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The Argus II Retinal Prosthesis System

Edward Bloch and Lyndon da Cruz

Abstract

The field of retinal prosthetics has seen significant advances in the past 3 decades. Encouraging results from different groups have shown coarse objective functional improvement, using a range of technological and surgical approaches. The Argus II retinal prosthesis system was the first of its kind to receive regulatory approval for commercial use in Europe and the USA. The device is designed to replicate the function of photoreceptors in converting visual information into electrical neural signals in patients with profound visual loss secondary to degenerative retinal disease. Results from a phase II study of 30 patients have demonstrated improved performance in basic tests of visual function, object recognition, letter reading, prehension, orientation and mobility tasks. It is now the most widely implanted retinal prosthetic device worldwide. This chapter provides an overview of the requirements of a retinal prosthetic system, the results from the Argus II device to date, and an insight into some of the challenges and future directions of visually restorative therapies.

Keywords: retinal prosthesis, Argus II, artificial vision

1. Introduction

Retinal diseases, including both inherited and acquired conditions, are a major cause of blindness. In 2010, the WHO estimated that 285 million people in the world were visually impaired from all causes [1]. Hereditary retinal disease represents another significant contributor to unavoidable worldwide blindness, with conditions such as retinitis pigmentosa (RP) affecting an estimated 1/4000 people, or 0.025% of the population, often of working age [2]. Representing a heterogeneous group of inherited diseases, RP affects the rod and cone photoreceptors (PRs), causing progressive, profound visual impairment, but with relative preservation of the inner retinal architecture [3]. This anatomical region consists of retinal ganglion cells (RGCs) and their nerve axons, which transmit visual information to the brain, along with other regulatory interneurons, such as bipolar, amacrine and horizontal cells, and Müller support cells (**Figure 1**). Preservation of these structures and the associated retinotopic map has led to RP becoming a model for many forms of visual restorative therapy, in particular, retinal prosthetics.

Another significant retinal cause of blindness is age-related macular degeneration (AMD), accounting for 5% globally [1]. It has been projected that, by 2040, this condition alone will affect 288 million people, 3.25% of the predicted global population [4, 5]. Late AMD comprises geographic atrophy (dry) and neovascular (wet) AMD, and is a significant cause of morbidity in the western world, with a

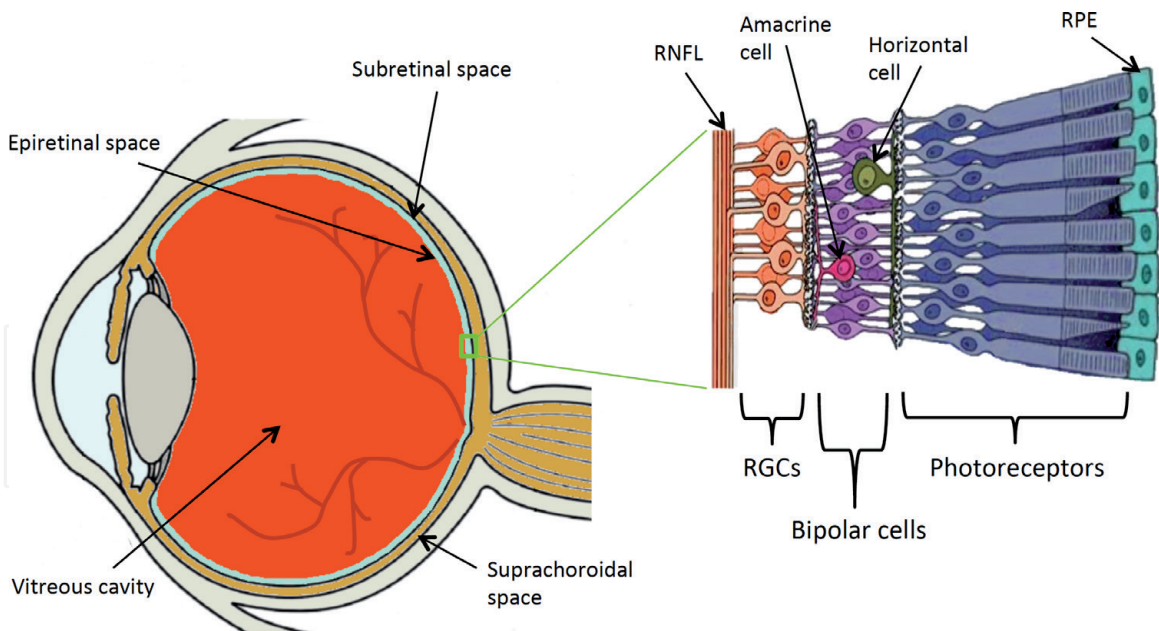


Figure 1.

A schematic demonstrating the anatomy of the eye and organization of the retina. RNFL: retinal nerve fibre layer; RGCs: retinal ganglion cells; RPE: retinal pigment epithelium.

prevalence of 2.4% in the UK [6, 7]. While anti-VEGF treatment has revolutionized the treatment of wet AMD, there is currently no treatment for the dry subtype, which results in degeneration of the PR layer and impairment of central vision in 1.3% of the UK population [7].

The concept of retinal prosthetics is centred on the phenomenon of electrically induced subjective visual percepts or ‘phosphenes’. These phosphenes have been elicited by applying electrical currents across the ocular surface since as long ago as the eighteenth century. In the early twentieth century, Förster demonstrated that phosphenes could be elicited in blind patients via direct stimulation of the visual cortex, leading, in 1968, to the first chronic implantation of an intracranial visual prosthesis [8, 9]. In the 1980s, advances in microfabrication, materials engineering and retinal surgery provided a fecund environment for emergence of the field of retinal prosthetics—devices that could deliver direct stimulation to the residual retinal neurons.

2. Principles of natural vision

In order to create a *retinal* prosthesis, it is necessary to account for the processes that take place within the human eye, where light is absorbed, converted to an electrical impulse and encoded into a neural signal. Physiological capture of the visual scene occurs via the natural optical system, comprising the cornea, iris and crystalline lens, which focus light onto the photosensitive retinal cells. Within the photosensitive rods and cones, a photochemical reaction leads to transduction of light into a graded electrical neural signal with eventual RGC stimulation. The axons of the RGCs constitute the optic nerve. In the native retina, a significant amount of information compression occurs at the level the PRs, the interneurons and the RGCs, from where it is encoded for transmission via the optic nerve to the midbrain and cortical visual pathways.

There are two types of PR, rod and cone cells, which number ~120 and 6 million respectively in each eye, resulting in an average input of 100 photoreceptors to each of 1.5 million RGCs [10, 11]. Rods are sensitive to low levels of light and are most

populous at about 20° eccentricity. The cone cells are responsible for colour vision and function best in bright light. They are most densely concentrated in the foveal region where they are in almost 1:1 ratio with RGCs, beyond which they decline considerably in density [12].

Following the transduction of photic energy into electrical impulses, bipolar cells effectively transmit the information from PRs to RGCs, but may have an excitatory (ON) or inhibitory (OFF) response to hyperpolarisation and are also influenced by the actions of horizontal and amacrine cells, which can introduce lateral inhibition of signals. Each RGC has a centre-surround receptive field organization and its stimulation pattern will depend both on the size of its receptive field, the input stimulation frequency, and whether it is an 'on-centre' or 'off-centre' cell. Furthermore, RGCs are not functionally homogeneous, with certain cell populations specialized in particular functions and projecting to specific midbrain regions. Most of the 1 million nerve axons of the RGCs pass via the optic nerve to their respective lateral geniculate nucleus (LGN), located within the thalamus. The LGN is a layered structure and each part receives axons from specific ganglion cell types. A degree of visual processing is thought to occur at this point, before projecting on towards the primary visual cortex, where all higher cognitive processing takes place [12].

The processing power of the retina enables us to resolve detail with remarkably high spatial and temporal resolution, across a broad spectrum of contrast and colour. Beyond this, higher neuro-cortical integration allows us to process and recognize objects, words and faces, appreciate distance, orientation and movement, while coordinating our visual interpretations with other sensory inputs and motor outputs. Together this information allows us to decide what is safe or dangerous, fast or slow, attractive or repulsive. All this activity occurs in milliseconds, with a seemingly infinite refresh rate. This phenomenon is reliant on a very complex system that can rapidly capture, assimilate, compress and process an enormous amount of visual information.

Clearly, creating a micro-electronic system, which can come close to replicating the processing capacity of the human visual system, is currently an unrealistic goal. Instead, we must focus on how visual processing software and hardware engineering can be combined to produce a device that can resolve the minimum interpretable visual information such as to be beneficial to patients with profound vision loss.

