Advances in retinal prosthesis systems

Edward Bloch, Yvonne Luo and Lyndon da Cruz

Abstract: Retinal prosthesis systems have undergone significant advances in the past quarter century, resulting in the development of several different novel surgical and engineering approaches. Encouraging results have demonstrated partial visual restoration, with improvement in both coarse objective function and performance of everyday tasks. To date, four systems have received marketing approval for use in Europe or the United States, with numerous others undergoing preclinical and clinical evaluation, reflecting the established safety profile of these devices for chronic implantation. This progress represents the first notion that the field of visual restorative medicine could offer blind patients a hope of real and measurable benefit. However, there are numerous complex engineering and biophysical obstacles still to be overcome, to reconcile the gap that remains between artificial and natural vision. Current developments in the form of enhanced image processing algorithms and data transfer approaches, combined with emerging nanofabrication and conductive polymerization techniques, herald an exciting and innovative future for retinal prosthetics. This review provides an update of retinal prosthetic systems currently undergoing development and clinical trials while also addressing future challenges in the field, such as the assessment of functional outcomes in ultra-low vision and strategies for tackling existing hardware and software constraints.

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Introduction

Hereditary retinal diseases, such as retinitis pigmentosa (RP), or degenerative conditions, including age-related macular degeneration (AMD), can lead to loss of photoreceptor (PR) cells, while generally preserving the inner retinal neurons.[1,2] In both cases, there are no current treatment options to reverse the profound visual disability associated with advanced disease. RP is thought to affect around 1/4000 people, and in the United Kingdom, inherited retinal disorders are the commonest reason for certification of blindness in working age people.[1,3] The estimated prevalence of geographic atrophy is 1.3% of the general UK population and is forecast to rise with the aging population.[4]

Recent advances in biotechnology have seen the first in-human trials, and in some cases market approval, of stem cell and gene therapies as well as retinal prostheses.[5–10] In terms of ocular and especially retinal treatments, it is retinal prostheses that have had the longest period of development to date.

The first notion of electrical-induced visual percepts or 'phosphenes' came about in 1755, when Charles Le Roy applied an electrical current across the ocular surface of a blind patient, who reported seeing flashes of light. Later, in 1929, Foerster[11] showed that acute external stimulation of the exposed occipital pole could also elicit subjective phosphenes. In 1968, Brindley and Lewin exploited this phenomenon, using an 80-electrode chronically implanted prosthesis to deliver electrical stimulation to the visual cortex and elicit phosphenes that coordinated with the retinotopic map previously described by Holmes in war-wounded patients.[12,13] Shortly afterward, Potts and Inoue[14] demonstrated that electrical current across the globe of patients with RP could elicit subjective phosphenes and evoke recordable

responses from electrodes placed over the occipital scalp.

In the 1980s, advances in materials and microelectronics fabrication, combined with developments in vitreo-retinal surgery, allowed for the emergence of the field of retinal prosthetics. Since then, several groups have formed around the world, with a range of approaches, but with the common goal of developing a device that can restore some form of vision in the context of profound vision loss. As well as retinal prostheses, other approaches include intracranial stimulation devices, which act on the cortical or thalamic visual pathways and optic nerve prostheses.[15] Another very different approach is to couple visual input to another functioning sensory system. Devices including lingual stimulation from a visual input, harnessing touch on the tongue, as well as auditory-based systems have been described.[16]

In this review, we have focused on those devices that are intended to deliver direct stimulation to the residual retinal neurons and, in particular, those that have progressed to the stage of human trials. It is not intended as an exhaustive list, but instead an update, and an overview of future directions.

Epiretinal prostheses

Epiretinal prosthesis systems are placed on the surface of the neurosensory retina, adjacent to the nerve fiber and ganglion cell layers. Surgical delivery of these devices is usually transvitreal through a pars plana sclerotomy. The microelectrode array is secured to the retinal surface with a tack. The advantage of this technique is that the surgical approach and field are more familiar to surgeons carrying out routine vitreo-retinal surgery, while revision of the device placement and explantation can be less complex. Furthermore, locating a device in the vitreous cavity can facilitate safe heat dispersion. Functionally, it may be disadvantageous to have stimulation applied to the retinal ganglion cells (RGCs) directly, as this bypasses the residual intraretinal processing system, limiting the ability to recreate the physiological retinal topographic organization. On the other hand, it has been reported that the upstream remodeling of bipolar or amacrine cells, following PR degeneration, may necessitate a device that circumvents this.[17] Also, due to the proximity of epiretinal devices to the passing axonal nerve fibers, ectopic visual percepts from inadvertent axonal stimulation could occur, thus reducing spatial resolution and obfuscating the intended stimulation pattern.

Argus II Retinal Prosthesis System

The Argus II epiretinal prosthesis (Second Sight Medical Products Inc., Sylmar, CA, USA) was the first device to receive CE marking, in 2011, and subsequently FDA approval, in 2013. It is the most widely used retinal prosthesis worldwide, with over 250 patients estimated to have undergone implantation to date.

