

Curr Opin Neurol. Author manuscript; available in PMC 2013 February 1

Published in final edited form as:

Curr Opin Neurol. 2012 February; 25(1): 67-75. doi:10.1097/WCO.0b013e32834f02c3.

Retinal Implants: Emergence of a multidisciplinary field

Abstract

Purpose of review—To summarize the current status of retinal prostheses, recent accomplishments, and major remaining research, engineering, and rehabilitation challenges.

Recent findings—Retinal research, materials and biocompatibility studies, and clinical trials in patients blind from RP are representative of an emerging field with considerable promise and sobering challenges. A summary of progress in dozens of labs, companies, and clinics around the world is presented through a synopsis of relevant papers, not only to summarize the progress, but also to convey the remarkable increase in interest, effort, and outside funding this field has enjoyed.

Summary—At the present time, clinical applications of retinal implant technology are dominated by one or two groups/companies, but the field is wide open for others to take the lead through novel approaches in technology, tissue interfacing, information transfer paradigms, and rehabilitation. Where the field will go in the next few years is almost anybody's guess, but that it will move forward is a certainty.

Keywords

Retina; retinal implant; visual prosthesis; bionic eye; biocompatibility; rehabilitation

I.Introduction

The principle underlying all retinal implants is the replacement of rod and cone photoreceptor function in patients with outer retinal degenerations. This is done through stimulation of secondary neurons in the retina, i.e., bipolar and/or ganglion cells. Stimulation in almost all instances is provided by an array of small electrodes.[1,2] Other approaches, through transfection of genes encoding for light sensitivity in secondary neurons[3,4] or through one of several neurotransmitter release mechanisms,[5,6] are also being explored. At the present time only patients with a history of functional vision that has been reduced to light perception are candidates for retinal implants, but in principle they may be used in the future to replace vision in only those retinal areas where it has been lost due to, e.g., macular degeneration.

Retinal implants can be divided into categories, on the basis of either their underlying principles of operation or their anatomical location. Most implant designs use an external camera and image processing to drive implanted electrodes,[7] with two notable exceptions: the microphotodiode array (MPA) developed by Retina Implant AG,[8] and the Stanford

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Conflict of interest

The author is a Center Principal Investigator for the Argus II Retinal Implant Feasibility study sponsored by second Sight Medical Products, Inc.

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retinal prosthesis.[9] The MPA consists of 1,500 small units, in which a photocell captures the local light intensity incident on a small retinal area and modulates the activity of a stimulating electrode; external energy is supplied to drive the stimulators. The Stanford array on the other hand projects a high intensity infrared image on the implanted photocells and generates sufficient current to excite the secondary neurons. In terms of placement, retinal implants can be situated on the inner (epiretinal) or outer (subretinal) retinal surface, below the choroid plexus (suprachoroidally) or outside the sclera (episclerally). Each of these placements carries both engineering and surgical benefits and challenges.

Retinal implants have been in the news in recent years through scientific reports and media publicity. For a fledgling field that may only benefit a rare category of patients, and whose demonstrated benefits until now have been quite modest, such strong interest barely two decades after its inception is remarkable. In 1991 a small team composed of a retinal surgeon and a few biomedical engineers decided that human tests were needed to answer the question whether stimulation of a blind retina with a small wire electrode would yield small enough phosphenes to allow creating an image through stimulation with many electrodes. That first experiment in an awake RP patient under local anesthesia, in the operating room at the Duke University Eye Center, stands at the basis of a field that now includes enthusiastic practitioners in countries around the globe. Well over \$100M in development funds has been spent by public and private sponsors in the US, Germany, Japan, Korea, Australia, and China, and the number of conference presentations and peer-reviewed publications has grown rapidly. From 1993 through 2005, the number of published conference abstracts and peer-reviewed presentations grew by some 30% annually, from 1 to almost 100; the number has since diminished somewhat and remained constant. The number is expected to rise again as recent new funding and increased clinical activity begin to bear fruit.

