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A review and update on the current status of retinal prostheses (bionic eye)

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Abstract

Introduction/background: The Argus® II is the first retinal prosthesis approved for the treatment of patients blind from retinitis pigmentosa (RP), receiving CE (Conformité Européenne) marking in March 2011 and FDA approval in February 2013. Alpha-IMS followed closely and obtained CE marking in July 2013. Other devices are being developed, some of which are currently in clinical trials.

Sources of data: A systematic literature search was conducted on PubMED, Google Scholar and IEEExplore.

Areas of agreement: Retinal prostheses play a part in restoring vision in blind RP patients providing stable, safe and long-term retinal stimulation.

Areas of controversy: Objective improvement in visual function does not always translate into consistent improvement in the patient's quality of life. Controversy exists over the use of an external image-capturing device versus internally placed photodiode devices.

Growing points: The alpha-IMS, a photovoltaic-based retinal prosthesis recently obtained its CE marking in July 2013.

Areas timely for developing research: Improvement in retinal prosthetic vision depends on: (i) improving visual resolution, (ii) improving the visual field, (iii) developing an accurate neural code for image processing and (iv) improving the biocompatibility of the device to ensure longevity.

Key words: retinal prosthesis, artificial retina, prosthetic vision, retinitis pigmentosa, therapy

Introduction

The dream of using electronic or artificial retinal replacements to treat blindness has long been held. With the advances in biotechnology, material science and understanding of visual and retinal neuroscience, this has finally become a reality for the first cohort of patients with outer retinal degeneration.

In the development of prosthetic vision, it is also possible to stimulate the visual pathway at other sites other than the retina to gain visual perceptions. These alternative approaches may be necessary in cases whereby the entire retina has been destroyed due to the disease nature, and include stimulation of the optic nerve head,[1–3] the lateral geniculate nucleus[4] and the primary visual cortex.[5,6] The visual pathway functions as a complex image processor as well as an information conduit. At higher levels, the visual signals arrive with significant processing completed. In reality due to its easier access, simpler processing and the retinotopic organization, the retina has been the primary focus for artificial stimulation. To date, visual prosthetic systems stimulating non-retinal sites are largely experimental and involve laboratory testing in animals and very limited numbers of human volunteers (see Table 1).

Retinitis pigmentosa (RP) denotes a group of hereditary outer retinal degenerative diseases, affecting 1 in 4000 live births and 17 000 people worldwide.[7] Affected individuals suffer from progressive visual loss which can be profound (0.5% with no light perception, 25% with ≤20/200 vision in both eyes).[8] Treatment options for RP, other than for the associated cataract and macular oedema, have been limited. While recent advances in gene therapy, neuroprotective agents and stem cell therapy have shown promising future therapeutic potentials,[9–12] retinal prostheses offer the only treatment option for patients at the severe end of the disease spectrum at present. There are currently two models of retinal prostheses available commercially: (i) Argus® II retinal prosthesis system (Second Sight Medical Product, Inc., Sylmar), which received CE (Conformité Européenne) marking in March 2011 and the Food and Drug Administration (FDA) approval in February 2013 and (ii) the alpha-IMS (Retinal Implant AG, Reutlingen), which obtained CE marking in July 2013. In addition, the Argus® II system is also presently under review by the Specialist Commissioning Group in the UK for the treatment of patients with end-stage RP in the National Health Service (NHS).

Apart from technological advances in prosthetic vision, development in other biomedical fields has also shed new hope on restoring vision in patients with end-stage retinal diseases, most notably the cellular therapy. Current stem cell strategies include replacing the damaged retinal pigment epithelial (RPE) cells with embryonic stem cell (ESC)-derived RPE cells to rescue and partially restore photoreceptor function in retinal degenerative diseases.[13,14] More recently studies replacing photoreceptors directly by subretinal insertion of committed precursors of photoreceptors from ESC have been reported.[15] Additionally, when the photoreceptors are still present, retinal gene therapy may be the key to preserve photoreceptor function and prevent cell death.[16]

In this review, we will focus our discussion on the current status of various retinal prosthetic systems under development. In particular, the Argus® II and alpha-IMS systems will be discussed in detail as they have been in extended clinical use.

Mechanism of the retinal prosthetic system

In RP and outer retinal dystrophies, the predominant pathology is the irreversible degeneration of the outer retina (i.e. the photoreceptors and the underlying RPE), while the remaining inner retina (i.e. bipolar cells, retinal ganglion cells) and the visual pathway downstream remain intact.[17] The success of a retinal prosthesis system, therefore, rests on reproducing the outer retinal function. This requires

(a) efficient capturing of the visual images from the outside world;
(b) transduction of the captured images into meaningful neurological signals;
(c) subsequent activation of the residual inner retina (ganglion cells), from where visual information can be relayed to the visual cortex by the optic nerve.

