

A Review in Innovation in Ocular Prostheses and Visual Implants: New Biomaterials and Neuro-Implants is the Challenge for the Visual Care

Patricia Durán Ospina^{*1}, Mayra Cáceres Díaz² and Jhonny Peña Plaza³

¹Fundación Universitaria del Área Andina Seccional Pereira, Research Group, Visual Health, Colombia, Microbiologist, Universidad de los Andes, Colombia

²Fundación Universitaria del Área Andina Seccional Pereira, Research Group, Visual Health, Colombia, Optometrist, Universidad de la Salle, Colombia

³Fundación Universitaria del Área Andina Seccional Pereira, Dentist, Universidad Santiago de Cali, Colombia

Abstract: *Objective:* To update in new biopolymers and innovations for ocular prostheses and visual implants for visual care. *Methodology:* The systematic review about biomaterials for ocular prostheses and visual implants was consulted on the following Journals Databases: Investigative Ophthalmology and Visual Science, Nature Eye, Ophthalmology, Br. J. Ophthalmology, Ophthalmic plastic in reconstructive surgery for a total review of 67 articles and 8 e-books were consulted with the following keywords: ocular prostheses and biopolymers, visual and ocular implants, artificial eye. Inclusion criteria: "ocular prostheses", retinal prostheses systems (RPS) and "visual implants". Search resources: MEDLINE, PubMed, SciELO, Biblioteca virtual en salud (BVS). *Results:* The traditional concept of ocular prostheses (ocular, orbital, epthesis, maxillofacial) and visual implants (retinal, optic nerve, cortical, subretinal, epiretinal and cortical implants, artificial silicon retinas and suprachoroidal transretinal stimulation (STS)) among others are changing on now days due to the new advances in technologies and also to the developing of new biomaterials, new microelectrodes and neural devices of several types around the world. Now, real "artificial eyes" are not only the craniofacial, maxillofacial, ocular and orbital prostheses, that replaces an absent eye after an enucleation. But also, new materials such as cryolite glass, gel from cellulose produced by *Zoogloea sp.*, glass, silicone and porous polyethylene, graphene, dental biopolymers among others are being implemented as a materials for heart, eye and other organs implants due to their characteristics to improve good biological compatibility, to be more resistant and to contribute to reduce allergies and improve durability. These implants are used for replacement of the orbital content of the anophthalmic cavities. In addition to this, the existing wearing protocols must be updated, as the three phases model of prosthetic eye wear: establishment of homeostasis deposits builds up, recovery from effects of handling the prosthesis, and the posterior homeostasis's stabilization for mucus and deposits, must be reduced in a near future by means of surface nanofilm or the inclusion of new biopolymers for fabrication to prevent the adherences and anticipate to immune responses after the implantation of these foreign bodies. *Conclusions:* The new emerging sciences that are applied to visual sciences will be helpful for the ocular prostheses and visual implant's users, involving a better performance for fabrication and implantation of these devices. New more biocompatible, resistant materials and the inclusion of microelectrodes for the fabrication of visual implants and also the implementation of the artificial intelligence for the eye have been developed by many researchers around world, because of emerging technologies which have been already patented and that are providing alternatives to patients who have lost their vision, and require visual rehabilitation and in a near future to recover their vision. Additional to the creation of new devices, there are some important processes that take a place such as: Complex biomathematical modeling, new surgical techniques, placement, trial In vivo animal experiments (multielectrode arrays) and In vitro animal experiments (patch clamping, extracellular recording, two-photon imaging) and in the same way, after patient's process follow up: simulated human psychophysics and some advances have been developed in 3D printers.

Keywords: Ocular prostheses, visual implants, artificial vision, neuro-prostheses, retinal implants, ophthalmology, ocular biopolymers, digital impression organ 3D printer.