Simulated prosthetic vision (SPV) studies have been undertaken to try and estimate the optimum spatiotemporal image processing techniques for specific task completion, as well as the basic hardware requirements to best deliver RGC stimulation patterns [13–17]. SPV studies have extensively investigated the spatial resolution, visual field and contrast required for assorted activities of daily living, concluding that a minimum resolution of ~600–1000 pixels over a visual field 15° × 15° can permit reasonable accuracy in manipulation, recognition, orientation and mobility tasks. The resolution of around 3 pixels/degree² is similar to that in some currently available photovoltaic retinal prosthetic systems while fields of at least 15° × 15° have been created. However, and disappointingly, there remains a mismatch in the functional aptitude demonstrated by subjects in SPV studies and that in recipients of visual prostheses. This suggests that other factors, such as the effects of behavioural adaptation, perceptual learning and cortical plasticity, as well as the loss of the intrinsic retinal processing capacity, could be critical requisites in the development of a visual restorative system that could deliver appreciable functional value [18, 19].

One of the advantages of a *retinal* prosthesis is that, by placing a device at the most distal part of a non-functioning visual system, it is possible to benefit from any residual downstream neuronal organization within the retina and visual

pathways. However this theory relies on the assumption that the proximal visual system remains intact. It has been demonstrated that outer retinal degenerative disease results in a cascade of reorganization and remodelling within the retina and central nervous system, even taking place before there is clinical evidence of PR loss [20–24]. A stepwise deterioration culminates in extensive neuronal cell migration, rewiring and death, accompanied by glial hypertrophy and retinal remodelling, rendering the retina incapable of processing or encoding visual data. This neuronal plasticity carries implications for all forms of visually restorative therapy, but particularly for prostheses, which are currently introduced at a late stage of visual impairment, where there has already been widespread reorganization with limited scope for rescuing vision. However, it may be that future iterations of bionic devices could even be introduced earlier in the disease process in an attempt to halt or reverse the remodelling process.

Another matter that remains unclear is the extent to which the human brain undergoes reorganization following loss of visual sensory input. Both animal and human studies have shown that there is the capacity for neuroplasticity as a functional adaptation to loss of a sensory modality [25–27]. For example, visual cortical activity has been demonstrated in blind subjects while reading Braille [28, 29]. Other studies of patients undergoing cochlear implant surgery, have shown correlation between the pre-operative auditory organization and activation and subsequent success of the neuroprosthesis [30, 31]. If a method could be developed by which a patient could be assessed for the feasibility of generating interpretable phosphenes, this would enhance patient selection and thus outcomes in this area of visual restoration. Further understanding of the nature of cortical plasticity in sensory loss and how subjects can adapt to a new form of vision with perceptual learning and rehabilitation, is sure to enhance the beneficial effect of visual restorative treatments in the future.

3. Principles of prosthetic vision

In order to simulate the complex series of events that take place between the outside world and the visual cortex, a prosthesis system needs to perform a specific sequence of actions, namely image capture, processing of the image, delivery of both image data and signal amplification to the microelectrode array, which in turn must deliver a suitable stimulation current (directly or indirectly) to the RGCs. All this must take place with a biocompatible system that can produce adequate stimulation currents without causing degradation to itself or to the target tissue. Furthermore, the device needs to be straightforward to implant, modify or explant, while remaining portable, discreet and fashionable.

3.1 Image capture

Presently, there are two principal means of ‘image capture’ that have found some success in retinal prosthetic systems. The first is to capture information from the visual scene using an external video camera, which is usually glasses-mounted. The video camera then transmits data directly to an external video-processing unit (VPU). The advantage of this approach is not only that it is technically simpler, but also it avoids any impediments to collecting high quality information about the visual scene, thus facilitating any downstream image processing. However, due to the fixed camera position, there is a risk of discrepancy between its orientation and that of the eye, risking inaccuracies in the perceived spatial location of an object of interest following retinal stimulation. Proposed

solutions to this problem include both the incorporation of an eye tracker to coordinate the direction of gaze with the stimulation pattern, or placement of the camera system intraocularly, for which there have been some preliminary attempts to design such a system [32].

The second image capture system that has shown promise is the photodiode array device. First developed by the Chow brothers as the artificial silicon retina (ASR), this comprises a passive microphotodiode array, which was intended to intrinsically transform ambient light that falls on it into an electrical current capable of stimulating retinal neurons. The ASR array consists of 5000 interconnected photodiode anodes with individual isolated cathodes, each with an iridium oxide electrode. This method was advantageous in as far as it allowed a large number of pixels to be stimulated simultaneously, it was wireless and also it allowed for precise coordination between the eye position and the projected visual scene [33, 34]. However, in its first iteration, it was unable to deliver sufficient stimulation current to deliver functional results and the parent company, *Optobionics*, has since closed down. Despite this initial failure, the concept of the photovoltaic array has been taken up and developed by other groups, with encouraging results. The *Retina Implant AG* group developed the Alpha IMS device that contains 1500 independent and autonomous photodiode-amplifier-electrode units. The ambient light creates the stimulation pattern and an external power source amplifies the electrical signal [35, 36]. The 'PRIMA' Photovoltaic Retinal Implant system (*Pixium Vision S.A.*) combines aspects of both forms of image capture, in that it uses an external camera to capture the visual information before processing and then transmitting the data as pulsed near-infrared light patterns from a specialized visual interface in a pair of glasses directly onto a subretinal photovoltaic array [37, 38].

3.2 Image processing

In some systems, the image processing takes place within an external analyser, which receives a high-quality signal from a camera system and transforms the data into a set of commands to be wirelessly transmitted to the microelectrode array to generate a specific stimulation pattern. In systems such as the Argus II retinal prosthesis, there are only 60 microelectrodes, meaning that even with perfect electrode contact and accurate retinotopic phosphene perception, the image resolution would still be low. As such, there is an emphasis on developing software algorithms that can filter the most relevant parts of a visual scene, before creating simple stimulation configurations that map the object of interest onto the array. This process is known as saliency mapping, and similar algorithmic methods of rapid recognition and segmentation of information have previously been used with success in the form of speech processors for cochlear implants [39–42].

Simulation studies have shown that by applying transformations, such as edge detection, greyscale histogram equalization, intensity and contrast enhancement, task performance using a low resolution viewing system can be improved (**Figure 2**). Similarly, software has been developed to allow magnification of areas of interest in the visual scene, or even projection of a simulated object or face onto the array, in response to detection of the respective entity in the captured environment [43, 44]. The intelligent retinal implant system (IRIS) II (*Pixium Vision S.A.*) has a 'neuromorphic image sensor', which is designed to capture the coordinates and intensities of changing pixels, the information from which can be encoded and divided into transient and sustained components. This can be used to direct image processing towards the most relevant parts of the visual scene, i.e. moving people or vehicles, while removing redundant excess visual information [45].

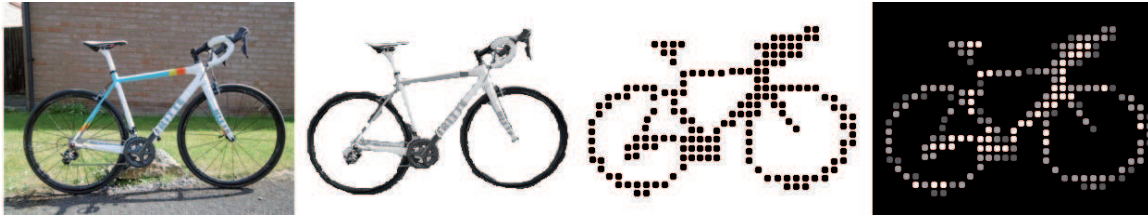


Figure 2.

An example of image processing transformations: the image of the bicycle first undergoes edge detection and is converted to greyscale. This is then transformed by circular binarisation into a black-and-white pixelated format. Finally the image is inverted, with the addition of four greyscale levels.

All these types of pre-processing are relevant for devices that do not have intrinsic photosensitivity, but instead rely on external image capture systems. In the case of the photovoltaic systems, there is a greater spatial resolution due to the high density of photodiode-amplifier-electrode units, each of which acts as an independent pixel. In theory, this enables greater intrinsic processing through more localized neuronal stimulation and may also incorporate some downstream processing from the residual retina to select and transmit the most salient visual information to the brain [46, 47].

3.3 Data and power transmission

Delivery of encoded visual information and power to the microelectrode array is generally either wireless (via inductively coupled coils) or directly onto the microphotodiode array via the natural optical system of the eye. In variations of the former approach, there are several considerations that need to be made. Inductive coil systems function through radio-frequency telemetry, whereby an AC current passing through the external coil induces an AC voltage in the internal coil, which can be subsequently be converted into DC power. A capacitor in series with the secondary coil permits amplification of the received voltage by creating a tuned resonance at the transmitter frequency, thus supporting efficient power transfer while minimizing the body's exposure to radiation. Although the data may be encoded onto the same signal as the power, it is more commonly accomplished with greater effect by using a separate, high frequency coil. The capacity for data and power transfer using this model is sufficient to support the resolution and refresh rate of current systems [48].