Table 1 Mechanisms and developmental stages of different visual prosthetic systems

Visual prostheses	Retinal prostheses				Optic nerve head prostheses	Cortical prostheses
	Argus® II	Alpha-IMS	IMI, IRIS	EPI-RET 3 ('wireless' implant)		
Image capture	Extrinsic video camera	Intrinsic optical system	Extrinsic video camera	Extrinsic video camera	Extrinsic video camera	Extrinsic video camera
Light waves transduction into electrical signals	Extrinsic conversion by an external VPU	Intrinsic conversion by direct activation of micro-photo-diodes (MPDA)	Extrinsic conversion by an external processing unit	Extrinsic conversion by an external processing unit	Extrinsic conversion by an external processing unit	Extrinsic conversion by an external processing unit
Number of electrodes	60	1500 micro-photodiodes, each connected to an amplifier and electrode	61	25	Spiral nerve cuff (MiViP);[1] 3 (AV-DONE): 16[3]	Dobelle: 64 Normann: 100
Field of vision	Up to 20°	11° × 11°	Up to 40°	Not available	14° × 41°	Not available
Site of stimuli	Inner retina with epiretinal electrodes	Outer retina with subretinal electrodes	Inner retina with epiretinal electrodes	Inner retina with epiretinal electrodes	Optic nerve head	Striate cortex of occipital lobe
Visual processing	Extrinsic processing by computer algorithms	Intrinsic intra-retinal processing	Extrinsic processing by computer algorithms	Extrinsic processing by computer algorithms	Extrinsic processing by computer algorithms	Extrinsic processing by computer algorithms
Status	Commercially available in Europe (CE mark March 2011) and the USA (FDA approval February 2013). Trials identifier: NCT01490827	Commercially available in Europe (CE mark in July 2013). Trials identifier: NCT01024803	Phase II clinical trial commenced January 2007. Clinical Trials identifier: NCT00427180	Completed acute clinical study. Awaiting further development and approval for chronic study	Experiments performed on volunteer human subjects	Experiments performed on volunteer human subjects

Image capture

There are two main methods of obtaining continuous visual inputs used by the current generation of retinal prostheses. One method uses an external video camera to capture the surrounding visual images, which are then processed in real time by computer algorithms and converted into electrical signals, e.g. the Argus® II retinal prosthesis system.[18] The second method takes a more naturalistic approach to image capture by making use of the subject's own optical system (the cornea and lens) to focus the visual images directly onto a photodiode, e.g. the alpha-IMS implant.[19]

Image translation

The external image-capturing system

When an external video camera is employed for image capture, substantial amount of image processing takes place externally. The visuo-spatial information from the video is converted and encoded into electrical field patterns, which can then be used to activate the electrodes to stimulate the residual inner retina. In the Argus® II retinal implant, this is achieved by real-time processing of the video images in a small portable computer unit known as the visual processing unit (VPU) (see Fig. 1a). Examples of other groups which also use an external imaging system are the two German Consortiums: Intelligent Medical Implant (IMI) and EpiRet GmbH, whose devices are the IRIS implant and the Epi-Ret 3 implant, respectively.[20,21]

One advantage of an external system is that as image processing occurs extrinsic to the implanted subject, it allows for improvement of the visuospatial signal encoding. One of the main features of the IRIS-IMI device is the superior rendering of image processing by their 'learning algorithms', leading to the name Intelligent Medical Implant (see later section on IRIS-IMI). More recently, Nirenberg and Pandarinath[22] reported breakthrough in the encoding and translation of video images into recognizable visual forms, as observed in the changes in visual behaviour of experimental mice. This encoding is being developed in collaboration with the programmers of the Argus® II retinal implants to allow incorporation into the next generation of retinal prosthetic systems.