Recent specific reviews with emphasis on engineering[10-13], basic science[14-16], and clinical[17-21] aspects have been published in special journal issues and in a volume highlighting new developments from the perspective of biomedical engineering, the major discipline that has contributed to this emerging field, has also appeared. This number and range of reviews is emblematic of the multiple disciplines contributing to the field of retinal implants, and of the interest among professionals in those fields. This general review summarizes the current status of retinal prosthesis development, recent accomplishments, and major remaining research, engineering, and rehabilitation challenges. We will refer to the more specific reviews as potential sources of further information, since they contain greater detail in their specific disciplines than can be provided in the space of this general review.

Only scant attention will be devoted to visual prostheses targeting proximal stages of the visual pathway: optic nerve, lateral geniculate nucleus, and visual cortex. The latter devices have been around for more than 50 years, yet unlike retinal implants they are not currently in clinical trials. Modern incarnations of cortical visual prostheses devices are expected to enter clinical tests in the next few years, however.[22]

II. Brief summary of accomplishments and remaining major hurdles

Much of what is currently known about the properties of retinal electrical stimulation has been gathered in two decades of animal and human testing, both through short-duration experiments in the operating room, and through chronic implantation with durations of a few weeks to several years. After the first decade of intra-operative testing in blind patients, the field remained divided between those confident that small and reproducible phosphenes could be elicited[23,24] and those who questioned whether stable long-term percepts could be obtained.[25,26] Acute experiments continue to be performed by groups in Australia,

Belgium, Canada, China, Germany, Japan, Korea, Spain, and the USA. A listing of active groups is maintained at http://www.io.mei.titech.ac.jp/research/retina/index.html#link. An excellent review of acute testing in blind human volunteers, as well as some results of tests in laboratory animals, can be found in [19].

Despite the skepticism voiced by some investigators, development of devices for chronic implantation in blind patients continues, and such implantations have been performed since 2002 by groups in the US (epiretinal[27,28]), Germany (epi-[29-31] and subretinal[8]), and most recently Japan (suprachoroidal[32]). Some 50 patients with end-stage retinitis pigmentosa have participated in these trials; most of these in the A16 (4×4 electrode implant, 6 patients) and Argus II (6×10 electrode implant, 30 patients) trials conducted by Second Sight Medical Products, Inc.(Sylmar, CA). Ten clinical centers participated in the latter study in the US and Europe, which generated a large volume of safety and efficacy data. The results were found to be sufficiently encouraging for the European regulatory agencies to allow marketing of the Argus II as of spring 2011. Figure 1 shows the implanted components of the Argus II system.

Wearers of the Argus II retinal implant are able to localize shapes and identify movement direction[33,34], most can trace a crude outline on a screen[35], and some have been documented to recognize letters and words[36]. Similar results have been reported for a recipient of the subretinal German MPA system [37], Figure 2 shows the Alpha IMS implant (A) and placement (B) of this latest incarnation of the MPA implant. Encouraging though this may seem, the reality is that retinal implants are in a very early stage of their development, similar to that of cochlear implants 3 decades ago. Retinal implant wearers report seeing blurred contours rather than images made up of small phosphenes, as might have been expected on the basis of early single-electrode tests. Perception of rapid movement flicker is greatly limited, again in apparent contradiction with the subjects' ability to see flicker up to 40 Hz in early acute tests.[24] Personal communications among prosthesis groups confirm that the findings are similar for all chronic implant types tested thus far. It appears that stimulation with multiple electrodes adds complex interactions to the retinal activity patterns that would be generated by single electrode stimulation. Possible reasons for this apparent discrepancy will be discussed in sections III - VII of this review.

III.Understanding the degenerated retina

Development of a successful retinal prosthesis hinges on the availability of a sufficient number of secondary target neurons in the degenerated retina, and of the ability of surviving retinal ganglion cells to continue sending signals to the lateral geniculate nucleus. Early histologic studies suggested survival of bipolar and, to a lesser extent, ganglion cells in ample numbers to convey visual information,[38] but the integrity and functionality of these cells could not be ascertained. When Marc and co-workers introduced a refined labeling technique that allowed visualizing retinal neurons and their processes on the basis of molecular markers, it became clear that a high degree of reorganization and cell migration (commonly referred to as "remodeling") takes place in retinal areas where photoreceptor function disappears.[39] Studies of this remodeling process continue to be refined in animal models[15] and through computational techniques.[40] Moreover, the Marc lab is continuing detailed studies of connectivity patterns in normal retina,[41] which will then allow better understanding of the remodeling process.