CLASSIFICATION OF OCULAR PROSTHESES AND VISUAL IMPLANTS

Traditionally, the aesthetics of the manufacturing and fitting of ocular prostheses is acceptable and responds efficiently to improve patient's confidence and physical and psychological help to improve their social acceptance and their quality of life. Recently, the introduction of the visual implants is a different alternative designed to transmit electronical signals

from the retina to the brain. According to the surgical technique and the position, they are inserted or transplanted into the body and tend to be used as a therapeutic instrument for visual rehabilitation. The artificial stimulation to the visual pathway allows the brain to recognize the electric signal as light. New electronical materials useful for the fabrication of these devices have been developed in the recent years. An ocular prosthesis, helps the patient psychologically and improves confidence, but doesn't have visual function. Different techniques are available to fabricate a custom ocular prosthesis. In contrast, visual implants are currently being developed as an innovation to restore

*Address correspondence to this author at the Fundación Universitaria del Área Andina Seccional Pereira, Research Group, Visual Health, Colombia. Microbiologist, Universidad de los Andes, Colombia; E-mail: pduran@funandi.edu.co

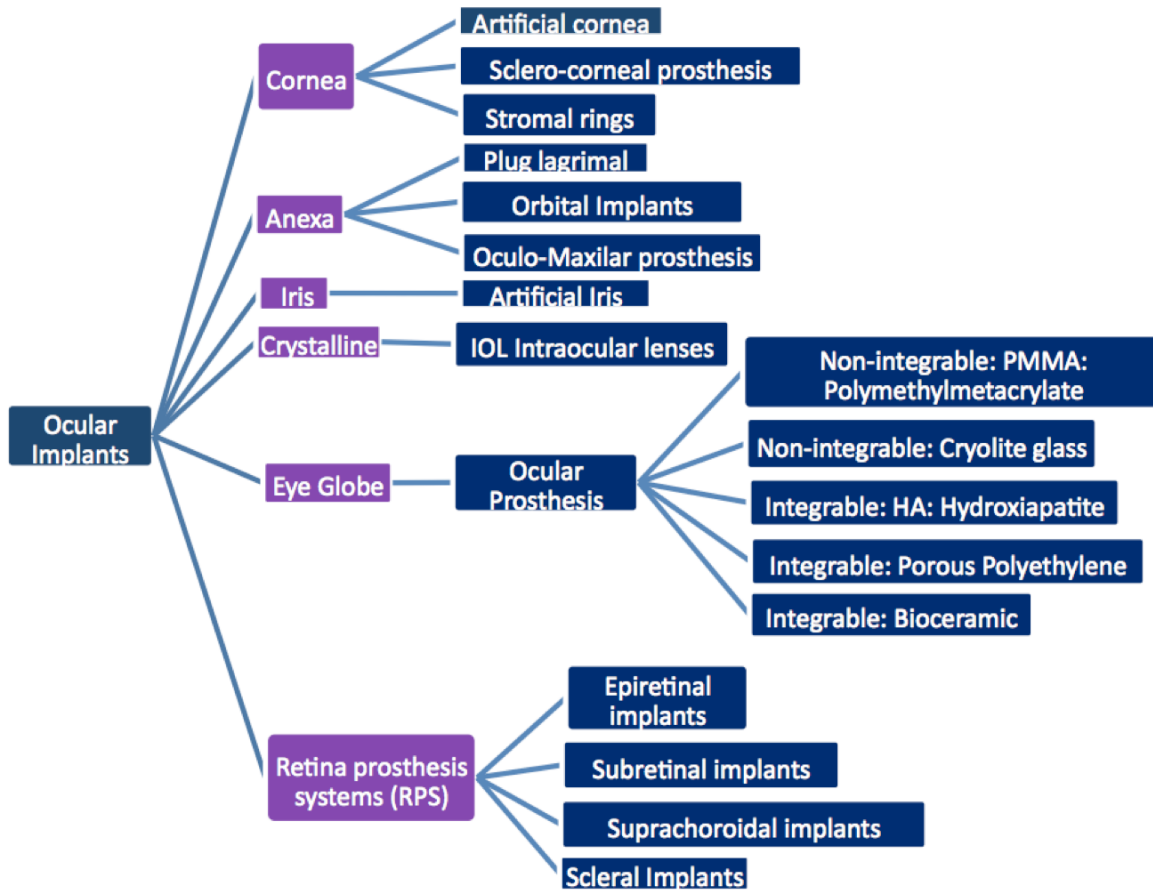


Figure 1: Classification of ocular prosthesis and visual implants.

nerve impulse between the eyeball and the cerebral cortex, linking transdisciplinary efforts, electronic engineers and ophthalmologists worldwide working to develop the bionic eye. The researchers are focus in the way to allow and improve the perception of spots of light and high contrast edges by means of devices’s stimulator as electrodes or optogenetics transducers Figure 1.