Location is an important consideration for an efficient inductive coil system. Many systems utilize a coil system that is similar to that of cochlear implants, with an electronics unit fixed to the bone postauricularly, which communicates with the retinal array via a tunnelled connecting wire. This approach was initially chosen due to the surgical familiarity to otolaryngologists and it allows for good coil contact for coupling. However, due to the prolonged duration of surgery, complex fabrication challenges and apparent reduction in system longevity, some systems have since been modified to incorporate a glasses-mounted transmitting coil which transmits to an implanted subconjunctival receiving coil, which is connected to the array via a sclerotomy. Another approach, as used in the EPI-RET3 implant, involves positioning a receiver coil into the lens capsular bag (following removal of the native lens). This approach still relies on an inductive power and data link, but negates the need for a transscleral wire, which carries a risk of infection and erosion. In addition, this system has a bi-directional enhancement system, which allows for simultaneous stimulation of and recording from the microelectrodes. Feedback from the system enables modification of the stimulation algorithms and patterns to accommodate any residual excitatory and inhibitory signal processing of the retinal neurons [49, 50].

3.4 Microelectrode array stimulation

There are several considerations when designing an electrode array to deliver electrical currents to the RGCs in order to replicate the spatial resolution (SR) of the natural retina. These include the electrode material, size, shape, spacing (pitch), tissue contact and the anatomical position of the array.

There are three primary sites for placement of a retinal stimulating microelectrode array (**Figure 1**): epiretinally (i.e. on the surface of the neurosensory retina), subretinally (i.e. between the retinal pigment epithelium and the degenerated outer retina) or suprachoroidally (i.e. between the sclera and the choroid). The advantage of the epiretinal placement is that the surgical approach is more familiar to vitreoretinal surgeons, allowing safer and easier implantation, adjustment and removal of devices. Furthermore, the interface with the vitreous cavity seems to permit safer heat dispersion. This set-up may be disadvantageous due to the fact that, in order to stimulate the RGCs, the stimulating current must pass through the retinal nerve fibre layer, which may produce ectopic visual percepts elsewhere in the retinotopic map.

In terms of a subretinal system, one proposed advantage is that by mimicking the position of the PRs in the natural retina, some of the stimulating current will pass via the residual bipolar system, exploiting graded response of the inner retinal neurons and thus the natural processing power of the retina. Moreover, it is felt that better electrode-tissue contact will be achieved with the subretinal than with the epiretinal approach. However, it has been noted that, due to underlying degenerative changes, surgical implantation can be difficult, and the longevity of these devices can be more limited [51].

Finally, suprachoroidal devices require a less invasive surgical procedure, which lends itself to easier repair or removal, but trials to date have been complicated by subchoroidal haemorrhage and fibrosis [52]. Due to the distance from the RGCs, these systems tend to require higher stimulation thresholds, leading to greater current dispersion and lowering the achievable SR. Overall, it seems that epiretinal and subretinal approaches have a superior performance in safety and efficacy to suprachoroidal implants. However, with pros and cons to both approaches, there is currently no clear evidence to suggest that, of these latter two, one system offers an overall advantage.

The challenge of electrode size and density is primarily a biological one, in as far as the native PR cells change in type, size, density and downstream signalling depending on their role and location in the retina. For example, cone PRs are, on average 6 μm in diameter, but in the centre of the fovea, they are around 1.5 μm in diameter and densely packed to permit the high resolution of vision that humans usually enjoy [53]. If we consider that normal vision is 20/20, meaning that the minimal angle of resolution at the retina is 1 arcminute, or the spatial frequency (SF) is 60 cycles per degree (cpd), then the SF required to achieve 20/200 (the approximate level of visual impairment) is 6 cpd. Since each degree angle subtended at the human retina is represented by $\sim 280 \mu\text{m}$, a SF of 6 cpd would necessitate a maximum pixel size of about 50 μm and, in turn an electrode size and pitch of 25 μm [54, 55]. Therefore, before factors such as electrode contact, dissipation of electrical current or heat are even considered, there is a significant theoretical constraint on the scale of manufacturing required to achieve a resolution corresponding to a visual acuity of 20/200.

Among the smallest electrodes that have undergone human implantation to date are those of the alpha IMS, which are $\sim 50 \mu\text{m}$ in diameter, with a 70 μm spacing, giving a theoretical maximum VA of about 20/250 [36]. Results have been reported of a grating VA of 3.3 cpd and optotype recognition acuity of 20/546 using this

device [56]. The Argus II device has 200 μm electrodes separated by 525 μm , which suggests a theoretical maximum VA of 20/1600. The best result, with grating acuity, has been reported as 20/1262 (just over 1 cpd) with this system [57].

Electrode shape is a factor that may significantly affect the integration of the device by creating an environment where retinal tissue can migrate around the array and create a close interface. Arrays have been designed with sunken chambers or 'wells', into which the inner nuclear layer cells have been shown to migrate. Another approach is the three-dimensional pillar array, with protruding electrodes, designed to produce an intimate apposition between the array and the neuronal cell bodies without requiring excessive remodelling of the retina [58].

Size, shape and contact of the electrode at the tissue interface are all important considerations to improve SR, but also have implications to the charge density per unit area. As the electrode size becomes smaller, there is an exponential increase in concentration of the current, which can result in target tissue damage [59]. Therefore there is an onus on finding materials that can permit the charge-injection requirements of neural stimulation, while minimizing conduction of heat or inducing tissue degradation. In addition to this, they must be biocompatible, waterproof and remain operational over an extended lifespan. While the precise electrochemical properties of the electrode-electrolyte interface, the capacitance and charge injection limits of different electrode materials is beyond the scope of this chapter, it is worth noting that new technologies, such as nanocoating, nanotubes and conductive polymers are providing promising developments in electrode fabrication, which may offer significant advantages over the more traditional metallic designs, such as iridium, platinum or titanium-based electrodes [60–62]. The emerging field of tissue electronics, which is focused on the use of organic conductive and semi-conductive polymer alternatives to inorganic electronic systems, is rapidly advancing. Recently, long-term *in vivo* studies of a fully organic multi-layer device in rats have shown success in recovery of subcortical and cortical light responses, as well as improvements in visual behaviour [63, 64]. While current electrode devices achieve RGC stimulation by direct current injection to trigger action potentials, it appears that organic coupling occurs in a more physiological manner by modulating local neuronal neurotransmitter release through discretely varying the membrane potentials [65]. It is probable that approaches using conductive polymers, or other chemical photoswitches (e.g. photochromic molecules or photoactive nanoparticles) permit a more natural interaction with the residual neuronal environment, which, in theory, could achieve cellular resolution.

4. Argus II retinal prosthesis system

The Argus II epiretinal device (*Second Sight Medical Products Inc.*) was the first retinal prosthetic system to obtain CE marking (2011) and FDA approval (2013) for commercial use, and is the most widely implanted retinal prosthetic worldwide. Comprising external and implantable components, it utilizes camera-based image capture and VPU processing, with wireless data and power induction, transmitting stimulation commands to an epiretinally located microelectrode array (**Figure 3**).

The Argus II system is implanted using standard pars plana vitrectomy and scleral buckling procedures, and usually the surgery includes removal of the native lens. Following removal of the vitreous and posterior hyaloid face, a conjunctival peritomy is performed and the recti muscles are isolated to allow fixation of an encircling band containing the internal coil and in-built application-specific integrated circuit. A 5 mm sclerotomy is created for insertion of the 60-microelectrode

array and the connecting cable. This lies flush on the epiretinal surface and is secured in place using a spring-loaded titanium tack (Figure 4). A scleral allograft (or similar alternative) covers the hermetically-sealed coil and electronics case, which is then re-covered by Tenon's capsule and conjunctiva, such that the internal components are invisible to the casual observer. To use the device, the external components are worn, including a glasses-mounted camera and external coil, and a portable VPU and power unit [57].

4.1 Development history

Throughout the 1990s, Humayun demonstrated that low current stimulation of dissected animal retinal tissue could produce localized retinal responses [66]. This was followed by acute epiretinal stimulation experiments of blind human volunteers, with various forms of retinal degeneration. It was shown that stimulation could elicit subjective phosphenes, which in many cases could be accurately

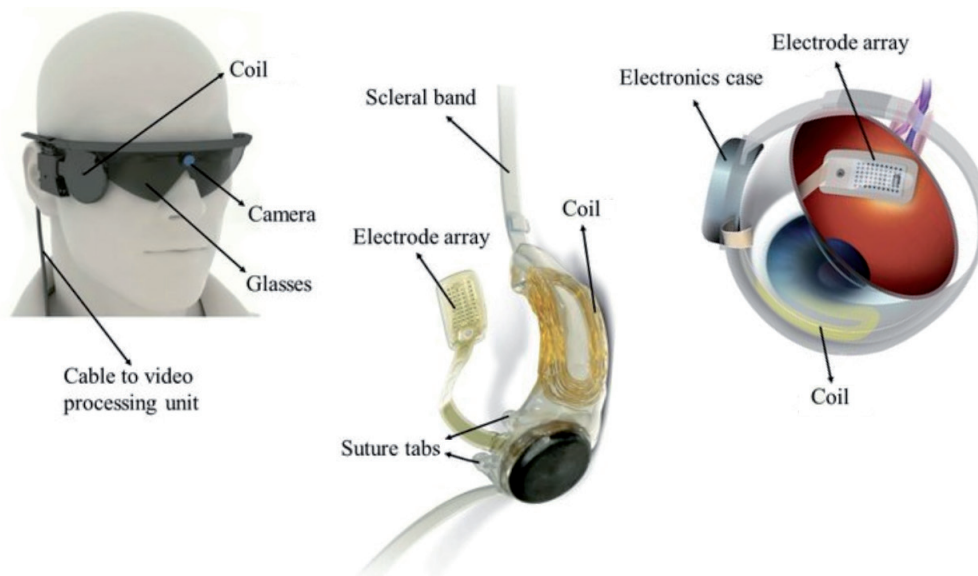


Figure 3.
The components of the Argus II retinal prosthesis system (adapted with permission from Second Sight Medical Products).