Functional results obtained in implant recipients suggest that retinal remodeling may create conductive circuits (neurites) in the degenerated retina that are not present in the normal retina. These circuits cause a dispersion of injected charge beyond where it would spread in passive tissue. It is not yet possible to obtain physiological results of similar detail during

retinal electrical stimulation, but in vitro tests with multi-electrode arrays in normal primate retina[42] and rabbit[43], and comparisons between normal and rd1 mouse ganglion cell function[44], are providing important information in this regard. *In-vivo* registration of the electrically evoked electroretinogram in retinal prosthesis wearers[45] is beginning to provide complementary information. At present, these recordings provide insufficient detail to verify charge distribution and interactions in response to complex stimulation patterns, but such details will emerge as recording techniques improve.

IV.Engineering and surgery for safer implantation and more effective stimulation

Each of the four implant locations under study (epi- and subretinal, suprachoroidal, and transscleral) presents challenges to the engineering and surgical teams. Not only should the insertion of the electrode array and any external connections be as atraumatic as possible, but removal of the device for repair or upgrade should also be possible without serious damage to the eye. Once in place, the device should be designed to provide the safest and most effective stimulation possible. For these reasons, bioengineering and surgical teams are playing a major role in the development of the field, especially among groups that may not be close to clinical implantation at this time. Recent publications from Australia and Japan (suprachhoroidal surgery[46] and long-term safety[47]), Boston (subretinal electronics[48]), and Finland (electrode materials[49]) provide examples of the geographic spread and multidisciplinary scope of these developments. These are complex development tasks, yet thanks to advancements in materials science, bioengineering, and ophthalmic surgery, they are among the easier ones in retinal prosthesis development.

V.Optimizing information transfer

A problem of greater complexity is the understanding how charge emitted by an implanted electrode will excite retinal cells. Location, geometry, and materials of the implant and of individual electrodes, stimulus parameters such as polarity, pulse duration and frequency, and timing relationships between stimuli at neighboring electrodes are among the major design and operational choices to be made. Often these choices are dictated, or at least limited, by considerations related to surgical implantation and removal, biocompatibility and long-term survival of implant and substrate, and other factors that have little to do with efficient tissue excitation of the cells. To understand how much each of these areas is still open to investigation of debate, consider the following examples of research reports published in the past year:

- Research groups in Australia, Switzerland and Utah are using finite element
 modeling methods to understand the charge distribution and flow from the
 electrode surface into the tissue, and the process of retinal cell excitation [13,50,51]
- A Stanford University research team, as part of its efforts to accomplish closer proximity between subretinal electrodes and target cells, is modeling membrane properties and excitation of retinal ganglion cells (RGCs)[52]
- At the University of Southern California researchers are studying the effects of long-term stimulation on retinal tissue *in vivo*[11]
- Groups in Germany and Boston are investigating methods to optimize encoding of visual information in the RGC firing pattern for improved understanding by the prosthesis wearer[53,54]

The study of visual information transfer and understanding by the prosthesis recipient has another aspect: the perceptual level. For at least two decades researchers have investigated

the ability of human observers to perceive, and interact with, filtered and distorted imagery as it might be conveyed by an implanted visual prosthesis. Early simulations envisaged images made up of regular arrays of small dots representing individual phosphenes, but as the scarcity of visual information reported by prosthesis wearers became evident, these simulations became more sophisticated. In the last year, simulations have been used to explore the ability of sighted individuals to interact with gaze-locked imagery (as a retinal implant wearer with a head-mounted camera would perceive the scene)[55], recognize characters[56], read[57], or recognize objects despite a distorted phosphene map[58]. They have also continued to study the effects of phosphene size, position, and mapping[59-61], a topic which may even be of greater relevance to optic nerve and cortical implants than to retinal prostheses.