The Argus II system is made up of an external and an implantable component (Figure 1). The external component consists of a glasses-mounted camera linked to a portable visual processing unit, which processes the image for transmission to an external communication coil (also glasses mounted). This coil provides power induction and data transmission via wireless radiofrequency (RF) telemetry to an internal matching coil, which is fixed to the sclera with a silicone scleral buckle. Once received, the RF signal is decoded back to an electrical signal and an application-specific internal circuit (ASIC) sets the output command, which passes directly to the intraocular retinal stimulator, comprising a 60-microelectrode array, each 200 μm in diameter, covering a 20° field of vision. The internal circuit is hermetically sealed and shown to have over 10 years' lifespan on accelerated aging tests.[18]

The Argus II phase II multicenter trial involved the implantation of 30 subjects to evaluate safety and effects on functional visual and real-world task performance. Overall, subjects performed better on grating visual acuity, square localization, and direction of movement tasks with the device on than off.[19–22] The proportion of subjects reaching significant differences in these tests was maintained over 5 years' follow-up,[7] with a best recorded acuity of 1.8 logMAR (20/1262 Snellen equivalent).[23] Similarly, orientation and mobility tasks were consistently better performed with the device on than off during the 5-year review period.[7,22] The 10 years' study follow-up will be completed in 2019. Other measures such as letter reading, grasping task performance, real-world functional tasks, and generation of reproducible phosphenes have all shown a significant difference with the device turned on in patients with Argus II retinal implants.[24–28] In 2012, Stanga and colleagues[29] demonstrated that different combinations of colors could be perceived simultaneously during paired electrode stimulation in three out of four Argus II recipients.
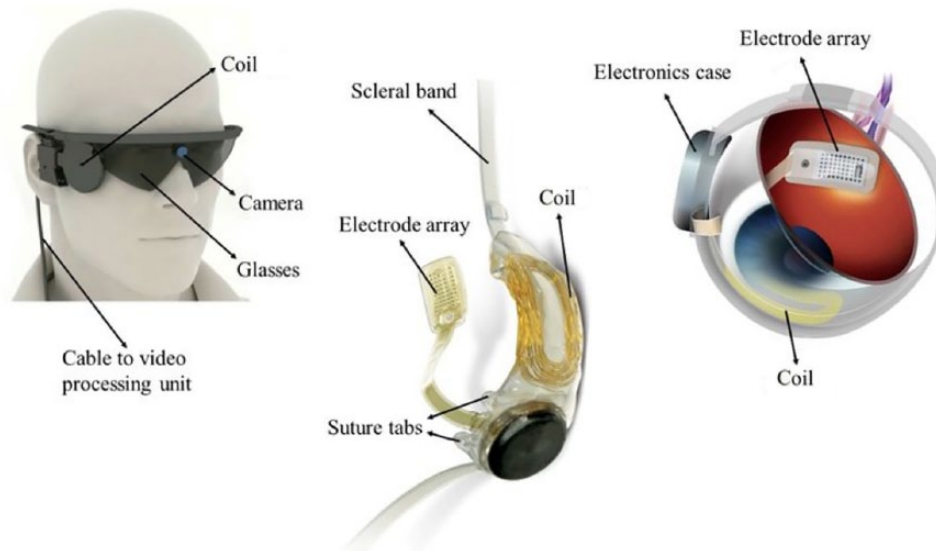
Figure 1. The Argus II Retinal Prosthesis System.
Source: Adapted from Second Sight Medical Products, Inc., Sylmar, CA, USA.

At 5 years postimplantation, there were 24 reported serious adverse events (SAEs) in 12 patients (40%), all of which were treatable with standard approaches.[7] These were, for the most part, restricted to the early to mid postoperative period, including conjunctival erosion, dehiscence, and hypotony. There were three cases of presumed endophthalmitis, although these all occurred prior to the introduction of intravitreal antibiotics into the surgical protocol, since when there have been no further reported cases.[7,19,22] Since the 3-year time point, there has only been one further reported SAE – a rhegmatogenous retinal detachment, which was successfully treated. Three devices were removed at the request of the patients, following conjunctival erosions, while two devices failed due to gradual loss of the RF link at 4 years.[7,22] The precise cause of late device failure due to interrupted RF connection is not clear, but may represent exposure of the implanted electronics or receiver coil, possibly damaged during implantation. The devices have remained implanted to monitor the long-term safety in the context of this potential complication.[7]

The Argus II underwent NICE assessment and it was felt that more data were required to ascertain patient benefit in terms of quality of life and activities of daily living. Further implantation of 10 patients is planned later this year with a program of focused rehabilitation. A Functional Low-Vision Observer Rating Assessment (FLORA) has been refined to assess patient-reported functional vision and well-being following partial visual restoration with Argus II.[30,31]

Intelligent Medical Implants learning device/ Intelligent Retinal Implant System II

An acute implantation study demonstrated that phosphenes could be elicited in 19 of 20 subjects, leading to the development of the Intelligent Medical Implants (IMI) Learning Device.[32,33] This device consisted of a microfabricated polyimide array, with 49 platinum microelectrodes, each with a diameter of 250 µm, spaced 120 µm apart, which was chronically implanted in seven patients. Results showed a good safety profile and reasonable longevity, with patient-reported phosphenes and patterns during stimulation.[34,35] The implant connected directly to an electronics module fixed to the external eye, which could only be stimulated in the clinical setting.