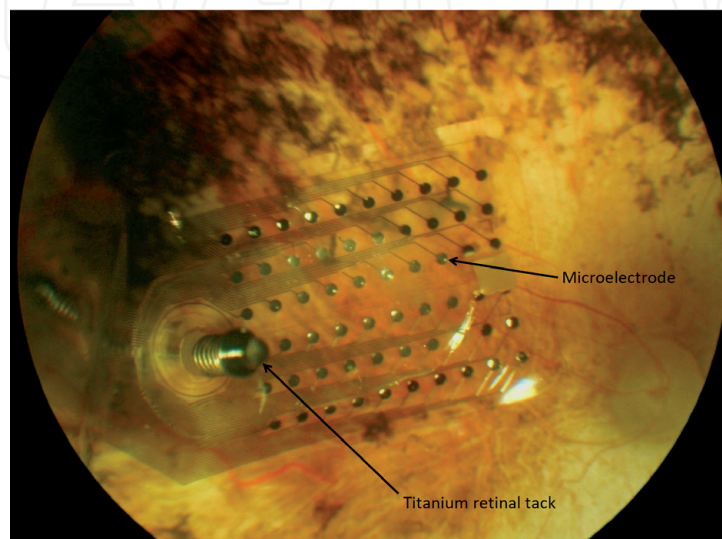


Figure 4.
Fundus photograph demonstrating an Argus II microelectrode array in situ.

localized and resolved to an equivalent acuity of up to 4/200 [67, 68]. In a subsequent series of acute stimulation tests using multielectrode arrays, two patients were able to identify crude forms from discrete patterns of electrical stimulation, using 400 μm electrodes arranged in 3×3 or 5×5 grids.

These promising results led to the development of the Argus I epiretinal prosthesis, which was the first device to undergo chronic testing in 2002 in six patients with end-stage RP. The Argus I device included a 4×4 array, comprising 16 alternating 250 and 500 μm diameter electrodes. The initial device design was based closely on that of cochlear implants, with an electronic unit surgically positioned in a postauricular recess of the temporal bone, from where a connecting cable would be passed along a groove in the bone and communicate with the intraocularly placed array. The external camera and VPU components captured the images, which, once encoded, were wirelessly transmitted via an antenna, that was magnetically held in position over the internal electronic unit. Results showed coarse functional performance was better than chance with the device on, with one patient able to detect light, motion and simple shapes [69–71]. In another subject, it was recently shown that the device continued to elicit phosphenes sufficient to permit target localization, orientation and mobility performance better than chance with the device on, 10 years postimplantation [72]. The overall safety and longevity of the device, which demonstrated coarse functional outcomes at a safe charge density limit, led to the development of the Argus II system, with a 6×10 microelectrode array and an optimized surgical approach.

4.2 Argus II results

The phase II multicenter clinical trial for the Argus II retinal prosthesis system began in 2006, enrolling 28 patients with end-stage RP, one with Leber congenital amaurosis and one with choroideremia. The primary endpoints of this study were safety and visual function, while secondary assessments of functionality included activities of daily living, such as orientation and mobility [57, 73, 74].

4.3 Safety outcomes

Within 12 months of the start of the trial, there were 18 reported serious adverse events (SAEs) requiring intervention, occurring in 10 of the 30 implanted patients. These included three cases of presumed endophthalmitis, three cases of conjunctival dehiscence, three cases of conjunctival erosion, two cases of hypotony, two arrays requiring re-tacking and one case each of rhegmatogenous retinal detachment, tractional retinal detachment, a retinal tear, corneal opacification and an inflammatory uveitis. The majority of these SAEs (78%) took place within the first 6 months after implantation and they were clustered among the initial 15 patients (72%). The reduction in SAEs in the second half of the trial was ascribed to refinement of both the device and the implantation procedure during the study, such as inclusion of prophylactic intravitreal antibiotics to the surgical protocol. All SAEs were successfully treated; in the cases of hypotony, the subjects required silicone oil tamponade (in one case for retinal detachment), which led to stabilization of the intraocular pressure [57, 73].

At 36 months, there were five additional reported late SAEs, including two further cases of hypotony and one each of infective keratitis, corneal melt and conjunctival erosion. Within this period, only one device required explantation, due to recurrent conjunctival erosion, and no eyes were enucleated [73]. At 5 years, the latest reported time point, there was only one additional SAE, which was a successfully treated retinal detachment, resulting in a total rate of 24 reported

SAEs among 12 (40%) of subjects. A total of three devices have been partially or completely removed at the request of the subjects, while a further seven subjects underwent elective repositioning during the trial to improve the contact of the array with the retina [74].

Overall, this is the largest and longest study of a retinal prosthesis system to date, demonstrating an acceptable safety profile and ongoing functionality and biocompatibility in the majority of subjects. Subsequent case series have shown improved safety profiles in parallel with growing surgical familiarity.

4.4 Functional outcomes

4.4.1 Visual function

There were three objective assessments used to evaluate visual function in the study. Firstly, a ‘square localization’ task, which involved the subject locating a white square displayed on a black background, indicated by touching the monitor. At 1 year, 94% of subjects could perform the task better with the device on than off. This was maintained at 3 years (89%) and 5 years (80.9%). The second task was ‘direction of motion’, which was assessed by asking the subject to indicate the direction of a high-contrast white line as it moved across the monitor. Initially 57% of subjects performed better than chance with the device on, which was once again maintained at 3 and 5 years (56 and 50%), respectively. Of note, these two tests of visual function were not performed in all subjects at the 1-year time point, due to their introduction partway through the study. Finally visual function was assessed using, ‘grating visual acuity’, which consisted of randomly generated widths of black and white gratings in one of four different orientations, displayed for 5 s on a screen. Throughout the study, 27–48% of patients scored better than 2.9 logMAR equivalent (mean 2.5 logMAR), depending on time point, with 38% performing significantly better with the device on than off at year 5. The best result recorded grating acuity was 1.8 logMAR, which approximates to a Snellen acuity of 20/1262 [57, 73–75]. The results from these tests of visual function are presented in **Figure 5**.

Dorn et al. tested the effect of providing scrambled spatial information to the device compared to one-to-one mapping, to investigate the degree to which the synchronization of multiple electrode stimulation conferred a benefit during motion detection. They found that of the 15 subjects who were able to perform the initial motion detection task better with the device on, 10 (67%) also performed better with one-to-one mapping of spatial information, than with scrambled information [76]. This suggests that the pattern of phosphenes being elicited was important for motion detection, and not that the patient was using the device to detect light, and simply scanning with their head to determine direction.

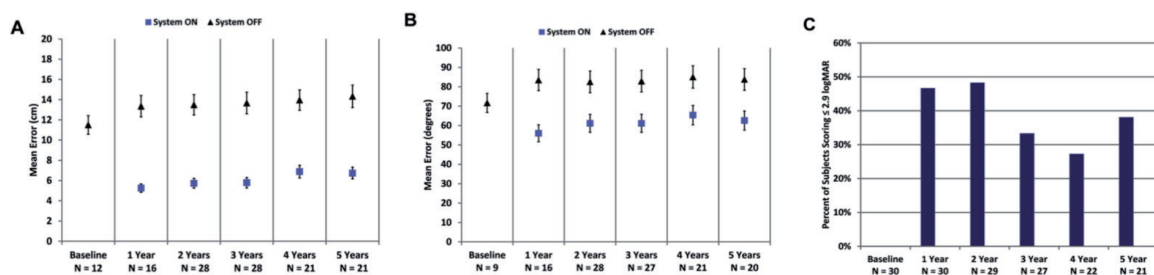


Figure 5. Results for square localization (A), direction of motion (B) and grating visual acuity (C) at yearly time-points. Credit: da Cruz et al. [74].