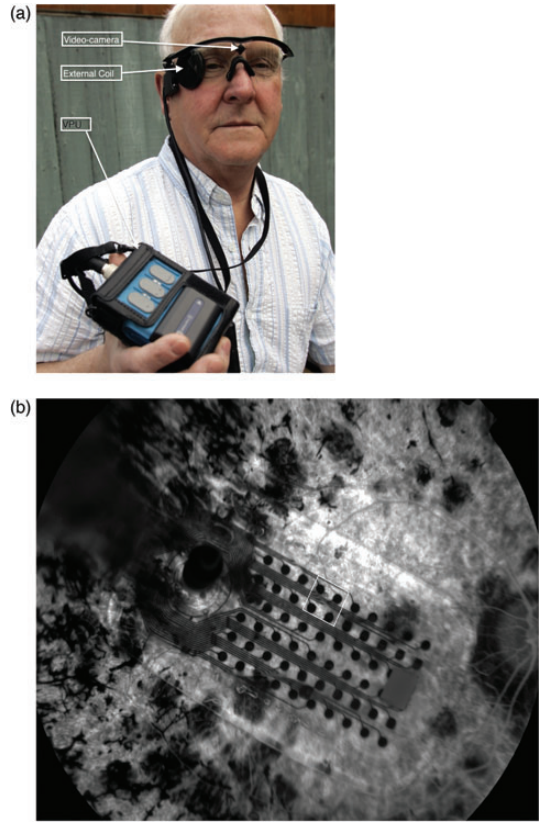

Fig. 1 (**a**) Photograph of an end-stage RP patient who underwent Argus® II implantation as part of the phase II clinical trial. This video camera is embedded in the inter-ocular bridge of the glasses frame. He is sown holding the video-processing unit (VPU), which converts the images captured by the video camera into electrical signals. These signals are then passed onto the External Coil for information relay. (**b**) Red-free fundus photograph of an Argus® II retinal implant placed on the retinal surface (epiretinally) over the macular region, within the retinal vessel arcades. There are 60 (10 × 6) microelectrodes in the array. Large clumps of intra-retinal pigmentation (bone-spicule pigments) and the pale atropic underlying RPE are seen, characteristic of end-stage RP. An area of four adjacent microelectrodes is marked by a white square. In Figure 2, a magnified view of the cone photoreceptors at the same location on a healthy retina will be shown.

The intrinsic image-capturing system

To make use of the subjects' own optical system for image capture, a photovoltaic component is placed in the posterior pole of the fundus, where it receives

incident light rays of normal images focused onto the retina. The photovoltaic component, in the form of a micro-photodiode array (MPDA), is capable of converting electromagnetic light waves into electric currents, with the aim to activate the residual inner retinal neurones directly. The earliest use of this technique was the sub-retinal Artificial Silicone Retina (ASR), devised by Chow and colleagues *et al.* in the 1980s.[23] However, this MPDA was not as efficient as native photoreceptors in light energy conversion and was only capable of generating electric currents in the order of nano-amperes (10^{-9}A), while the inner retina neurones require a threshold of ~10 mA (10^{-6} A) for activation.[24,25]

The alpha-IMS implant circumvented this problem by supplying an external power source, which amplifies the small currents generated by the MPDA sufficiently to activate the inner retina, while retaining the retinotopic organization of the stimuli.[19] In this system of intrinsic image capture, direct activation of the residual inner retina takes place instantaneously in a retinotopic manner. Image processing can potentially begin within the residual intra-retinal neural network.

Inner retina activation

Microelectronic stimulation (by microelectrode arrays)
Stimulation of nerve endings with microelectrodes to activate voltage-gated ion channels in neurones is the basic mechanism of retinal activation for all current retinal prostheses. In a normal human retina, signals in bipolar cells and horizontal cells are represented in the form of *graded* intracellular electrical responses. In the retinal ganglion cells, these local electrical responses are turned into action potentials and propagated down the optic nerve. Only retinal ganglion cells and amacrine cells are capable of producing action potentials.[26,27]

The microelectrode arrays have been placed at 3 different sites:

1. Epiretinal placement (i.e. on retinal surface, secured by a retinal tack), e.g. Argus® II, Epi-Ret 3;
2. Subretinal placement (i.e. in between the RPE layer and the neurosensory retina), e.g. alpha-IMS;
3. Suprachoroidal placement (i.e. in between the sclera and the choroid).[28]

Regardless of their placement the common goal of the microelectrode arrays is to initiate action potentials in the retinal ganglion cells in a retinotopic manner. Both the epiretinal[29] and suprachoroidal[30] implants have been shown to directly stimulate the retinal ganglion cells predominantly, while the subretinal implants evoke retinal ganglion cell responses by both activating the bipolar cells, as well as directly stimulating the retinal ganglion cells.[24] Whether this prior activation of bipolar cells contributes towards intrinsic image processing, thereby improving image interpretation by the visual cortex, is unclear as there is extensive charge diffusion as well as marked intra-retinal neural remodelling in these end-stage retinas.[31]

Decisions on the choice of implant location also take into account factors such as implant biocompatibility, stability of the implant/retinal tissue interface, safety in terms of electrode charge density during active stimulation and the ease of surgical implantation or removal if required.

Aside from implant location, the other issue of greater interest is the level of visual resolution that retinal prostheses can deliver. In human retina there are ~120 million rods, 6 million cones and 1.5 million ganglion cells. There is marked convergence in the retinal periphery where hundreds of rods feed into one peripheral bipolar cell, while in the central macular region (fovea), the ratio of cones to retinal ganglion cells approaches 1:1. Achieving this 1:1 ratio is unlikely with a retinal device because as the individual microelectrode diameter becomes smaller, the charge density (per unit area) increases exponentially[32] for the same supra-threshold stimulating current, thereby increasing the risk of tissue damage.[33] The microelectrodes array is also limited in its function by its size, as while larger overall stimulating area might offer a greater potential visual field for the patients, it would result in greater overall charge, which again may cause tissue damage.