VI.Learning from implantees

As more clinical trials get under way, and some retinal implants gain approval for clinical implantation, an increasing amount on information can be gained from implant recipients. In recent years, a substantial number of reports related to patient experiences have been published. A group in Osaka, Japan, recently published a detailed description of their surgical methods and outcomes for a suprachoroidal implant, and of the implantee's ability to perform simple localization and discrimination tasks with this 3×3 electrode implant.[32] Researchers associated with Second Sight's A16 retinal implant project have published a series of papers concerning the properties of phosphene perception in their 6 subjects: effect of distance between electrodes and retina[62], perceived brightness as a function of pulse strength[63], ability to convey simple patterns[64], and temporal interaction between stimuli at neighboring electrodes[65]. Recipients of the newer Argus II implant have been reported to perform tasks such as wayfinding[34], object localization[33], visually guided line tracing[35], and character and word recognition[36]. The latter accomplishment has also been reported for recipients of the 1500 unit Retina Implant MPA[37]. Lastly, the German Epiret3 consortium has reported results in 6 patients. Their subjects were capable of discriminating the orientation and location of electrode pairs[29]. This same group also reported surgical outcomes [66], which are of special interest since the implant was designed to be removed from its support posts without damage to the underlying retina.

Even while preparing for the clinical test stage, researchers should consider how to evaluate visual function and performance without and with the implant[21], and some groups have spent considerable time and effort developing evaluation methods[67,68]. Others are exploring ways to select the best implant recipients through OCT-based retinal analysis[69], assess patient expectations and personality traits[70], or develop a broad range of functional and psychological measures[71].

VII.Rehabilitation

If one thing has become clear from the reports about visual function and task performance with retinal implants, it is that successful use of these devices requires a lengthy process of fitting and training. Fitting refers to the initial post-operative setup of device parameters to allow basic information to be presented and perceived at all available electrodes. For most implants this entails determining threshold stimulation levels at all individual electrodes; obtaining information about perceived brightness as a function of suprathreshold stimulus strength; choosing optimal stimulus timing at waveforms; adjusting settings across electrodes to equalize perceived stimulation levels; and examining interactions between neighboring electrodes by adjusting stimulation to minimize such interactions. All this is done before any real-time image input is sent to the implant, to avoid uncomfortable stimulation levels and to maximize the chance that this information will be understandable.

The implant recipient is an active participant in this process, and the quality of the outcome will depend on the efficiency and accuracy of this process, and all the more so as the number of electrodes is increased in future implant generations.

Training refers to the much lengthier secondary process that starts when the implant recipient first learns to control and use the implant Settings may be provided, such as adjustments to different lighting conditions, filters for edge detection, and an inverse polarity switch to better see dark objects against a light background. The implant wearer has to learn when and how to make these adjustments. Most importantly, training needs to be provided that will allow the implant wearer to maximize the benefits of the technology in performing daily tasks: not just to recognize objects and surroundings, but also how to adjust them to improve success, e.g., by creating contrast in the visual scene whenever possible (e.g., by placing a light-colored dish on a dark placemat rather than directly on the white table.[72]

As the first retinal implants are beginning to enter clinical application, the collaboration between researchers, clinicians, and low vision rehabilitation specialists becomes increasingly important. Together these groups are developing the elements of a future prosthetic vision rehabilitation curriculum that will play a vital role in the development of retinal prostheses from an experimental tool into clinically accepted device.[73]

VIII.Regulatory aspects

In addition to technical, surgical, and rehabilitation aspects, the development of retinal prostheses is providing an important case study in the adoption of evaluation criteria for a new class of devices by regulatory bodies, particularly the US Food and Drug Administration (FDA) and European Medical Authority (EMA). Although the development process (feasibility studies and usually a pivotal trial providing safety and efficacy data) and general criteria (risk/benefit considerations on the basis of reported adverse events, perceived risk, and demonstrated and anticipated health benefits and quality of life) are similar to those of other drugs and devices, specific measures to establish efficacy will need to be developed that are within the scope of current device capabilities, yet sufficiently quantifiable to meet regulatory standards. The rules for the approval process are evolving, but an article by a researcher at the FDA[74] and a workshop jointly sponsored by the National Eye Institute and FDA (http://www.nei.nih.gov/news/meetings/FDA_2011.asp) underscore the high level of interest for these issues in both regulatory and sponsoring agencies.