Since acquiring IMI in 2007, Pixium Vision S.A. has further refined the device, now known as the Intelligent Retinal Implant System (IRIS) II. The IRIS II prosthesis comprises a glasses-mounted visual interface transmitting to a pocket processor, which creates stimulation commands, which are transmitted to an extra- and intra-ocular implanted component, containing a 150-microelectrode array (Figure 2). Although this system is similar to the Argus II, the IRIS system differs in a number of ways. First, it uses a neuromorphic image sensor to respond in a continuous mode to the visual input,

Figure 2. The Intelligent Retinal Implant System (IRIS) II. Source: Adapted from Pixium Vision S.A., Paris, France.

providing both the coordinates of changing pixels and their light intensities. The visual information encoded in this output can be divided into transient and sustained components, which can be processed using algorithms to enhance image quality and to reduce the visual scene to the most important elements. This process is designed to mimic the temporal resolution of the retina while reducing the volume of redundant visual information presented during stimulation calculation. Second, the commands generated by the pocket processor travel to the visual interface and are transferred optically via an infrared (IR) array directly to the implant, permitting higher data transfer rates and miniaturization of the implant itself. A high data transfer rate is essential for stimulating greater numbers of electrodes at a higher refresh rate while accommodating for the data communication overhead.[36] Power is supplied through a separate transmitter coil system, at a lower frequency, using RF telemetry in a similar fashion to the Argus II. Finally, and perhaps most uniquely, the device includes a learning retinal encoder, which allows for individualized calibration, following as few as 100 iterations, to assign areas as excitatory or inhibitory, thus mimicking the retinal ON/OFF pathways.[37,38]

The IRIS II obtained CE approval in 2016 and early results were promising; 6-month data for the initial 10 subjects implanted as part of a clinical trial were presented at the International Eye and Chip Conference in 2017, reporting improvements demonstrated in square localization, direction of motion, picture recognition, and visual field testing, with a rate of 0.4 SAEs per subject. However, having conceded that the lifespan of the device was found to be shorter than expected, Pixium have postponed the trial pending further refinement of the device and surgical method.[39]

EPI-RET3 Retinal Implant System

The EPI-RET3 differs from the Argus and IRIS implants in that the internal components are entirely intraocular. It comprises a receiver coil and chip, that is positioned in the aphakic capsular bag and a retinal stimulator connected directly to the epiretinal stimulation array. This technology negates the need for a physical transscleral cable, instead providing the implant with energy or data via inductive links, thus reducing the risk of complications, such as infection or erosion. As with other epiretinal devices, the EPI-RET3 comprises an external camera and visual processor, which wirelessly transmits the calculated spatiotemporal pattern of stimulation pulses to the internal component (Figure 3).[40]

The device uses ultrahigh-frequency-pulsed charge-controlled stimulation to reduce large stimulation artifacts. This allows for bidirectional stimulation and recording by the microelectrodes. During experiments using animal models of RP, it was noted that there was spontaneous RGC activity in areas adjacent to regions of stimulation. Furthermore, biphasic pulses appeared to have an inhibitory effect on some RGC responses, probably due to the action of residual interneurons, such as amacrine or bipolar cells. Using this bidirectional enhancement system, it is possible to characterize response types from specific retinal areas and to modify stimulation algorithms to accommodate intrinsic activity of retinal neurons and thereby deliver more effective stimulation patterns.[38,41]

In the first clinical trial, a basic 25-electrode system was implanted for a short period into six subjects. In all patients, the implantation was uncomplicated, except for one case of sterile hypopyon, which resolved with treatment. The system was removed at 4 weeks as planned. One case developed a giant retinal tear during removal, requiring further surgery.[42,43] All six patients reported patterned phosphenes with low threshold stimulations in regions corresponding to the stimulated retina. The phosphene characterization varied greatly between patients.[44]

Future feasibility trials for EPI-RET3 have been focused on the development of a very large electrode arrays for epiretinal stimulation (VLARS), covering 37° of the field of vision.[45] However, no results have since been published from this group.

Subretinal prostheses

The rationale behind the placement of a subretinal implant is that by positioning the device at the
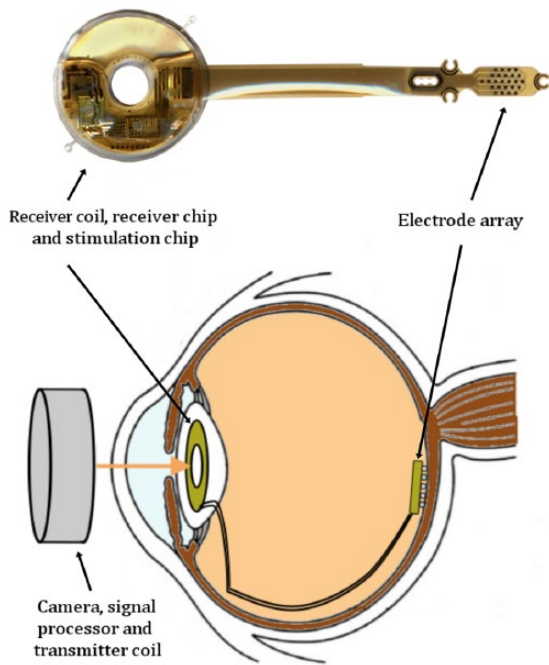
Figure 3. The EPI-RET3 Retinal Prosthesis System. Source: EPI-RET3 Team, RWTH Aachen, Germany.