Ocular prostheses were made and still fabricated in inert and non-integrable material such as polymethylmetacrylate (PMMA) and cryolite glass, but

on these days, integrable materials for anophthalmic cavities as a gel from cellulose produced by *Zoogloea sp.* [1] porous polyethylene dental biomaterial composites and graphene among others are been implemented as a materials for heart, eye and other organs implants due to their characteristics to improve good biological compatibility, to be more resistant and to contribute to reduce allergies and improve durability.

The future development of the ocular prostheses is focused on the impression of digital measurements, 3D modeling software and digital impression of the iris,

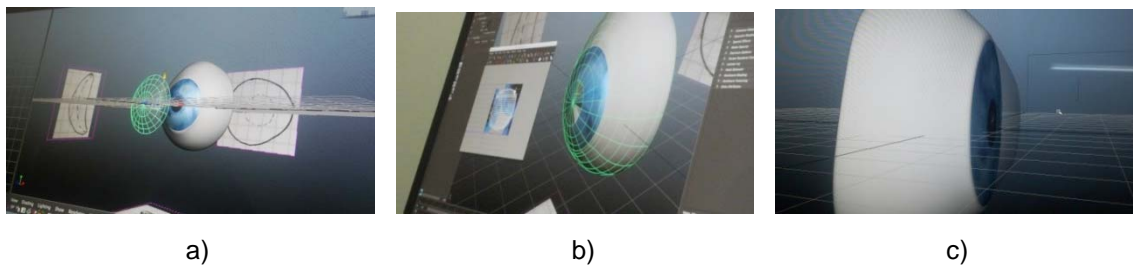


Figure 2: Digitalization of ocular prostheses on Maya 3D. a) Basic models and final prototype b) Digital iris colour c) Final 3 D digital prototype of prostheses’s modelation in Software Maya 3 D. Centro de simulación integral en salud, Fundación Universitaria Del Área Andina. 2013, Colombia. Courtesy Patricia Durán Ospina, Miguel Aceves Mejía Muñoz.

Ocular prostheses and implant materials	
Plastic/Glass/Biopolymer Type	Definition / Characteristics
PMMA	Artificial acrylic resin polymethylmetacrylate (PMMA) is the most popular material due to his material is freedom of fragility and surface etching from dissolution by the socket secretions and is adjustable to size and eye’s form. (2, Colen)
Hydroxyapatite (HA)	Developed since 1989, use it for orbital Implants. This material is porous in nature allows fibro-vascular ingrowth throughout the implant and permits insertion of a coupling device, reduced risk of inflammation or infection associated with earlier types of exposed integrated implants. It material requires being cover with exogenous material, such as polyethylene, vycril mesh.
Porous Polyethylene	It is a polyethylene porous of high density. It is firm but malleable material ant has a smooth surface, don’t requires cover. (e.g. Medpore ®)
Bioceramic	Orbital implant. It is made of aluminium oxide (Al2O3). It is inserted in the posterior Tenon's space with the scleral covering looking at front after enucleation. It is durable, stable and has low friction.
Cryolite glass	Ocular prosthesis, it is made of glass and makes a reflection, more natural than the plastics. There are two types: single-wall and double-wall, depends on the characteristics of the patient.
Dental Resins composites	Ocular prosthesis, dental resins composites, acrylic resins

Figure 3: Ocular prostheses and ocular implant materials.

Figure 4. And the whole prostheses and this would reduce the manufacturing time and large-scale personalized productions for each patient. Recently, the 3D organ printing will in the near future, allow new materials lift manuals instead of prints digital prints and three-dimensional modeling for high accuracy. See Figure 2.