IX.Devices stimulating the proximal visual pathway

Although strictly outside the scope of this review, the related development of visual prostheses addressing later stages along the visual pathway – optic nerve, lateral geniculate nucleus and visual cortex – should be mentioned. The optic nerve prosthesis is being explored primarily as an alternative to the retinal implant that avoids surgical manipulation of the fragile degenerated retina, and its major challenge is the selective and reproducible long-term stimulation of small numbers of fibers among the several 100,000 that may still be available in late stage retinal degeneration patients.[38] Development and *in-vivo* testing of at least one optic nerve prosthesis is currently on-going, with clinical tests anticipated in the next few years.[75]

Several research teams are developing cortical prosthesis prototypes, and a considerable amount of testing in primates[76,77] suggests that clinical pilot studies may be forthcoming. The safety record of some past cortical implant projects has not been good, so the burden of proof on new implant designs prior to regulatory approval will be high. Other active studies

in preparation for the introduction of new cortical visual prostheses use transcranial magnetic stimulation to study visual perception in adventitiously blind patients. Interviews with former cortical prosthesis recipients help determine suitable profiles for future implantees and management of patient expectations. [78]

X.Conclusion/Future directions

Within twenty years after the first human tests of retinal electrical stimulation in a blind RP patient, the first clinically approved implantation of an Argus II retinal prosthesis was performed in Pisa, Italy, on October 29, 2011. By any standard this is a remarkably quick development for a conceptually novel implantable medical device. At the same time, it is clear to those participating in the development effort that all developments up to this point are only a prelude, and that the real work is yet to come. Over the next 10 years we can expect major efforts to be devoted to the development of novel electrode materials and configurations that will reduce the distance between electrodes and target cells, and thus reduce the charge required per electrode, allowing for more and smaller electrodes and higher resolution. Continued studies of the degenerated retina, including electrophysiologic testing, will improve the understanding of signal processing within the retina, and transfer to the optic nerve and central visual system. This improved understanding of retinal signal processing will in turn allow more effective image pre-processing methods to match the properties of the remodeled retinal circuitry.

To those familiar with cochlear implants, the analogy between the two systems will be unmistakable. This is true at the level of the operational principles, but even more so in terms of the fitting and training procedures. There is much the retinal prosthesis community can learn from the 3 decades of experience and gradually increasing success of the cochlear implant.[79]

Acknowledgments

The author is grateful to the National Eye Institute for grant support (R21EY019991 and R01EY021220)

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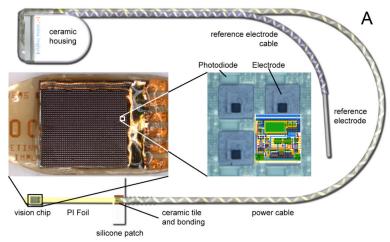
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Summary Points

- Retinal prostheses are making the transition from bench to bedside
- Development teams around the world are studying multiple approaches to stimulate secondary cells in the retina of patients whose photoreceptors have degenerated to leave them with complete blindness
- Similar to cochlear prostheses before them, retinal prostheses are expected to undergo a long development process
- This development process will encompass concerted efforts in bioengineering, surgical techniques, recipient testing, and rehabilitation



1. The Argus II epiretinal implant system (Second Sight Medical Products Inc., Sylmar, California, USA, www.2-sight.com). The implanted system consists of a scleral band containing the secondary coil receiving the RF signal carrying power and data, and a hermetic capsule containing electronics to demultiplex data for the 60 implanted electrodes; and a ribbon cable passing through the sclera and leading to the 6_10 electrode implant, held in place over the macular area by a single retinal tack.





The Alpha IMS subretinal implant system (Retina Implant AG, Reutlingen, Germany) www.retina-implant.com. **A.** Lower left: subretinal chip with 1500 photodiodes, amplifiers and electrodes, on a subretinal polyimide foil, connected intraorbitally to the subdermal power cable that ends in a secondary coil encapsulated in a ceramic housing under the skin behind the ear. The silicone patch covers the exit of the foil trough choroid and sclera near the temporal equator of the eye. The reference electrode is placed near the orbital rim. Enlarged chip and unit cells are shown in center. **B:** Sketch of the subdermal power supply cable and secondary coil (white) in a patient. The external primary coil (black) receives power and control signals from a control box operated by the patient; the coil provides inductive transdermal transmission and is kept in place by magnetic force. Insert: fundus photo with the implant under the translucent retina next to the optic nerve head; implant field of view is 11° × 11° (provided by Eberhart Zrenner[37]).