level of the degenerated PRs, the intrinsic signal processing capacity of the retinal interneurons can be exploited, producing a more physiological form of vision, with less demand for image processing. Moreover, the device is situated closer to the target retina and may benefit from the natural retinal signal amplification, requiring lower stimulation intensities. This, however, assumes retention of the anatomical organization of the retinal interneuron network, which is unlikely to be the case, even prior to detectable PR cell death.[46,47]

Unless the system has intrinsic photosensitivity and amplification capacity, it will, like the epiretinal devices, require a power source and a connection serving the delivery of data. In terms of surgery, some reports have suggested that placement of subretinal implants can be technically more challenging, both due to retina-retinal pigment epithelium (RPE) adhesion, as a consequence of the underlying degeneration, and the surgical approach being less familiar to surgeons carrying out routine retinal surgery.

Boston Retinal Implant

The Boston Retinal Implant Project (BRIP) was one of the first endeavors of its kind and led one of the earliest acute trials in human subjects, wherein it was shown that reproducible percepts could be induced with single-electrode stimulation in patients with end-stage RP and one patient with normal vision prior to exenteration for orbital cancer.[48] The BRIP device is, in many respects, similar in design to the Argus II implant, but it is implanted in the subretinal space, in order to obviate the need for device fixation and to minimize gliosis that may occur with tack insertion.[49]

The BRIP group is currently performing preclinical trials for a 256-channel device, with a view to performing phase I clinical trials in the near future. The group is committed to developing an implant that provides functionally 'useful' vision, before adopting a corporate strategy for ongoing development.[50]

Artificial silicon retina

This device, developed by Optobionics (Glen Ellyn, IL, USA), was the first passive prosthesis to attempt wireless retinal stimulation using ambient light. The 2-mm-wide, 25-µm-thick artificial silicon retina (ASR) array consists of 5000 microphotodiodes of 20-µm-diameter associated with 9-µm-diameter iridium-tipped microelectrodes and separated by 5 µm. In a pilot study of six patients, in whom the implant was placed in the superior retina, it was demonstrated that phosphenes could be perceived in the region of the field of vision corresponding to the device in four patients. Furthermore, overall visual function was enhanced in retinal areas distant from the implant, with reported improvements in visual function. This led the group to suggest that either the surgery or the focal electrical stimulation by the implant could induce a generalized neurotrophic effect on the retina,[51] which was also demonstrated on rodent models.[52,53] A further 4 patients were implanted, giving a total of 10 patients implanted with the ASR chip, 6 of whom received long-term follow-up. The ASR implants demonstrated good safety and longevity profiles,[54] and while a temporary improvement in generalized visual function was demonstrated, compared with the control eye, this was ascribed to the effect of neuroprotective growth factors rather than the retinal prosthesis *per se*. It has been concluded that a device relying on ambient light alone is unable to generate sufficient photocurrent to directly stimulate a meaningful number of neurons. The company has subsequently closed and there have been no further published results from this group.[55] Ultimately, however, the pioneering work by this group has since led to the development of promising next-generation photovoltaic systems.

Alpha IMS and AMS

The Alpha IMS (Retina Implant AG, Reutlingen, Germany) is the first and only subretinal implant to obtain CE marking, which was granted in 2013. In a similar fashion to the ASR, it incorporates a photovoltaic array, termed a multiphotodiode array (MPDA), which comprises a 3-mm² microchip containing 1500 independent photodiode–amplifier–electrode units, each of which will convert ambient luminance into an electrical signal. However, it differs from the ASR in that it is an 'active' device, using an extrinsic power source to amplify the signal. This is supplied via a silicone supply cable, which links to a fixation pad looped through the orbit, passing subcutaneously and then under the temporal muscle to a subdermal coil, which is fixed to the postauricular cranial bone. A removable external coil magnetically attaches to the subdermal coil, allowing electromagnetic power induction and control of contrast sensitivity and brightness from a handheld unit.[56,57] Due to the extra-orbital placement of the induction coil and the intra-ocular placement of the array, coordination between different surgical specialist teams is required, leading to longer operating times. Moreover, RPE degeneration and adhesion to the retina can lead to difficulty with subfoveal device placement. These factors may contribute to the higher reported rates of device repositioning, replacement surgery, and device failure.[57,58]