In the current generation of retinal prostheses, the Argus® II microelectrode array consists of 60 circular microelectrodes of 200 μm in diameter.[18] Each microelectrode covers an area equivalent to hundreds of photoreceptors (see Figs 1b and 2). The alpha-IMS subretinal implant consists of 1500 MPDA elements, each coupled to a square microelectrode of 50 μm × 50 μm (2500 μm^2).[19] Stimulation of one electrode

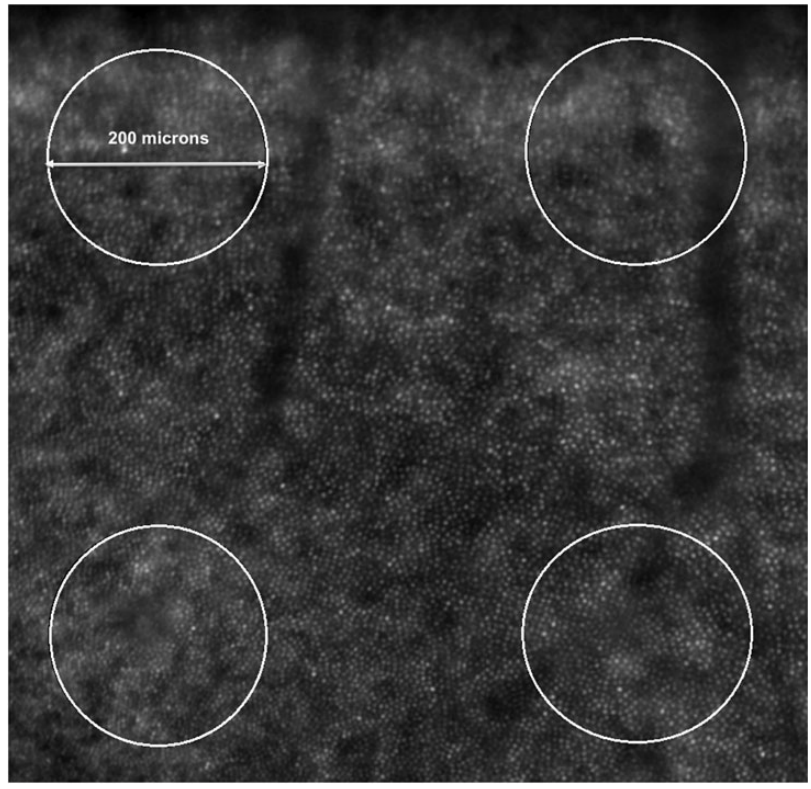

Fig. 2 This is an adaptive optics (Imagine Eyes—rtx1™) retinal image of a healthy 33-year-old subject, taken at 3 degrees temporal to fixation of his right eye. Individual cone photoreceptors can be seen as discrete dots. Within this mosaic macular region, the ratio of photoreceptors to retinal ganglion cells approaches 1:1, allowing maximal visual resolution. In comparison, the four white circles are representative of the retinal surface areas covered by the Argus® II microelectrodes, with a diameter of 200 μm each, drawn to scale. Activation of one microelectrode would therefore result in equivalent simultaneous activation of hundreds of photoreceptors. The resolution achievable with this current generation of retinal implant is thus limited.

within the central macular region would therefore result in simultaneous activation of a similarly large number of retinal ganglion cells, as the cones to ganglion cells ratio is close to 1:1 in this region, thereby compromising the resolution. The visual resolution achievable with the current generation of retinal prostheses is discussed within the section for each device below.

Other methods of retinal stimulation. *Optogenetics, optoelectronics and acoustic retinal prosthesis*. As well as directly applying electrical charges to initiate action potentials, three other methods are in development. The optogenetic approach aims to replace the lost photoreceptors by turning the remaining inner retinal cells (e.g. bipolar cells, retinal ganglion cells) into photosensitive cells. This is achieved by incorporating photosensitive cation channels such as channelrhodpsin-2 or halorhodopsin into the remaining bipolar cells/retinal ganglion cells using virus vectors.[34,35]

Even though the transfected neurones become light sensitive, they require constant luminance of 100 mW/cm^2 for action potential initiation. Natural ambient light (which has a variation of 15 log units in intensity)[26] does not have the intensity to activate the retina reliably.

Wang *et al.*[36] from Stanford University devised an optoelectronic system, which combines the subretinal

silicon MPDA similar to that of the ASR (Optobiotics) or the alpha-IMS system, with the targeted stimulation of the MPDA by pulsed near infra-red (NIR) lights to achieve inner retina activation. This has the potential of overcoming the limitation of microelectrode size and charge density with microelectrodes. It also offers the flexibility to process visual images with advanced encoding algorithms, before converting images into NIR pulses for subsequent MPDA stimulation.