4.4.2 Orientation and mobility

In the phase II clinical trial, two tests of orientation and mobility were employed. The first involved locating a simulated black door on a white background across the room. The second consisted of the subject following a 6-inch-wide white line on the floor, either configured as a straight line, or with a 90° turn along its length. Successful performance was maintained at ~50 and 70% in each respective task with the device on, which was significantly better than 15–30% success with the device off [57, 73, 74]. Dagnelie et al. found a similar rate of performance success using a real world ‘sidewalk tracking’ test in 27 implanted subjects, showing that 67% performed above chance with the device on, compared to 22% with the system off [77]. **Figure 6** illustrates the testing environments for orientation and mobility tasks.

4.4.3 Shape and object recognition

Arsiero et al. demonstrated, among implanted subjects, recognition of eight simple, solid, white shapes on a black background was significantly better the device on (31%) than off (13%), which improved further to 57% when the shapes were presented as outlines [79]. Luo et al. built upon this, presenting seven implanted subjects with eight high-contrast everyday items, both in the solid and outlined forms. It was found that subjects could identify solid objects to the same degree of accuracy with the device on as they could with the device on in the scrambled mode. Although superior to having the device off, this suggested that subjects were relying on visual cues other than the form presented but the array stimulation pattern. When the shapes were presented in their outlined forms, this significantly improved performance with the device on, above either that of the scrambled mode or with the device off [80].

Another real-world task described by Dagnelie et al., consisted of a ‘sock sorting’ task, in which subjects were asked to sort a randomly arranged collection of 10 black, 10 white and 10 grey socks into separate piles, according to colour. Each test was performed on a wooden table, or on a background of the subject’s choice (i.e. black or white). In both scenarios, the subjects performed significantly better on average with the device on than off [77].

4.4.4 Letter reading

In a study of 21 implanted subjects, da Cruz et al. studied functional form vision by assessing ability to discriminate high-contrast letters. Letters were grouped according to typographical complexity and randomly displayed on a computer

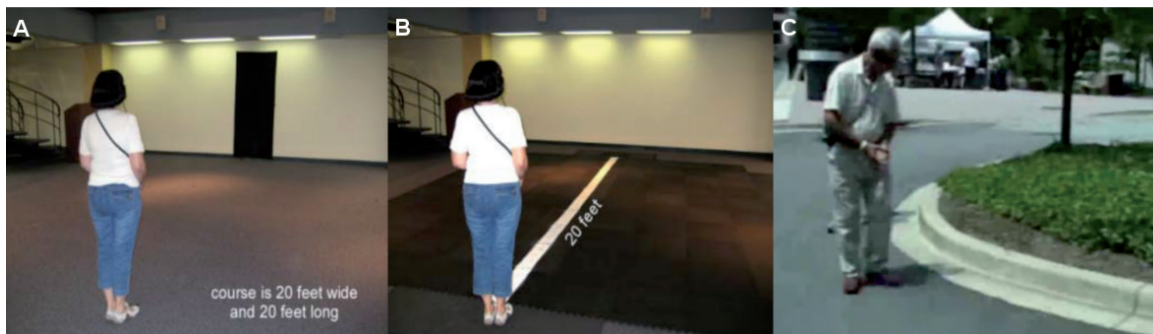


Figure 6. Photographs of subjects performing door finding (A), line tracking (B) and sidewalk tracking (C) tasks. Credit: Humayun et al. [78], Dagnelie et al. [77].

screen. Measurements from all subjects revealed a correct identification of 72% of group A (least complex) letters, presented at 30 cm, such that they subtended a visual angle of 41.27° . In the study, 19 and 20 subjects respectively completed the group B and group C letters, correctly identifying 55 and 52% in each instance. In all cases, performance was significantly better with the device turned on than off. A subset of six subjects who identified more than 50% of group A letters in fewer than 60 s went on to complete tests to assess the minimum letter size that could be resolved, while four of these six subjects were also assessed for performance on 2-, 3- and 4-letter word identification. The minimum letter size correctly identified was 0.9 cm, subtending a visual angle of 1.7° . On average, four subjects could identify 6.8 out of 10 words, ranging from 11 to 20 cm in height. In all cases, the performance was significantly better when the device was switched on in standard mode, than when scrambled or off [81]. These results are very promising for the capacity of some patients to achieve good spatial resolution, approaching the theoretical limit of the system.

4.4.5 Prehension tasks

In a series of experiments using a 3D motion-capture system, Luo et al. measured the ability of five subjects to grasp a white block on a black table (**Figure 7**). With the device turned on, subjects would successfully initiate and complete a grasping action 74% of the time, compared to 0% with the device off [82, 83]. Unlike other object recognition tasks, this study suggests a good capacity for the system to permit performance of hand-eye coordination tasks in a 3D environment, similar to that of the real-world.

4.5 Patient-reported outcomes

An important consideration in visual restoration is the extent to which the recipients judge the system to be beneficial in everyday life. The Functional Low-vision Observer Rated Assessment (FLORA) was developed by Geruschat et al. in order to evaluate the impact of partial restoration of ultra-low vision in subjects undergoing Argus II implantation. Initial results using the FLORA tool demonstrated that it was able to provide useful information about the everyday functional benefit of prosthesis-derived visual restoration, as well as identifying areas in which rehabilitation could be utilized to maximize subjective value. At 1 year, the assessment demonstrated an 80% reported positive effect, which dropped to 65% at 3 years. No patients reported a negative effect using this self-reporting tool [84, 85].

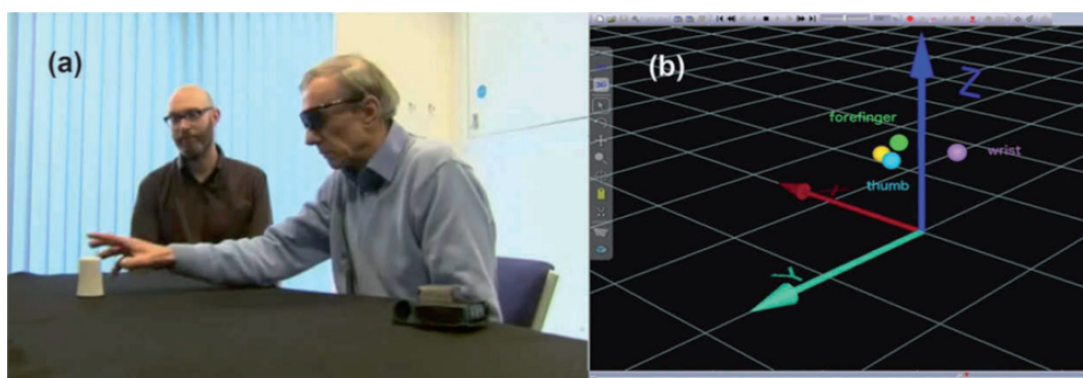


Figure 7. Subject performing prehension task (a) with live infrared motion capture of subject's hand (b). Credit: Luo et al. [82].

5. Future directions

There are several other groups across the world using a variety of techniques to develop retinal prosthetic systems. Currently the intelligent retinal implant system (IRIS) II (*Pixium Vision S.A. France*) is the only other *epiretinal* device that has received CE approval. The external components and power induction mechanism of this system are fairly similar to the Argus II system. However, unlike the Argus II system, the 150-microelectrode array receives stimulation commands directly from an infrared array, which is integrated into a glasses-mounted visual interface, thus facilitating high data transfer and device miniaturization [45]. While initial data from the clinical trial were promising for functional and safety outcomes with the IRIS II, the study was postponed following concerns about device longevity [86].

The aforementioned Alpha IMS and its successor, the Alpha AMS (*Retina Implant AG, Germany*), have both been approved for commercial use in Europe. Utilizing photovoltaic technology, the Alpha IMS has 1500 autonomous photodiode complexes, giving a higher theoretical resolution than the Argus II. To date, this system has yielded safety and functional results similar to the Argus II, albeit with inferior longevity, possibly due to the surgical approach, involving subretinal device placement and a tunnelled link to a postauricular coil for electromagnetic power induction [35, 36, 87]. Preliminary data from trials of the Alpha AMS report considerable improvements in the lifespan of this system.

Finally, the Photovoltaic Retinal Implant (PRIMA) bionic vision system (also *Pixium Vision S.A.*) is currently undergoing a safety and performance evaluation feasibility study [88]. This subretinal system comprises a modular array set-up with 1 mm-wide hexagonal chips, each containing 142 30 μm -thick pixel cells, each $\sim 70 \mu\text{m}^2$, which receive visual data from a visual interface as pulsed near infrared light. Multiple photodiodes in series are stimulated, generating sufficient current to polarize the adjacent neuronal tissue with a local concentric return to limit signal diffusion. This system is unique in that it is scalable through insertion of additional chips and does not require any direct transscleral delivery of power or data [37, 89, 90].

Several other groups are also investigating alternative methods of neural stimulation, including optic nerve, cortical and thalamic prostheses [91]. As increasing numbers of patient volunteers undergo implantation with these systems, more data will become available, thus guiding the optimal design characteristics for future generations of devices.