The Alpha IMS clinical trial in 2010–2014 aimed to assess the improvement in daily living and mobility, as well as visual acuity and object recognition. Patient experience of the device in daily life varied from six subjects (21%) who reported very good experiences, recognizing letters or unknown objects, including houses and cars, to eight subjects (28%) who reported no benefit at all. It was reported that 25 subjects (86%) could perceive light with the implant, with significant improvement in light localization, while 6 subjects could detect motion. The best visual acuity recorded on contrast-reversal Landolt C-ring testing was 20/546. Object recognition tests revealed significant improvement with the device on during the initial 3 months but fell below significance from month 6.[59,60] The safety profile of the device was generally felt to be clinically acceptable, with only two SAEs (among 75 reported total AEs) in nine subjects within 1 year of implantation.[61]

The subsequent iteration, the Alpha AMS, which is larger and incorporates 1600 photodiode complexes, received CE approval in 2016 (Figure 4).
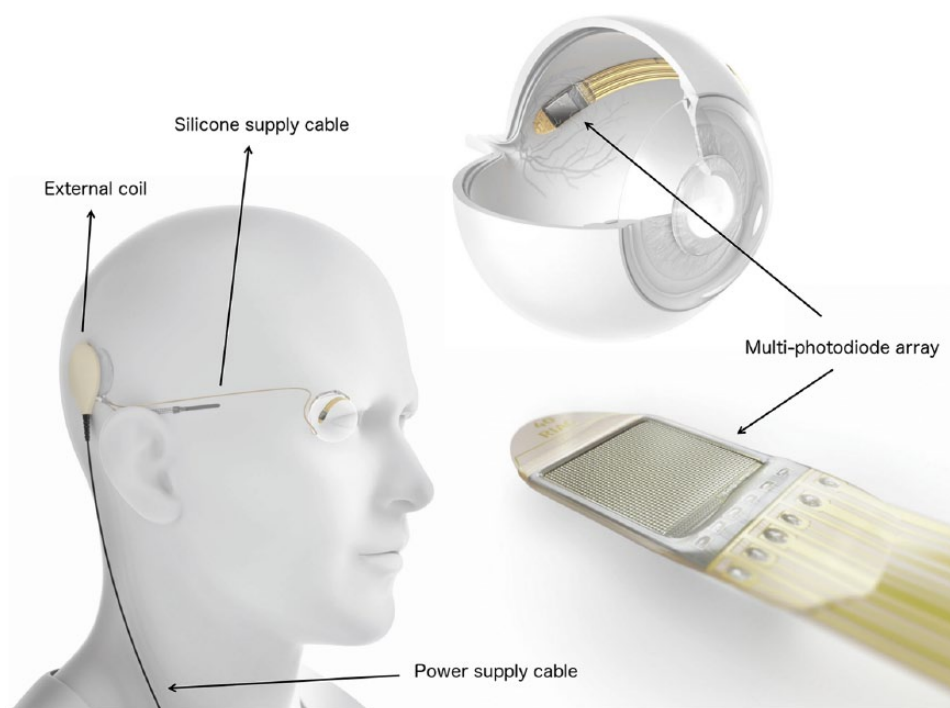
Figure 4. The Retina Implant Alpha AMS System.
Source: Adapted from Retina Implant AG, Reutlingen, Germany.
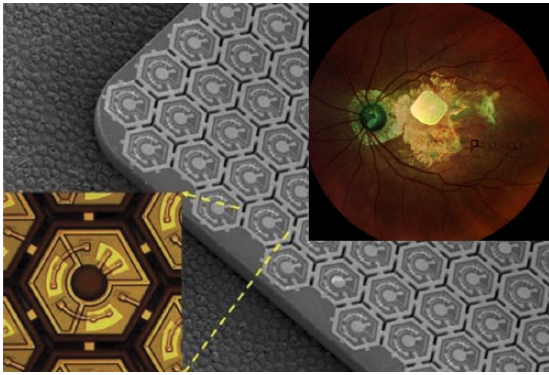
Figure 5. Schematic of the Photovoltaic Retinal Implant (PRIMA) Bionic Vision System. Inset: device in a patient with geographic atrophy.
Source: Adapted from Palanker et al, Stanford University, and Pixium Vision S.A., Paris, France.

Results of 1 year showed similar functional benefits and number of SAEs (eight in nine subjects) to the Alpha IMS, although the authors report a considerable improvement in the functional longevity of the device.[6]

Photovoltaic Retinal Implant (PRIMA) bionic vision system

This relatively recent venture (Pixium Vision S.A.) has taken various pre-existing implant concepts and created a novel model of photovoltaic stimulation. In this modular array setup, a 1-mm-wide hexagonal chip, containing 142-pixel cells of 30-µm-thick, is inserted subretinally (Figure 5). Each pixel receives visual information in the form of pulsed near-IR light directly from a pair of specially constructed glasses. This photic energy passes from a stimulating electrode to a return electrode, each connected to multiple photodiodes in series and coated in sputtered iridium oxide. In turn, these photodiodes generate an electrical current that polarizes the adjacent neuronal tissue. This modular arrangement is thought to both improve spatial resolution and also be more readily scalable to a larger visual field, without the need for transscleral wires or additional power induction, as in the Alpha IMS.[62–64]