The third method of inner retinal stimulation, still at experimental stage, is the use of ultrasound waves to stimulate the retinal ganglion cells. Naor *et al.*[37] have shown, as proof of principle, that acoustic waves are capable of eliciting propagated responses from retinal ganglion cells, resulting in measurable visual evoked potentials in experimental rats.

Retinal prostheses in clinical practice

Argus® II: Second Sight Medical Products, Sylmar, CA, USA

The Argus® II retinal prosthesis was first implanted in a human clinical trial in 2008 (clinicaltrials.gov Identifier: NCT00407602), and has since received CE marking and FDA approval for its use as a humanitarian device for the treatment of end-stage RP. It is currently being implanted in Italy and Germany through the state health systems, and is being assessed within the NICE framework for potential funding through the NHS in the UK.

The Argus® II retinal prosthesis consists of three external parts (see Fig. 1a):

(a) a glasses mounted video camera;
(b) a portable computer (the VPU) for processing the captured images;
(c) an external coil, built into the side arm of the glasses, for wireless communication using radio-frequency (RF) telemetry and induction of power.

The internal part consists of

(a) an internal coil which receives RF telemetry from the external coil and converts the RF back into electric signals;
(b) an application-specific-internal-circuit (ASIC), receives data and power in the form of electric signals from the internal coil and generates appropriate electrical pulses for microelectrode stimulation;
(c) a 60-microelectrode epiretinal array covering a 20° field of vision, held in place by a retinal tack (see Fig. 1b).

The internal coil and ASCI are sealed in a protective hermetic casing, which is placed on the surface of the globe, while the 60-microelectrode array is the only portion of the device that is placed intra-ocularly. These two portions are connected via a cable that traverses the sclera. Surgically, the Argus® II device can be implanted using common vitreoretinal surgical techniques with a surgical time of ~2–3 h. It has also been shown that the device can be safely removed without any serious adverse effect.[18]

Data from the 30 patients implanted during the phase II clinical trial showed a good safety profile, including the demonstration that the Argus® II is safe for magnetic resonance imaging (MRI) up to the strength of 3-T in its switched-off state (without the external parts).[38] Three Argus® II patients have since undergone MRI brain scans for unrelated medical conditions, with no detrimental effects to the patients or to the device function.[39] Conjunctival erosion is the commonest complication experienced by the patients (10%) with all except one being treated satisfactorily by re-suturing. During the trial, one patient's device had to be explanted due to recurrent erosions and one patient developed retinal detachment which was successfully repaired. Two patients developed endophthalmitis but all were treated successfully with intra-vitreal antibiotics and the patients retained good functional use of their device. All the three patients were implanted early on in the trial and with amendment to the implantation protocol, none of the subsequent patients developed endophthalmitis.[18]

Twenty-eight patients underwent functional assessments and all reported reliable perception of phosphenes. Orientation and mobility functions were tested by following a white line on a dark floor, and locating a dark door on a white wall from the centre

of a room. Patients performed significantly better with the device switched on compared with the device switched off.[18] More than half of these patients (15/28) were also able to identify the direction of motion, as tested by showing them a high-contrast bar moving in varying directions on a flat LCD screen.[40]

In assessing visual discriminatory function, some of the patients were able to localize squares[41] or even discriminate different geometric shapes[42] when presented with high-contrast targets on a flat LCD screen, using the Argus® II device. More recently, da Cruz *et al.* published outcomes from 21 eligible subjects showing more accurate discrimination of large letters with device on compared with their native vision ($P < 0.001$). Four subjects were able to consistently read unrehearsed short words of up to four letters.[43] The best grating visual acuity is logMAR 1.8 (Snellen equivalent of 20/1262) from worse than logMAR 2.9 pre-op.[18]

Alpha-IMS: Retinal Implant AG, Reutlingen, Germany

The first generation of Retinal Implant AG devices were originally implanted in 11 subjects in 2005 as part of an acute clinical trial (Clinical Trials.gov NCT00515814).[44] It consisted of a 16 electrode array for direct electrical stimulation of the retina, as well as the light-sensitive photovoltaic MPDA. The implant was placed subretinally and powered externally by a percutaneous wire, which exited in the retro-auricular region of the subject as a connection plug. Although visual function improvement was demonstrated, the implant was removed from all the subjects after a few weeks as per protocol (except in one subject who declined removal) and no long-term durability data are available from the acute trial.[45] A second-generation device, the alpha-IMS, which features some design improvement, showed good safety profile with promising visual outcomes including the first demonstration of letter and word recognition in an implanted subject.[19,46]

A multi-centre phase II clinical trial with alpha-IMS has begun (www.clinicaltrials.gov, NCT01024803), with the ophthalmology department of the John Radcliffe Hospital at Oxford and King's College Hospital in London being amongst the trial centres. The alpha-IMS received its CE marking in July 2013.