Advancements in visually restorative medicine are not limited to prosthetics, with other regenerative technologies, including stem cells, gene therapy and optogenetics, demonstrating exciting developments in the endeavor to treat blindness [92–97]. In particular, optogenetics, an approach that is focused on targeting microbial opsin (light-dependent ion channels) to surviving retinal neurons to rescue or restore visual function, has shown exciting results in *in vivo* animal and *in vitro* human studies [98–100]. In addition to the aforementioned organic approaches, these techniques are attractive insofar as they offer a biocompatible, autonomous and scalable alternative to inorganic systems, which could be administered earlier in the disease course as a rescue therapy. It is widely anticipated that these strategies will soon build on the initial success of synthetic prosthetics, or potentially complement them in the form of biohybrid implants.

The success of the Argus II is representative of the enormous progress that has been made in the field of retinal prosthetics over the past 3 decades. However, there remain significant challenges to be overcome before the concept of ‘bionic vision’ is fully realized. Despite this, retinal prostheses have delivered the most compelling

form of artificial vision to date, bearing testimony to the value of close collaboration between engineers, clinicians, patients and industry in pushing the boundaries of what is conceivable, let alone scientifically feasible.

Conflict of interest

The authors declare no potential conflicts of interest or financial support with respect to the authorship and/or publication of this chapter.

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References

- [1] World Health Organization. WHO: Global data on visual impairments. 2010. Available form: www.who.int. (accessed 30 September 2018)
- [2] Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. *The Lancet*. 2006;**368**:1795-1809. DOI: 10.1016/S0140-6736(06)69740-7
- [3] Santos A, Humayun MS, de Juan E, Greenburg RJ, Marsh MJ, Klock IB, et al. Preservation of the inner retina in retinitis pigmentosa. A morphometric analysis. *Archives of Ophthalmology*. 1997;**115**:511-515
- [4] Wong WL, Su X, Li X, Cheung CMG, Klein R, Cheng C-Y, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. *The Lancet Global Health*. 2014;**2**:e106-e116. DOI: 10.1016/S2214-109X(13)70145-1
- [5] United Nations. UN: World population projected to reach 9.7 billion by 2050. <http://www.un.org/> (accessed 30 September 2018)
- [6] Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. *The New England Journal of Medicine*. 2008;**358**:2606-2617. DOI: 10.1056/NEJMra0801537
- [7] Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *British Journal of Ophthalmology*. 2012;**96**:752-756. DOI: 10.1136/bjophthalmol-2011-301109
- [8] Foerster O. Beiträge zur Pathophysiologie der Sehbahn und der Sehsphäre. *Journal für Psychologie und Neurologie*. 1929;**39**:463-485
- [9] Brindley GS, Lewin WS. The sensations produced by electrical stimulation of the visual cortex. *Journal of Physiology (London)*. 1968;**196**:479-493. DOI: 10.1111/(ISSN)1469-7793
- [10] Molday RS, Moritz OL. Photoreceptors at a glance. *Journal of Cell Science*. 2015;**128**:4039-4045. DOI: 10.1242/jcs.175687
- [11] Curcio CA, Allen KA. Topography of ganglion cells in human retina. *The Journal of Comparative Neurology*. 1990;**300**:5-25. DOI: 10.1002/cne.903000103
- [12] Purves D. Vision: The eye. In: Purves D, Augustine GJ, Fitzpatrick D et al, editors. *Neuroscience*. 5th ed. Sunderland: Sinauer Associates, Inc. 2012
- [13] Dagnelie G, Barnett D, Humayun MS, Thompson RW Jr. Paragraph text reading using a pixelized prosthetic vision simulator: Parameter dependence and task learning in free-viewing conditions. *Investigative Ophthalmology & Visual Science*. 2006;**47**:1241. DOI: 10.1167/iovs.05-0157
- [14] Sommerhalder J, Pérez FA. Prospects and limitations of spatial resolution. In: *Artificial Vision*. Vol. 519. Cham: Springer International Publishing; 2016. pp. 29-45. DOI: 10.1007/978-3-319-41876-6_4
- [15] Sommerhalder J, Rappaz B, de Haller R, Fornos AP, Safran AB, Pelizzone M. Simulation of artificial vision: II. Eccentric reading of full-page text and the learning of this task. *Vision Research*. 2004;**44**:1693-1706. DOI: 10.1016/j.visres.2004.01.017
- [16] Pérez Fornos A, Sommerhalder J, Pittard A, Safran AB, Pelizzone M. Simulation of artificial vision: IV. Visual information required to achieve simple pointing and

manipulation tasks. *Vision Research*. 2008;**48**:1705-1718. DOI: 10.1016/j.visres.2008.04.027

[17] Hayes JS, Yin VT, Piyathaisere D, Weiland JD, Humayun MS, Dagnelie G. Visually guided performance of simple tasks using simulated prosthetic vision. *Artificial Organs*. 2003;**27**:1016-1028

[18] Beyeler M, Rokem A, Boynton GM, Fine I. Learning to see again: Biological constraints on cortical plasticity and the implications for sight restoration technologies. *Journal of Neural Engineering*. 2017;**14**:051003. DOI: 10.1088/1741-2552/aa795e

[19] Chen SC, Suaning GJ, Morley JW, Lovell NH. Simulating prosthetic vision: II. Measuring functional capacity. *Vision Research*. 2009;**49**:2329-2343. DOI: 10.1016/j.visres.2009.07.003

[20] Jones BW, Watt CB, Frederick JM, Baehr W, Chen C-K, Levine EM, et al. Retinal remodeling triggered by photoreceptor degenerations. *The Journal of Comparative Neurology*. 2003;**464**:1-16. DOI: 10.1002/cne.10703

[21] Marc RE, Jones BW, Watt CB, Strettoi E. Neural remodeling in retinal degeneration. *Progress in Retinal and Eye Research*. 2003;**22**:607-655. DOI: 10.1016/S1350-9462(03)00039-9

[22] Cuenca N, Pinilla I, Sauv e Y, Lund R. Early changes in synaptic connectivity following progressive photoreceptor degeneration in RCS rats. *The European Journal of Neuroscience*. 2005;**22**:1057-1072. DOI: 10.1111/j.1460-9568.2005.04300.x

[23] Jones BW, Marc RE. Retinal remodeling during retinal degeneration. *Experimental Eye Research*. 2005;**81**:123-137. DOI: 10.1016/j.exer.2005.03.006

[24] Marc RE, Jones BW, Anderson JR, Kinard K, Marshak DW, Wilson

JH, et al. Neural reprogramming in retinal degeneration. *Investigative Ophthalmology & Visual Science*. 2007;**48**:3364-3371. DOI: 10.1167/iovs.07-0032

[25] Ptito M. Cross-modal plasticity: Lessons from the visual system. *Journal of Vision*. 2006;**6**:11-11. DOI: 10.1167/6.13.11

[26] Merabet LB, Rizzo JF, Amedi A, Somers DC, Pascual-Leone A. What blindness can tell us about seeing again: Merging neuroplasticity and neuroprostheses. *Nature Reviews Neuroscience*. 2005;**6**:71-77. DOI: 10.1038/nrn1586

[27] Bavelier D, Neville HJ. Cross-modal plasticity: Where and how? *Nature Reviews Neuroscience*. 2002;**3**:443-452. DOI: 10.1038/nrn848

[28] Sadato N, Pascual-Leone A, Grafman J, Iba ez V, Deiber M-P, Dold G, et al. Activation of the primary visual cortex by Braille reading in blind subjects. *Nature*. 1996;**380**:526-528. DOI: 10.1038/380526a0

[29] Sadato N, Yonekura Y, Ishii Y, Deiber MP, Ibanez V, Hallett M. Neural networks for braille reading by the blind include visual cortex. *NeuroImage*. 1996;**3**:S340. DOI: 10.1016/S1053-8119(96)80342-9

[30] Giraud A-L, Lee H-J. Predicting cochlear implant outcome from brain organisation in the deaf. *Restorative Neurology and Neuroscience*. 2007;**25**:381-390

[31] Roland PS, Tobey EA, Devous MD Sr. Preoperative functional assessment of auditory cortex in adult Cochlear implant users. *The Laryngoscope*. 2001;**111**:77-83. DOI: 10.1097/00005537-200101000-00013

[32] Nasiatka P, Ahuja AK, Stiles N, Hauer M, Agrawal RN, Freda R, et al. Intraocular camera for

retinal prostheses. *Investigative Ophthalmology & Visual Science*. 2005;**46**:5277

[33] Chow AY. The artificial silicon retina microchip for the treatment of vision loss from retinitis pigmentosa. *Archives of Ophthalmology*. 2004;**122**:460. DOI: 10.1001/archophth.122.4.460

[34] Chow AY, Bittner AK, Pardue MT. The artificial silicon retina in retinitis pigmentosa patients (an American Ophthalmological Association thesis). *Transactions of the American Ophthalmological Society*. 2010;**108**:120-154

[35] Stingl K, Bach M, Bartz-Schmidt KU, Braun A, Bruckmann A, Gekeler F, et al. Safety and efficacy of subretinal visual implants in humans: Methodological aspects. *Clinical & Experimental Optometry*. 2013;**96**:4-13. DOI: 10.1111/j.1444-0938.2012.00816.x