In addition to this, it is important to maintain the implants in optimal conditions prior use in order to obtain a reproducible prosthesis, 3D scanning (Maya 3D, software) permits be accurate in measurements, and a final impression in a 3D printer will be the most accuracy way to reduce costs, make them in series and only personalized to adjust the changes in size and color for each patient. The existing wearing protocols for adaptation and taking measurements must be update, as the three phases model of prosthetic eye wear: establishment of homeostasis deposits build up, recovery from effects of handling the prostheses, and the posterior homeostasis’s stabilization for mucus and deposits, must be reduced in a near future by means of surface nanofilm or the inclusion of new biopolymers for fabrication to prevent the adherences and anticipate to immune responses after the implantation of this foreign bodies [2].

On the other hand, other authors classified orbital implants in seven types: I. Non-integrated: These do not usually contain any specific apparatus for attachment to the extra-ocular muscles (silicones sphere, polymethylmetacrylate), II. Quasi-integrated (or more, rarely, semi-integrated) to those has specific apparatus for attachment to the extra-ocular muscles

and there is no interruption of conjunctival lining. (Cutler implant I, Allen, Universal implant), III. Magnetically integrated: those incorporate in the frontal part which allows movement transfer to the ocular prosthesis. (Roper-Hall implant) IV. Mechanically integrated, attached to the extra-ocular muscles (Cutler implant II). V: Porous, quasi integrated, made of porous material, potentially allowing fibrovascular tissue in growth (Hydroxyapatite, polyethylene and oxide aluminium) VI: porous quiasi-integrated, made by porous material, potentially allowing fibrovascular tissue in-growth (Guthoff, poliethylene), and VII. Biogenic: composed totally o partially of a biological graft (autograft, allograft, xenograft) as cancellous bone, and biological material [3].

The ocular implants for the different ocular structure can be classified by: ocular structure, biopolymer types, surgical technique there is not an official classification for these. For this purpose the last graphic shows some of the most useful ocular implants available for recover the visual integrity. Iris implants including LCD technique as a passive circuit to control pupil diameter in a few micrometers square integrated circuit chip was reported on recent years [4,5]. Artificial retina device is composed of units of electrodes, an integrating silicon disk and micro photodiodes to produce stimulus from retina over the visual cortex [6]. Figure 3, summarized materials and biopolymers have been using from for ocular prostheses and ocular implant materials.

As an innovation, new materials has been incorporated such as a new dental resins composites, acrylic resins mixing microwave system thermo-

polymerization and self-curing acrylic resin, which are widely used in dentistry but being tested for better biocompatibility in ocular anatomy physiology.

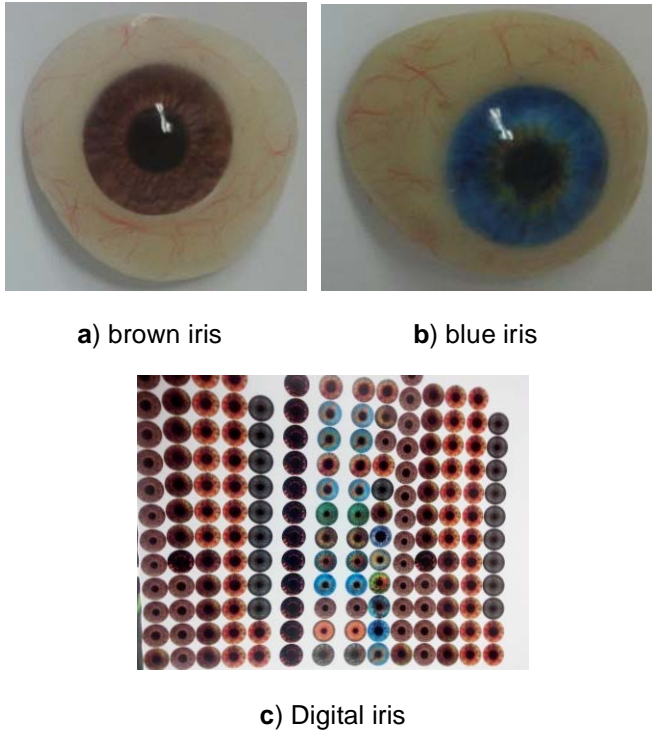


Figure 4: Ocular prostheses made with digital iris impression and dental composites. **a)** And **b)** are ocular prostheses made in dental resins composites and acrylic resins. **c)** digital iris printed. Ocular prostheses elaborated in dental resins composites at prostheses laboratory, Visual Health Research Group. Centro de simulación integral en salud. Fundación Universitaria Del Área Andina, Colombia.