The alpha-IMS, unlike the Argus® II, utilizes the subject's own eye to capture the images and hence does not have an external video camera. Structurally, the alpha-IMS is also made up of an internal part and an external part. The internal part (see Fig. 3a and b) consists of

(a) a subretinal photovoltaic silicon MPDA;
(b) an internal induction coil which is buried subdermally in the retro-auricular region;
(c) a silicone cable connecting the MPDA to the internal coil.

Within each MPDA, there are 1500 photosensitive pixel-generating elements; each photodiode is further connected to an independent titanium nitride microelectrode via an amplifier. The MPDA is designed to be inserted subretinally to allow reception of the visual images focused on to the retina by the front of the eye. Image conversion is achieved by light intensity-dependent generation of photocurrent by each photodiode, which is then amplified logarithmically before feeding into the associated microelectrode to stimulate the immediate retinal neurones.[19] Ideally, the 3 mm × 3 mm microchip implant should be placed sub-foveally or as close to the fovea as possible to allow optimal stimulation of the MPDA by the incoming light, resulting in a visual field of 11° × 11°. The silicone cable connecting the MPDA leaves the eye trans-choroidally to reach the lateral orbital rim, before tunnelling underneath the temporalis muscle in the sub-periosteal space to reach the retro-auricular region where it terminates in the internal coil (see Figure 3b). Electrical energy is generated by internal coil induction with an external coil, and subsequently used to amplify the MPDA-electrode system response.[47]

Due to the extensive extraocular path of the connecting silicone cable, surgical implantation of the alpha-IMS device requires a multi-disciplinary surgical team involving vitreoretinal, oculoplastics and ENT/maxillofacial surgeons. The entire procedure typically takes ~6–7 h and surgical removal is possible without serious complications.