[36] Stingl K, Bartz-Schmidt KU, Besch D, Braun A, Bruckmann A, Gekeler F, et al. Artificial vision with wirelessly powered subretinal electronic implant alpha-IMS. *Proceedings of the Biological Sciences*. 2013;**280**:20130077-20130077. DOI: 10.1098/rspb.2013.0077

[37] Lorach H, Palanker D. High resolution photovoltaic subretinal prosthesis for restoration of sight. In: *Artificial Vision*. Vol. 19. Cham: Springer International Publishing; 2016. pp. 115-124. DOI: 10.1007/978-3-319-41876-6_9

[38] Mandel Y, Goetz G, Lavinsky D, Huie P, Mathieson K, Wang L, et al. *In vivo* performance of photovoltaic subretinal prosthesis. In: Manns F, Söderberg PG, Ho A, editors. *SPIE BiOS*. Vol. 8567. San Francisco: SPIE; 2013. p. 856709. DOI: 10.1117/12.2001750

[39] Itti L, Koch C, Niebur E. A model of saliency-based visual attention for rapid scene analysis. *IEEE Transactions*

on Pattern Analysis and Machine Intelligence. 1998;**20**:1254-1259. DOI: 10.1109/34.730558

[40] Wilson BS, Finley CC, Lawson DT, Wolford RD, Eddington DK, Rabinowitz WM. Better speech recognition with cochlear implants. *Nature*. 1991;**352**:236-238. DOI: 10.1038/352236a0

[41] Feng C, Dai S, Zhao Y, Liu S. Edge-preserving image decomposition based on saliency map. In: *2014 7th International Congress on Image and Signal Processing (CISP)*. IEEE; 2014. pp. 159-163. DOI: 10.1109/CISP.2014.7003769

[42] Parikh N, Itti L, Weiland J. Saliency-based image processing for retinal prostheses. *Journal of Neural Engineering*. 2010;**7**:016006. DOI: 10.1088/1741-2560/7/1/016006

[43] Stanga P, Sahel J, Mohand-Said S, da Cruz L, Caspi A, Merlini F, et al. Face detection using the Argus[®] II Retinal Prosthesis System. *Investigative Ophthalmology & Visual Science*. 2013;**54**:1766

[44] Thompson RW, Barnett GD, Humayun MS, Dagnelie G. Facial recognition using simulated prosthetic pixelized vision. *Investigative Ophthalmology & Visual Science*. 2003;**44**:5035-5042

[45] Hornig R, Dapper M, Le Joliff E, Hill R, Ishaque K, Posch C, et al. Pixium vision: First clinical results and innovative developments. In: *Artificial Vision*. Vol. 9. Cham: Springer International Publishing; 2016. pp. 99-113. DOI: 10.1007/978-3-319-41876-6_8

[46] Zrenner E, Bartz-Schmidt KU, Benav H, Besch D, Bruckmann A, Gabel VP, et al. Subretinal electronic chips allow blind patients to read letters and combine them to words. *Proceedings of*

- the Biological Sciences. 2011;**278**: 1489-1497. DOI: 10.1098/rspb.2010.1747
- [47] Wang L, Mathieson K, Kamins TI, Loudin JD, Galambos L, Goetz G, et al. Photovoltaic retinal prosthesis: Implant fabrication and performance. *Journal of Neural Engineering*. 2012;**9**:046014. DOI: 10.1088/1741-2560/9/4/046014
- [48] Loudin JD, Butterwick A, Huie P, Palanker D. Delivery of information and power to the implant, integration of the electrode array with the retina, and safety of chronic stimulation. In: Dagnelie G, editor. *Visual Prosthetics: Physiology, Bioengineering, Rehabilitation*. New York: Springer Science+Business Media. 2011
- [49] Schloesser M, Cota O, Heil R, Brusius J, Offenhausser A, Waasen SV, et al. Embedded device for simultaneous recording and stimulation for retina implant research. In: 2013 IEEE Sensors. IEEE; 2013. pp. 1-4. DOI: 10.1109/ICSENS.2013.6688173
- [50] Walter P. A fully intraocular approach for a bi-directional retinal prosthesis. In: *Artificial Vision*. Vol. 2009. Cham: Springer International Publishing; 2016. pp. 151-161. DOI: 10.1007/978-3-319-41876-6_12
- [51] Gekeler F, Sachs H, Kitiratschky VBD, Stingl K, Greppmaier U, Zrenner E, et al. Re-alignment and explantation of subretinal prostheses: Surgical aspects and proteomic analyses. *Investigative Ophthalmology & Visual Science*. 2013;**54**:1036
- [52] Ayton LN, Blamey PJ, Guymer RH, Luu CD, Nayagam DAX, Sinclair NC, et al. First-in-human trial of a novel suprachoroidal retinal prosthesis. *PLoS One*. 2014;**9**:e115239. DOI: 10.1371/journal.pone.0115239
- [53] Kolb H. Photoreceptors. In: Kolb H, Fernandez E, Nelson R, editors. *The Organization of the Retina and Visual System*. Utah: Webvision. 1995
- [54] Cohen E. Retinal prostheses. In Kolb H, Fernandez E, Nelson R, editors. *The Organization of the Retina and Visual System*. Utah: Webvision. 1995
- [55] Zrenner E. Fighting blindness with microelectronics. *Science Translational Medicine*. 2013;**5**(210):1-7. DOI: 10.1126/scitranslmed.3007399
- [56] Stingl K, Schippert R, Bartz-Schmidt KU, Besch D, Cottrill CL, Edwards TL, et al. Interim results of a multicenter trial with the new electronic subretinal implant alpha AMS in 15 patients blind from inherited retinal degenerations. *Frontiers in Neuroscience*. 2017;**11**:445. DOI: 10.3389/fnins.2017.00445
- [57] Humayun MS, Dorn JD, da Cruz L, Dagnelie G, Sahel J-A, Stanga PE, et al. Interim results from the international trial of second sight's visual prosthesis. *Ophthalmology*. 2012;**119**:779-788. DOI: 10.1016/j.ophtha.2011.09.028
- [58] Butterwick A, Huie P, Jones BW, Marc RE, Marmor M, Palanker D. Effect of shape and coating of a subretinal prosthesis on its integration with the retina. *Experimental Eye Research*. 2009;**88**:22-29. DOI: 10.1016/j.exer.2008.09.018
- [59] Butterwick A, Vankov A, Huie P, Freyvert Y, Palanker D. Tissue damage by pulsed electrical stimulation. *IEEE Transactions on Biomedical Engineering*. 2007;**54**:2261-2267
- [60] Wang K, Fishman HA, Dai H, Harris JS. Neural stimulation with a carbon nanotube microelectrode array. *Nano Letters*. 2006;**6**:2043-2048. DOI: 10.1021/nl061241t
- [61] Harris AR, Wallace GG. Organic electrodes and communications with excitable cells. *Advanced Functional Materials*. 2017;**28**:1700587. DOI: 10.1002/adfm.201700587