Preclinical results using this approach in animal models have been encouraging. Visual-evoked potential (VEP) testing in implanted Royal College of Surgeons rats in response to photovoltaic stimulation demonstrated a similar shape and amplitude to VEPs in wild-type rats, with decreased latency due to the absence of phototransduction. The amplitude of the VEP could also be scaled by modulating light intensity with liquid crystal displays or pulse duration with digital light processing micro-mirror arrays.[65] Contrast sensitivity, on the other hand, was limited, with only 100% contrast eliciting a VEP response above the noise level.[66] By switching from cathodic-first pulses of current to anodic-first, it has been shown *in vitro* and *in vivo* that stimulation thresholds can be decreased well below the ocular safety limit for near-infrared (NIR) irradiance while retaining spatial frequency.[66–68] It has been postulated that an equivalent spatial resolution in humans could yield a grating acuity of 20/250, with scope to further reduce pixel size and pitch.[69]

Five patients with dry AMD have been implanted with the PRIMA device in France, with plans to implant five more in the United States during 2018, as part of a safety and performance evaluation feasibility study over 36 months. Preliminary results are anticipated in 2019.[70]

Suprachoroidal prostheses

The third position of placement of prostheses for local retinal stimulation has been the suprachoroidal space. In this position, the system does not necessitate transvitreal surgery and is therefore potentially less invasive and more easily accessible for repair or replacement. However, the suprachoroidal space is highly vascular and there is a significant risk of hemorrhage and there remains a risk of fibrosis postimplantation. Furthermore, due to its distance from the neurosensory retina, this design appears to require greater stimulation power to elicit visual percepts. Suprachoroidal placement also risks greater spread of current, thereby reducing the spatial resolution.

Bionic Vision Australia

The Bionic Vision Australia (BVA) team has developed a series of suprachoroidal implant prototypes over the past 10 years. The first of these was a 24-channel system, consisting of 20 stimulation channels and 4 return electrodes. In a similar fashion to the Alpha AMS and cochlear implants, this system involves dissection of the temporalis muscle for attachment of a percutaneous connector to the bone. From there the connecting wire is passed through a tunnel in the muscle fascia and via a lateral orbitotomy and

peritomy, at which point the lateral muscle is temporarily disinserted to allow for placement of the array into the suprachoroidal space.[71,72] This device has no photovoltaic properties, relying on a head-mounted camera and image processor to provide the electrode stimulation patterns.

In 2012, three subjects with advanced RP were implanted for 2 years as part of a pilot study. The surgery took between 3 and 4 h and it was reported that all patients developed a combined subretinal and suprachoroidal hemorrhage postoperatively.[72] During testing, phosphene location, shape, and size were mapped using a finger-mounted motion tracker and eye-facing camera to monitor gaze. Phosphenes could be elicited in all patients, and although variable in character, location, and stimulation thresholds, they were reported to be controllable and retinotopically locatable in two patients.[73,74] Light localization, optotype recognition, and grating acuity tests, as well as tasks of daily living, were performed using a head-mounted camera. Light localization was better than chance in all participants, while only one subject completed the visual acuity task, averaging 20/8397, significantly better with device on than with the device off.[72,75] In a series of psychophysical tasks delivered by direct electrode stimulation, two of the subjects demonstrated better than chance character recognition and static object localization, while one was able to detect dynamic image trajectory.[76] At the time of explantation, electrical stimulation was still possible, although it was noted in all cases that a fibrous capsule had developed around the implant.[77]

The primary limitations of suprachoroidal stimulation relate to the proximity of the device to the retinal neurons. The BVA group is developing a next-generation 44-channel fully implantable device,[78] while also designing a 99-channel device, the Phoenix-99, which will incorporate a dual monopolar and hexapolar ('quasi-monopolar') stimulation pattern, to try and address the issues of retinotopic discrimination and high stimulation thresholds.[73,79]

Suprachoroidal–transretinal stimulation

The suprachoroidal–transretinal stimulation (STS) system is under development by Japan's Artificial Vision Project in conjunction with NIDEK. Like the BVA system, the STS requires a temporalis incision and tunneled connection between a decoder, an internal coil and a stimulating electrode array, and return electrode. Once suprathreshold light is detected by a glasses-mounted camera and processed by a computer within the arm of the spectacles, the external coil will relay a signal via the secondary coil to the decoder, which, in turn, generates a biphasic pulse to stimulate individual electrodes. Unlike other systems, the current STS consists of a '3D' (three-dimensional) 49-microelectrode array, with electrodes that protrude from the array by 0.3 mm, which is inserted into a 6 mm $\times$ 5 mm scleral pocket. Power is provided externally through a portable battery pack.[80]