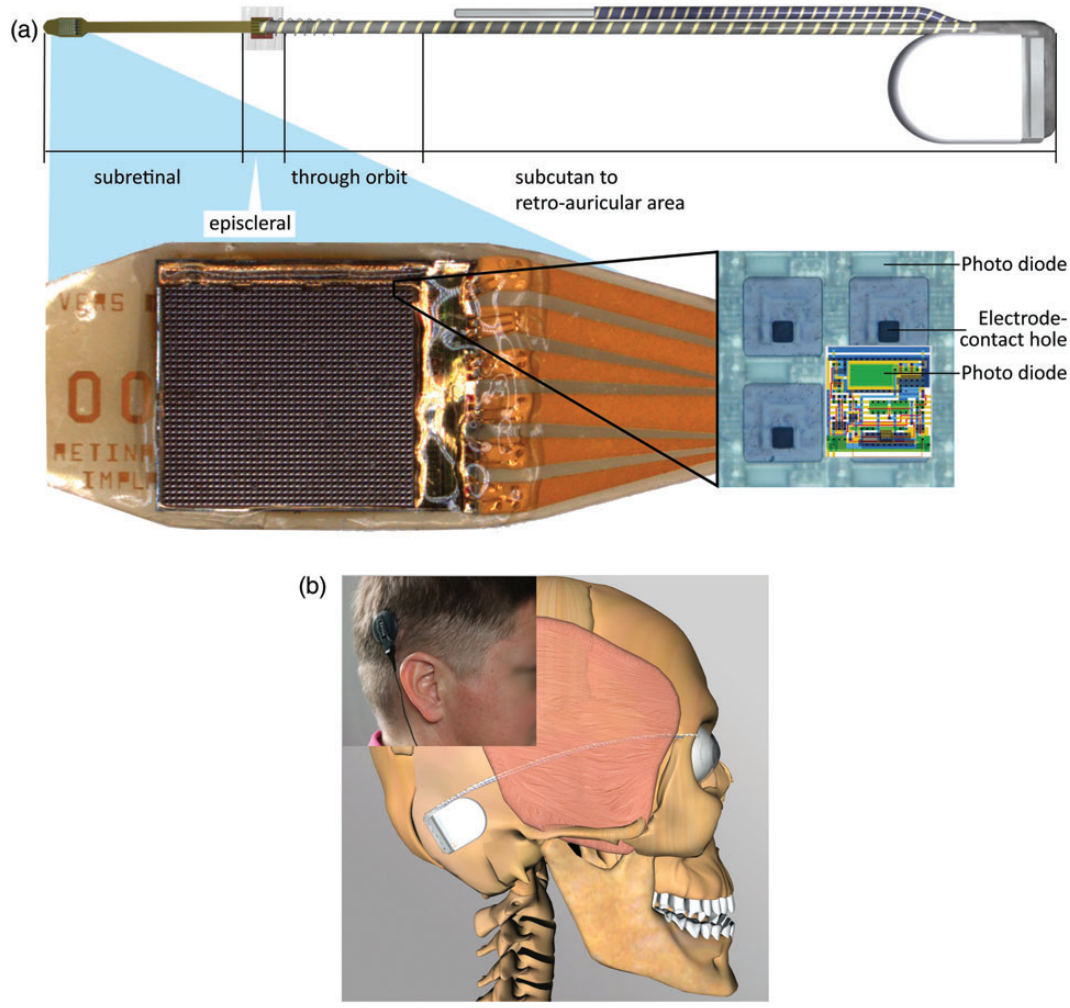

Fig. 3 (**a**) Photograph of the alpha-IMS implant, with a magnified view of the subretinal MPDA. The MPDA is a light-sensitive 3.0 mm × 3.1 mm CMOS chip with 1500 pixel-generating elements. Each pixel is composed of one photodiode, which feeds into one microelectrode via an amplifier. The wirings within the MPDA converge to form a foil, which exits the eye ball at its equator. The foil, encased in a silicone cable, continues through the orbit and courses subperiosteally (see b) as it traverses temporally, to end in the retro-auricular subcutaneous space as an internal coil (images reprinted with kind permission from Retina Implant AG, http://retinal-implant.de/en/doctors/technology/default.aspx). (**b**) Schematic drawing showing the subperiosteal course of the implant cable, from the orbit to the retro-auricular region, where it ends as the internal coil. The inset shows a photograph of an external coil held in place by magnetic attraction to the subdermal internal coil. The external coil supplies external electric power to the internal coil via RF telemetry (images modified and reprinted, with kind permission from Retina Implant AG, http://retinal-implant.de/en/doctors/technology/default.aspx).

Preliminary results on the performance of the first generation implant have been reported on three patients.[19] All the three subjects are able to respond to flash light reliably, discern orientations of moving gratings and recognize some objects such as cups or saucers on the table. One subject in particular was able to recognize geometric shapes and read large letters to formulate simple words. A possible explanation for his superior visual performance is that his MPDA is implanted sub-foveally, whereas the other two subjects' are located extra-foveally.

Stingl *et al.*[46] have since published a report on the first 10 patients implanted with the second-generation device, followed up for 3–9 months. Two adverse events were reported: one patient developed post-operative subretinal bleed with secondary intra-ocular pressure rise to 46 mmHg, which settled on medical treatment. The other patient suffered intra-operative optic nerve damage when the tip of the implant touched the optic nerve, resulting in no perception of light (NPL) vision post-operatively. Despite the adverse events, the visual outcomes have been favourable: three patients were able to recognize individual letters spontaneously when presented under high contrast conditions, with the best visual acuity reported to be logMAR 1.43 (Snellen visual acuity 20/546).

German consortiums: IRIS—IMI GmBH and Epi-Ret 3—Epi-Ret GmBH

IMI GmbH (founded in 2002) developed the IRIS (Intelligent Retinal Implant System), while Epi-Ret (founded in 1995) developed the Epi-Ret 3 implant. Similar to the Argus® II, both devices have an external unit consisting of an external video camera, portable processing unit and external coil and an internal unit consisting of the receiver internal coil, processing circuitry and an epiretinal stimulating electrode array.

A unique feature of IRIS is the 'learning algorithm' built into the processing system.[48] This feature allows the software to remember previous choices made during training concerning filters and other alterable parameters that are applicable in future use. In 2005, a 49-electrode system was implanted into four patients in an acute clinical trial and they were able to discern simple lines and spots, as well as detect horizontal movements.[49] In 2007, a multi-centre clinical trial commenced (www.clinicaltrials.gov, NCT00427180). In this trial, a 61-electrode prototype system (IRIS) was being implanted into RP patients, with a visual field of up to 40°.[21] The 4-month outcome of a patient who received the IRIS implant was published as an abstract in the 2009 European Association for Vision and Eye Research Conference, in which the patient reported reliable visual percepts with stimulation.