- [62] Richardson-Burns SM, Hendricks JL, Foster B, Povlich LK, Kim D-H, Martin DC. Polymerization of the conducting polymer poly(3,4-ethylenedioxythiophene) (PEDOT) around living neural cells. *Biomaterials*. 2007;**28**:1539-1552. DOI: 10.1016/j.biomaterials.2006.11.026
- [63] Ghezzi D, Antognazza MR, Mete M, Pertile G, Lanzani G, Benfenati F. A polymer optoelectronic interface restores light sensitivity in blind rat retinas. *Nature Photonics*. 2013;**7**(5):400-406
- [64] Maya-Vetencourt JF, Ghezzi D, Antognazza MR, Colombo E, Mete M, Feyen P, et al. A fully organic retinal prosthesis restores vision in a rat model of degenerative blindness. *Nature Materials*. 2017;**16**:681-689. DOI: 10.1038/nmat4874
- [65] Benfenati F, Lanzani G. New technologies for developing second generation retinal prostheses. *Lab Animal*. 2018;**47**:71-75. DOI: 10.1038/s41684-018-0003-1
- [66] Humayun M. Bipolar surface electrical stimulation of the vertebrate retina. *Archives of Ophthalmology*. 1994;**112**:110-116. DOI: 10.1001/archophth.1994.01090130120028
- [67] Humayun MS. Visual perception elicited by electrical stimulation of retina in blind humans. *Archives of Ophthalmology*. 1996;**114**:40-46. DOI: 10.1001/archophth.1996.01100130038006
- [68] Humayun MS, de Juan E, Weiland JD, Dagnelie G, Katona S, Greenberg R, et al. Pattern electrical stimulation of the human retina. *Vision Research*. 1999;**39**:2569-2576
- [69] Humayun MS, Weiland JD, Fujii GY, Greenberg R, Williamson R, Little J, et al. Visual perception in a blind subject with a chronic microelectronic retinal prosthesis. *Vision Research*. 2003;**43**:2573-2581. DOI: 10.1016/S0042-6989(03)00457-7
- [70] Humayun MS, Freda R, Fine I, Roy A, Fujii G, Greenberg RJ, et al. Implanted intraocular retinal prosthesis in six blind subjects. *Investigative Ophthalmology & Visual Science*. 2005;**46**:1144
- [71] Caspi A, Dorn JD, McClure KH, Humayun MS, Greenberg RJ, McMahan MJ. Feasibility study of a retinal prosthesis: Spatial vision with a 16-electrode implant. *Archives of Ophthalmology*. 2009;**127**:398-401. DOI: 10.1001/archophthalmol.2009.20
- [72] Yue L, Falabella P, Christopher P, Wuyyuru V, Dorn J, Schor P, et al. Ten-year follow-up of a blind patient chronically implanted with epiretinal prosthesis Argus I. *Ophthalmology*. 2015;**122**:2545-2552.e1. DOI: 10.1016/j.ophtha.2015.08.008
- [73] Ho AC, Humayun MS, Dorn JD, da Cruz L, Dagnelie G, Handa J, et al. Long-term results from an epiretinal prosthesis to restore sight to the blind. *Ophthalmology*. 2015;**122**:1547-1554. DOI: 10.1016/j.ophtha.2015.04.032
- [74] da Cruz L, Dorn JD, Humayun MS, Dagnelie G, Handa J, Barale P-O, et al. Five-year safety and performance results from the Argus II retinal prosthesis system clinical trial. *Ophthalmology*. 2016;**123**:2248-2254. DOI: 10.1016/j.ophtha.2016.06.049
- [75] Ahuja AK, Dorn JD, Caspi A, McMahan MJ, Dagnelie G, Dacruz L, et al. Blind subjects implanted with the Argus II retinal prosthesis are able to improve performance in a spatial-motor task. *The British Journal of Ophthalmology*. 2011;**95**:539-543. DOI: 10.1136/bjo.2010.179622
- [76] Dorn JD, Ahuja AK, Caspi A, da Cruz L, Dagnelie G, Sahel J-A, et al.

The detection of motion by blind subjects with the epiretinal 60-electrode (Argus II) retinal prosthesis. *JAMA ophthalmology*. 2013;**131**:183-189. DOI: 10.1001/2013.jamaophthalmol.221

[77] Dagnelie G, Christopher P, Arditi A, da Cruz L, Duncan JL, Ho AC, et al. Performance of real-world functional vision tasks by blind subjects improves after implantation with the Argus[®] II retinal prosthesis system. *Clinical & Experimental Ophthalmology*. 2017;**45**:152-159. DOI: 10.1111/ceo.12812

[78] Humayun MS, Dorn JD, Ahuja AK, Caspi A, Filley E, Dagnelie G, et al. Preliminary 6 month results from the Argus II epiretinal prosthesis feasibility study. *Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. 2009;**2009**:4566-4568. DOI: 10.1109/IEMBS.2009.5332695

[79] Arsiero M, da Cruz L, Merlini F, Sahel J, Stanga P, Hafezi F, et al. Subjects blinded by outer retinal dystrophies are able to recognize shapes using the Argus II retinal prosthesis system. *Investigative Ophthalmology & Visual Science*. 2011;**52**:4951

[80] Luo YH-L, Zhong J, Merlini F, Anafloos F, Arsiero M, Stanga P, et al. The use of Argus[®] II retinal prosthesis to identify common objects in blind subjects with outer retinal dystrophies. *Investigative Ophthalmology & Visual Science*. 2014;**55**:1834

[81] da Cruz L, Coley BF, Dorn J, Merlini F, Filley E, Christopher P, et al. The Argus II epiretinal prosthesis system allows letter and word reading and long-term function in patients with profound vision loss. *The British Journal of Ophthalmology*. 2013;**97**:632-636. DOI: 10.1136/bjophthalmol-2012-301525

[82] Luo YH-L, Zhong JJ, da Cruz L. The use of Argus[®] II retinal prosthesis by

blind subjects to achieve localisation and prehension of objects in 3-dimensional space. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2015;**253**:1907-1914. DOI: 10.1007/s00417-014-2912-z

[83] Kotecha A, Zhong J, Stewart D, da Cruz L. The Argus II prosthesis facilitates reaching and grasping tasks: A case series. *BMC Ophthalmology*. 2014;**14**:71. DOI: 10.1186/1471-2415-14-71

[84] Geruschat DR, Flax M, Tanna N, Bianchi M, Fisher A, Goldschmidt M, et al. FLORA[™]: Phase I development of a functional vision assessment for prosthetic vision users. *Clinical & Experimental Optometry*. 2015;**98**:342-347. DOI: 10.1111/cxo.12242

[85] Geruschat DR, Richards TP, Arditi A, da Cruz L, Dagnelie G, Dorn JD, et al. An analysis of observer-rated functional vision in patients implanted with the Argus II retinal prosthesis system at three years. *Clinical & Experimental Optometry*. 2016;**99**:227-232. DOI: 10.1111/cxo.12359

[86] Muqit M, LeMer Y, De Rothschild A, Velikay-Parel M, Weber M, Dupeyron G, et al. Results at 6 months. Available from: www.pixium-vision.com [Accessed: 30 September 2018]

[87] Kitiratschky VBD, Stingl K, Wilhelm B, Peters T, Besch D, Sachs H, et al. Safety evaluation of "retina implant alpha IMS"—A prospective clinical trial. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2014;**253**:381-387. DOI: 10.1007/s00417-014-2797-x

[88] Pixium Vision: Dry AMD PRIMA. <https://www.pixium-vision.com/> (accessed 30 September 2018)

[89] Lorach H, Goetz G, Smith R, Lei X, Mandel Y, Kamins T, et al. Photovoltaic restoration of sight with high visual

acuity. *Nature Medicine*. 2015;**21**: 476-482. DOI: 10.1038/nm.3851

[90] Mandel Y, Goetz G, Lavinsky D, Huie P, Mathieson K, Wang L, et al. Cortical responses elicited by photovoltaic subretinal prostheses exhibit similarities to visually evoked potentials. *Nature Communications*. 2013;**4**:564. DOI: 10.1038/ncomms2980

[91] Zrenner E, Greger B. Chapter 1—Restoring vision to the blind: The new age of implanted visual prostheses. *Translational Vision Science & Technology*. 2014;**3**:3-13. DOI: 10.1167/tvst.3.7.3

[92] da Cruz L, Fynes K, Georgiadis O, Kerby J, Luo YH, Ahmado A, et al. Phase 1 clinical study of an embryonic stem cell-derived retinal pigment epithelium patch in age-related macular degeneration. *Nature Biotechnology*. 2018;**36**:328-337. DOI: 10.1038/nbt.4114

[93] MacLaren RE, Groppe M, Barnard AR, Cottrill CL, Tolmachova T, Seymour L, et al. Retinal gene therapy in patients with choroideremia: Initial findings from a phase 1/2 clinical trial. *Lancet*. 2014;**383**:1129-1137. DOI: 10.1016/S0140-6736(13)62117-0

[94] Marc R, Pfeiffer R, Jones B. Retinal prosthetics, optogenetics, and chemical photoswitches. *ACS Chemical Neuroscience*. 2014;**5**:895-901. DOI: 10.1021/cn5001233

[95] Simunovic MP, Shen W, Lin JY, Protti DA, Lisowski L, Gillies MC. Optogenetic approaches to vision restoration. *Experimental Eye Research*. 2019;**178**:15-26

[96] Fenno L, Yizhar O, Deisseroth K. The development and application of optogenetics. *Annual Review of Neuroscience*. 2011;**34**:389-412. DOI: 10.1146/annurev-neuro-061010-113817

[97] Busskamp V, Picaud S, Sahel J-A, Roska B. Optogenetic therapy for retinitis pigmentosa. *Gene Therapy*. 2012;**19**:169-175. DOI: 10.1038/gt.2011.155

[98] Sengupta A, Chaffiol A, Macé E, Caplette R, Desrosiers M, Lampič M, et al. Red-shifted channelrhodopsin stimulation restores light responses in blind mice, macaque retina, and human retina. *EMBO Molecular Medicine*. 2016;**8**:1248-1264. DOI: 10.15252/emmm.201505699

[99] Chaffiol A, Caplette R, Jaillard C, Brazhnikova E, Desrosiers M, Dubus E, et al. A new promoter allows optogenetic vision restoration with enhanced sensitivity in macaque retina. *Molecular Therapy*. 2017;**25**:2546-2560. DOI: 10.1016/j.jymthe.2017.07.011

[100] Chuong AS, Miri ML, Busskamp V, Matthews GAC, Acker LC, Sørensen AT, et al. Noninvasive Optical Inhibition with a Red-Shifted Microbial Rhodopsin. Vol. 17. *Nature Publishing Group*; 2014. DOI: 10.1038/nn.3752