In a pilot study of two patients using a prototype nine-electrode implant, it was shown that phosphenes could be reproducibly elicited in the area of the visual field corresponding to the implant, during direct stimulation. Using a headband-mounted camera, following which the images are converted to 3 $\times$ 3 squares with a pixel resolution of 40 $\times$ 40, both patients could identify and discriminate objects using head scanning with between four and six electrodes, while one patient could also detect motion and perform grasping tasks better than by chance.[81] Following the surgical success of both single and dual 49-electrode arrays in animal models, three patients underwent implantation of this second-generation device. While the safety profile of the device was reassuring, with no SAEs requiring further surgery at 1 year, the tests of function were less consistent. One subject could localize a square better with the device on during all of the follow-up, while two subjects were able to walk along a white line and recognize an everyday object better than chance, but not reproducibly at separate time points.[82] One subject with Stargardt disease and hand movements vision in the left eye underwent implantation with an STS device in the fellow eye. Results suggest that the subject could reach more accurately using a combination of natural and artificial vision than with residual natural vision alone.[83] Larger numbers are required to draw firmer conclusions about the efficacy of suprachoroidal and transscleral implants in their present formats; however, results to date suggest greater limitations to this approach than for epiretinal or subretinal implants.

Challenges in prosthetic vision

The classification of retinal prostheses according to their anatomical placement serves best to demonstrate the different surgical approaches and theoretical differences in which residual

retinal cells are stimulated. However, apart from these aspects, all devices face challenges in the form of image capture, processing, delivery of data and power, biocompatibility, and hermeticity. During the last quarter century, the field has witnessed progress from intra-operative focal electrode stimulation to chronic implantation of multi-electrode arrays for over 10 years, demonstrating significant, albeit coarse, functional improvement. In general, advances in image processing algorithms and optical data transfer rates, combined with developments in the field of microelectronics and material microfabrication, continue to drive the field forward, projecting a hugely encouraging outlook for the future progress of visual restorative therapy.

To date, no single approach has yielded results that suggest a significant advantage over other systems, but the substantial progress over the past three decades represents unprecedented endeavor, innovation, and collaboration, across the field as a whole.

Assessing functional outcomes

One of most pressing issues that has begun to limit the broader use of prosthetic retinal devices is how to assess its 'usefulness' and function in terms of patient benefit and consequently how to predict in which direction to develop these devices. Numerous studies have incorporated performance-based measures and self-reporting questionnaires to attempt to understand the relative importance of visual parameters in performance of everyday tasks in visually impaired subjects. This has demonstrated the importance of visual acuity, visual field, and contrast sensitivity for acceptable day-to-day visual functioning.[84–88] Simulation studies can estimate the visual requirements to deliver a sufficient image resolution and field of view with a prosthetic system, in order to perform useful tasks. Overall, a minimum spatial resolution of 3–4 pixels per degree[2] (i.e. a 600–1000 pixel array with a 15° × 15° field of view) is thought to be able to permit an acceptable accuracy in pointing, manipulation, mobility, and object recognition activities,[89–92] and even higher resolution is necessary for reading.[93,94] This is approximately 10 times greater than the resolution provided by the current Argus II system.

Most conventional tests of basic visual function such as ETDRS and Snellen visual acuity are not validated for quantification of vision below a certain threshold, though calculated equivalents in these scales are often mentioned in published articles and in this review. Coarser tests of function, such as grating visual acuity, Basic Light and Motion Assessment (BaLM) and the Freiburg Visual Acuity Test (FrACT), have shown some capacity to deliver reliable evaluations of ULV in some studies.[95–97]

In terms of functional outcomes, self-reporting and performance-based testing can give some indication of qualitative benefit. However, there is currently no universally accepted functional outcome measure for providing reliable and quantitative evidence for the functional value of therapies in those with ultra-low vision (ULV). Functional vision tests in ULV should not only be valid, reliable, and repeatable in the conventional sense, but ought to also have ecological validity, that is, relate to an appreciable change in the subject's real-world task performance. Furthermore, they should be sensitive to response to treatment and allow estimation of a quantifiable 'minimally important difference', at which a subject perceives a useful functional improvement.[98]

Many of the aforementioned functional tests, such as square localization, recognition of white objects on a black background, or following a white line on the floor, are limited in terms of ecological validity due to their departure from a real-world environment. On the other hand, real-world functional assessments, such as FLORA, which involve an observer-rated calculation of visual ability during activities of daily living in residential settings, suffer from the inability to provide a standardized metric for measuring functional benefit across different subjects. One solution, in the context of navigational function, can be offered using standardized, simulated real-world environments, such as the Pedestrian Accessibility and Movement Environment Laboratory at UCL, although this is expensive to manufacture, maintain, and reproduce across the number of groups working in the area. Other approaches include the use of salience maps to determine the spatial allocation of a subject's visual attention toward objects of interest within a presented visual scene. Simulated tests of picture and face discrimination have demonstrated good ability of subjects to identify salient features, with a pronounced learning effect during retesting.[99,100]

Currently, progress in the field of restorative visual medicine is reliant on the validation of a standardized test battery that incorporates both objective and subjective measures of visual task performance, in order to demonstrate a reliable metric of functional benefit. As increasing numbers of patients with ULV receive various emerging therapies, we anticipate that this demand will be met.