The Epi-Ret 3 is the third generation device by Epi-Ret GmH. The main difference between Epi-Ret 3 and other video glasses devices is that the internal coil and ASIC hermetic case are packaged into a compact disc form similar in dimension to that of an intra-ocular lens and inserted into the capsular bag.[50] The acute trial of EPI-RET 3 was carried out in 2007 in which six patients were implanted with the device for 4 weeks. All the patients reported phosphene phenomena such as dots, arcs or lines.[51]

Other retinal prosthetic systems

Other groups that have been involved in the development of prosthetic vision include the Optobionic Corporation (by Dr Alan Chow) who developed the artificial silicon retina.[52] These silicon wafer discs were 2 mm in diameter and 25 μm thick, containing 5000 photodiodes each, and were designed for subretinal implantation. Unfortunately, the silicon photodiodes alone were unable to generate adequate electric currents to activate the overlying bipolar cells.[24]

The Boston Retinal Implant Project (established in 1980s) initially worked on an epiretinal system using an external video camera for image capture, external computer image processing and direct stimulation of the retina with epiretinally implanted microelectrode array. The group's early pioneering work on establishing safety threshold for micro-stimulation and on biocompatibility and hermetic sealing of the implant materials have been invaluable for the development of future generations of retinal prostheses.[53,54]

Ongoing retinal prosthesis projects

Most recently, a group of researchers formed the Bionic Vision Australia consortium in March 2010 after receiving a major grant from the Australian Research Council in December 2009. The project led by Professor Anthony Burkitt aims to develop two different types of retinal prostheses:

(a) a wide-view device containing 98 electrodes to improve field of vision for navigation;[55]
(b) a high-acuity device containing 1024 electrodes for detailed central vision.[56]

Developments of both devices are still in their infancy with their first prototype containing 24 electrodes being implanted in September 2012.

Areas of controversy

Current retinal prostheses can be grossly divided into those that use an external apparatus for image capture (e.g. Argus® II) versus those that utilize the patient's own optical focusing system (e.g. alpha-IMS). One of the main criticisms of using an external imaging system is that image capturing occurs independently of eye position. Normal localization of an object in visual space is dependent on the retinotopic position of the target relative to the position of the subject's eye and head. As such hand eye co-ordination could theoretically be limited. Although this may initially be an issue, there is evidence that Argus® II subjects showed functional improvement in orientation and mobility,[18] as well as their ability to localize squares by pointing on the LCD flat screen, with the use of the device.[41]

Conversely, the use of an external image capture and processing system may bypass the loss of intra-retinal processing due to intra-retinal neural remodelling in these patients with end-stage RP.[57] Neural remodelling could pose a potentially serious problem for the intrinsic image-capturing system, as it relies on the integrity of the residual intrinsic retinal network for image processing.

A great challenge with the artificial vision offered by the retinal prostheses is the problem of image persistence. At present, even though the Argus® II retinal prosthesis reliably produces phosphenes in response to visual stimuli, the perceived image may fade quickly in a matter of seconds. For a subject to continuingly 'see' an object, he/she may need to 'refresh' the images captured by the video camera by shaking his/her head, so as to reproduce the phosphenes. As human eyes naturally undergo constant micro-saccades even when fixating on an object, these micro-movements may provide a means of constantly refreshing the visual stimuli to provide constant phosphene perception in an intrinsic image-capturing system (e.g. alpha-IMS). However, it is interesting to note that two of the Argus® II patients perceive constant images without having to consciously shake their heads.[58] It is possible that these two patients have retained greater number of the W- or X-type of retinal ganglion cells, which have been shown to give sustained responses to light stimuli.

A final area of contention is over the optimal placement of the prostheses, i.e. subretinal versus epiretinal. The advantage of subretinal implants may be the direct stimulation of bipolar cells as photoreceptors naturally do. This may allow natural image processing within the retina prior to ganglion cell activation. However, as previously discussed, current generation of subretinal electrodes are in the order of tens of micrometres (μm) in diameter and would not stimulate individual bipolar cells. Furthermore, Chen *et al.*[59] suggested that the electrical field from the microelectrode stimulation spreads through the entire retina, stimulating both bipolar and ganglion cells, rendering the position of the stimulating array irrelevant, whether epiretinal or subretinal.

Areas for future developments

Over the past two decades, the development of retinal prostheses has come a long way to achieve the bio-stability and safety that is required for the integration of an electronic system into humans. The next goal would be to improve the quality of vision. To achieve this, improvement on all the following three aspects are necessary:

(a) Improve the visual acuity by achieving specific, focal activation of retinal ganglion cells.
(b) Improve the visual field by increasing the area of retina we can activate safely without tissue damage.
(c) Improve our understanding of intra-retinal visual processing circuitry so that we could eventually formulate an accurate encoding system to convert the high quality of images we capture with video cameras today into neurologically meaningful signals for our visual cortex interpretation.

Conclusion

After decades of research, the dream of producing a bionic eye to provide artificial vision for blind patients has finally been realized. Two separate

devices have received CE marking in Europe: the Argus® II system in March 2011 and alpha-IMS in July 2013. The Argus® II also received FDA approval in February 2013. The transition from research project to proof-of-concept studies and final regulatory clinical trials has opened a completely new area of retinal therapy, and given patients with profound vision loss due to RP a treatment for the first time. It is likely that the technology will improve, with the number of patients that may benefit increase with time, leading to further hope for those who are currently untreatable.

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