthesis that interfaces to the natural neural system using neurotransmitters. Some attempts have been made to design retinal prosthesis using a neurotransmitter based approach [22,25,26,29]. However, none of these have been developed into clinically viable therapies due to the principal issue of having to supply spent neurotransmitter, either via a reservoir or sequestration. A reservoir of neurotransmitter poses significant risk since any rupture of the reservoir would result in catastrophic damage of the surrounding neural tissue. Sequestration of neurotransmitters is not easily possible since the neurotransmitters, such as GABA and glutamate, are taken up by glia and broken down.

One approach to mitigate this is to use an alternative chemical stimulation method, namely ionic stimulation. Ionic stimulation could circumvent the above issue by actively sequestering ions from the extracellular fluid. Another approach that has been explored is the use of ionic modulation to lower the electrical threshold for neural stimulation [32]. In this approach, a calcium sensitive ionophore is used to locally sequester the calcium around the nerve using electrical control. Though, this is a viable approach, it requires large induction times ($\sim$1 min), which would prevent it for being used in sensory perception types of devices. Alternative approaches using direct $Ca^{2+}$ stimulation has also been demonstrated [15].

We have been pursuing a different approach of direct neural stimulation via potassium ions. It is well know that neurons can be stimulated by elevated extracellular concentrations of potassium [31]. Furthermore, neurons are most permeable to potassium in the resting state, making them the most viable ionic stimulation species. Another advantage of the potassium based approach that active sequestration can be performed using synthetic ionophores. Efforts are currently underway in our lab to fabricate a renewable chemical neural interface using potassium ions. Results from in vitro potassium based stimulation of rabbit retinas are shown in Fig. 5 [33]. As can be seen from Fig. 5, the increase above the background is only around 2×. This could potentially lead to a very low-power renewable method of stimulation.

## 5. Conclusion

Numerous effort are underway all around the world in hopes of restoring some useful vision to the blind. From the conventional electronic retinal implant to the more biological optogentic based molecular prosthesis and new approaches such as ionic stimulation, great progress has been made. There remain a few key challenges that need to be overcome to ensure viability of these approaches for a long-term cure. However, it remains clear that whatever the final form of the prostheses, a retinal prosthesis to help the blind will soon become a reality.

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