



## Retinal stimulation strategies to restore vision: Fundamentals and systems



Lan Yue <sup>a,\*,1</sup>, James D. Weiland <sup>a,1</sup>, Botond Roska <sup>b,c,1</sup>, Mark S. Humayun <sup>a,\*\*,1</sup>

<sup>a</sup> USC Eye Institute, Institute for Biomedical Therapeutics, University of Southern California, Los Angeles, CA 90033, USA

<sup>b</sup> Neural Circuit Laboratories, Friedrich Miescher Institute for Biomedical Research, Maulbeerstrasse 66, 4058 Basel, Switzerland

<sup>c</sup> Department of Ophthalmology, University of Basel, Basel, Switzerland

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### ABSTRACT

Retinal degeneration, a leading cause of blindness worldwide, is primarily characterized by the dysfunctional/degenerated photoreceptors that impair the ability of the retina to detect light. Our group and others have shown that bioelectronic retinal implants restore useful visual input to those who have been blind for decades. This unprecedented approach of restoring sight demonstrates that patients can adapt to new visual input, and thereby opens up opportunities to not only improve this technology but also develop alternative retinal stimulation approaches. These future improvements or new technologies could have the potential of selectively stimulating specific cell classes in the inner retina, leading to improved visual resolution and color vision. In this review we will detail the progress of bioelectronic retinal implants and future devices in this genre as well as discuss other technologies such as optogenetics, chemical photoswitches, and ultrasound stimulation. We will discuss the principles, biological aspects, technology development, current status, clinical outcomes/prospects, and challenges for each approach. The review will cover functional imaging documented cortical responses to retinal stimulation in blind patients.

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### Contents

1. Introduction	22
1.1. Retinal degenerative diseases	22
1.2. Treatment options and opportunities for retinal stimulation	23
2. Electrical retinal stimulation and system	23
2.1. Fundamentals of electrical retinal stimulation	23
2.2. Proof-of-concept studies: leap from phosphenes to prosthetic vision	25
2.3. Retinal prosthetic systems and clinical implications	25
2.3.1. Epiretinal prostheses	25
2.3.2. Subretinal prostheses	28
2.3.3. Suprachoroidal prostheses	30
2.4. Challenges and system approaches	31
2.4.1. Visual acuity	32
2.4.2. Visual field	33
2.4.3. Stimulation selectivity and efficiency	34
2.4.4. Eye movement and intraocular camera	35

\* Corresponding author.

\*\* Corresponding author.

E-mail address: [lyue@usc.edu](mailto:lyue@usc.edu) (L. Yue).

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2.4.5.	Stimulation encoding	36
2.5.	Cortical changes in retinal degeneration	37
3.	Light retinal stimulation: optogenetics and chemical photoswitches	37
3.1.	Opsin-based approaches	37
3.1.1.	Animal opsins and status	37
3.1.2.	Microbial opsins and status	38
3.1.3.	Light stimulation system	39
3.2.	Chemical photoswitches	41
3.2.1.	Photoisomerizable ligands	41
3.2.2.	Photovoltaic switches	41
3.3.	Clinical perspectives	42
4.	Ultrasound stimulation and prosthesis	42
5.	Future directions	42
	Acknowledgement	43
	References	43

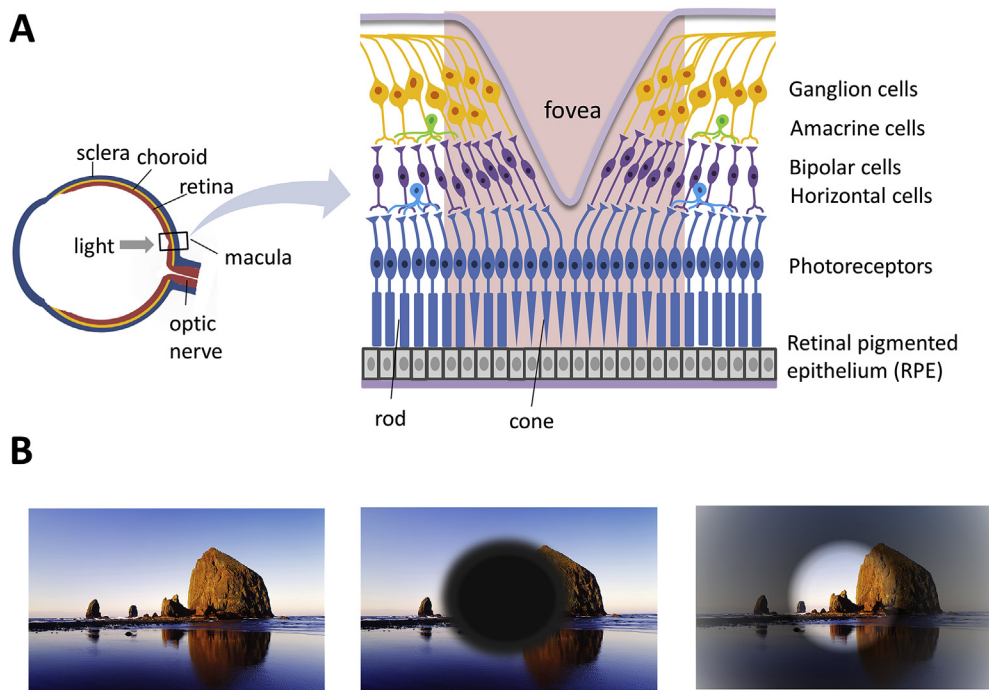
**1. Introduction**

*1.1. Retinal degenerative diseases*

Retina is a stratified light sensitive tissue that lines the back of the eye. It is ~0.5 mm in thickness and the retinal neural network consists of several layers of cells bodies and their neural processes of dendrites and axons, as illustrated in Fig. 1A. The Retinal Pigment Epithelium (RPE) cell layer, lying adjacent to the neural retina, is involved in recycling the visual pigments and maintaining the health of photoreceptors, the light sensor in healthy retina. Visual signals, initiated at the photoreceptors, sequentially travel through the bipolar cells and ganglion cells and propagate to the higher visual centers in the brain via the optic nerves (axons of the ganglion cells). Signals also receive lateral modulation from horizontal cells and amacrine cells, as part of the neural processing in inner

retina. As shown in Fig. 1A, cell distribution profiles are very different in central vs. peripheral retina. Cone photoreceptors are densely packed in the macula while rod photoreceptors predominate in the peripheral region. Retinal signaling in the macular region is analogous to “private line” transmission from individual cones whereas a high level of convergence occurs in peripheral retina.

Retinal degeneration involving progressive deterioration and loss of function of photoreceptors is a major cause of permanent vision loss (Busskamp et al., 2010; Curcio et al., 2000). Age-related macular degeneration (AMD) and retinitis pigmentosa (RP) are the two most prevalent forms of retinal degenerative diseases. Epidemiologic studies show that the onset of AMD occurs predominantly in the elderly while RP afflicts children and young adults (Wong et al., 2011). Together, they account for millions of cases of blindness and visual impairment worldwide. Fig. 1B shows



**Fig. 1.** Retina and retinal degenerative diseases. (A) Schematic representation of the stratified structure of neural retina. Pink-shaded area represents the macular region. (B) Effects of retinal degeneration on visual field. Left: Visual field of a normally sighted subject; Middle: Central vision loss in macular degeneration. Right: Peripheral vision loss in retinitis pigmentosa.

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