Hardware and software constraints

Using basic tests of visual function, the highest estimated acuity achieved to date is with the Alpha IMS, with which 20/546 was recorded, followed by 20/1262 with the Argus II.[6,23] This is significantly inferior to natural vision, both in terms of resolution and form. Spatial resolution of prosthetic systems is limited by several factors, including electrode density, size, number and pitch, electrode contact, and visual encoding. Issues with temporal resolution and image persistence further limit the interpretation of prosthetic vision.[101]

Existing electrode arrays are thought to have a theoretical maximum resolution that is at least 12 times less than that of the normal retina.[102] The maximal electrode density is currently limited by heat generation that occurs during signal transmission. However, even if it is possible to develop an implant with a similar size and density of microelectrodes to native cone PRs, there would still exist the biological challenge of recreating the visual encoding capacity of the retinal interneurons, especially at the fovea, where the neuronal layers do not directly overlie the PRs. In theory, a maximum pixel diameter of about 50 μm, separated by 25 μm, would be necessary to achieve a spatial frequency equivalent to the minimum angle of resolution achieved in 20/200 vision (the approximate level of visual impairment). At present, the MPDA systems containing autonomous pixels appear to hold the most promise for maximizing electrode density at this scale but have not yet achieved results that reflect the theoretical limit of the devices, probably, in part, due to the aforementioned remodeling process that the degenerative retina undergoes[17] and electrode–target tissue distance. Incorporation of bidirectional stimulation, as in the EPI-RET3, is important to allow signal feedback and modulation of the stimulation algorithms to exploit any residual retinal processing and mimic RGC receptive fields, thus enhancing contrast and spatial resolution.[38]

The issue of electrode contact is being addressed by some groups using 3D electrodes to improve local contact, such as the NIDEK group and the Nano Retina group, who are developing the Bio-Retina array with nano-coated electrode tips.[103] While embedded electrodes may reduce charge density and stimulation artifact, it is conceivable that such penetration of the retina could lead to greater risk of complication, such as hemorrhage or further retinal degeneration, and make removal or repositioning of devices more problematic.

In addition, there are hardware constraints limiting the field of vision that current implants can deliver. In the case of external image capture systems, the patient must become adept at head scanning, both to maximize the accumulation of information from a visual scene and to prevent 'fading' of images due to repetitive stimulation. This latter issue can be partly resolved through the use of photovoltaic systems or an intra-ocular camera, which exploits the natural microsaccadic eye movements to prevent this fading phenomenon and also avoids any decoupling of the visual interface and stimulating array when the head or eye moves. Development of very large electrode arrays (VLARS) is underway[45] but will ultimately be a trade-off between expanding the field of vision, minimizing implantation trauma, and coping with high levels of heat dissipation. The concept of using modular elements, as in the PRIMA device, to enlarge the functional visual field, may represent a preferable strategy.

The longevity of the subretinal photovoltaic systems appears to be shorter than for epiretinal devices, probably because of the current limitations in material engineering. Development is underway for novel biocompatible materials, such as laser-microstructured diamond electrode arrays, with greater longevity and chemical stability,[104] or liquid crystal polymers that are also ultra-thin, lightweight, and deformable.[105] In addition, the field of tissue electronics, concerned with the development of organic conductive and semi-conductive polymers, is emerging as an alternative to inorganic systems. Initial animal models have demonstrated efficacy, and it is postulated that the graded modulation of neurotransmitter release afforded via an organic array may create a more physiological interaction with the neuronal tissue, potentially enhancing the resultant spatial resolution.[106–108]

There is also much focus on how software algorithms can be refined to filter the image and detect relevant features of the visual scene. This image processing method, termed saliency mapping, has been used to develop computational models for rapid recognition and segmentation of image information for over a decade and is now widely utilized in the emerging field of computer vision and machine learning.[109–112] In the field of retinal prosthetics, this information can be used to apply transformations to the encoded stimulation pattern, such as edge detection, grayscale histogram equalization, contrast and intensity enhancement, as well as image magnification.[112,113] Simulation studies suggest that use of such processing algorithms can boost task performance, including face and object recognition and navigation.[114–118]

Finally, another factor that is certain to play a role in the future success of retinal prosthetics is the ability of recipients to adapt to using this novel but rudimentary visual input. The relatively poorly understood phenomenon of cortical plasticity and perceptual learning has been thoroughly addressed with respect to visual restoration in excellent previous reviews.[119,120]

Conclusion

The field of visual restorative therapy is rapidly advancing and holds great promise for the introduction of real, measurable treatments of blinding conditions in the near future. Although not limited to retinal prostheses, with significant progress being made in other strategies, such as optogenetics, stem cells, and gene therapy, this represents the most advanced form of treatment for profound vision loss that is currently available. It is likely that the future will see integration of prosthetic devices with regenerative medicine technologies, in the form of 'biohybrid' implants.

This review summarizes just some of the considerable progress has been made in the field of retinal prostheses in the past decades. However, the remaining challenges are as diverse as they are numerous, and overcoming them will rely on continued close collaboration between engineers, healthcare workers, industry, and patients to eventually transform this concept from science fiction into science fact.

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