Not only for aesthetic purposes, but also functional, the visual implants recently tested in patients with retinitis pigmentosa, have been investigated for more than ten years and today there are patents and multiples models that can bring benefits to these populations. The first models of visual implants were made in a hundred stimulation channels, to produce a series of stimulation, since then the new innovations are: biphasic constant current waveforms, RF (inductively-coupled) data and power, reverse telemetry and platinum electrode array, ceramic and epoxy packages. The introduction of smaller external cameras is another challenge and more electrodes for fine vision, according to the implant location (epiretinal, subretinal suprachoroidal and trans-scleral).

The visual implants are designed with an external small cameras mounted on glasses to gather visual data and the stimuli can be monitored in a personal pocket computer or as a subdermal coil behind the ear

which provides power and sends control signals via a subdermal cable and a thin intraocular foil to the chip in the eye. Figure 5 summarize some visual implants that have been patented and that being tested which are already being implanted in patients with some visual implants that have been patented and are being tested which are already being implanted in patients with retinitis pigmentosa and other conditions.

Visual implants	
Type	Definition / Characteristics
Cortical implant (Retinal Implants)	Cortical implant on the visual cortex, most of the visual pathway from an external camera the signal goes to the visual cortex, which is the brain's visual center. (e.g. Argus II)
Cortical implant (intracortical penetrate the cortex)	Artificially communicate electronic image information (Illinois Institute of Technology: IIT). It is also a pair of glasses that are equipped with a camera to gather visual data
Photovoltaic visual model	It is a camera mounted on a pair of glasses. The image goes to a pocket personal computer (design in Stanford University). The glasses use pulsed infrared illumination in the 880–915 nm range to project the image onto a sub-retinally implanted photodiode array.
Alpha-IMS subretinal implant	It is a subdermal coil behind the ear which provides power and sends control signals via a subdermal cable and a thin intraocular foil to the chip in the eye. The implant's core is an active subretinal chip with 1500 pixels. Retina Implant AG (Germany).

Figure 5: A review of visual implants.

Trial surgeries in model animals are showing a small subretinal hematoma developed in both eyes within 2 weeks postoperatively and a dark pigment changes which then stabilized, same as edema and higher intraocular pressure [8]. The subretinal implant is a chip with 1500 pixels, each one has a photodiode (to analyses brightness of the incoming light), also has an amplification circuit and an electrode for transfer to the other retina's layers. This chip records image five to seven time per second. The chip's size is 3 mm X 3mm [9, 10]. Recently, el Argus II RPS were tested in 28 subjects with retinosis pigmentaria, it was the first retinal prosthesis to receive regulatory approval for implantation in Europe outside of a trial. In this trial, the authors report good results in identifying words after 34 months of implantation; this means that soon may be adapted elsewhere in the world to contribute to improving the quality of life and visual health of these patients [11]. No single implants for retina, iris chips are also being investigated for the entry and exit of light

using a small LCD, positioned over an iris image, in which ring-shaped pixels will appear black or transparent depending on the ambient light, to simulate the “dynamic pupil” [12].

Likewise, studies have been reported for implementation of new surgical techniques for implementing these neural prosthesis, to enhance the performance, the electrodes for the biosignal recording or electrical stimulation should be located in closer proximity to target neurons and to “guide the neurons” to the microelectrode’s position by means of applying laser treatment during surgery to improve the performance of the neural prosthesis [13]. Although these findings require further study to enhance the contrast, color vision, other efforts are being made regarding to improve prosthetic capabilities to increasing resolution of the device’s stimulators as more electrodes or optogenetic transducers (channel rhodopsin-2 (ChR2), using mice as a model, researchers are incorporating ganglion cells responses using cell responses combining the code and the high-resolution stimulation, so that the prosthetic system captures this transformation and produces the retina’s code, that is, it converts visual input into the same patterns of action potentials that the retina normally produces to increase the image quality and resolutions [14].

Some authors reported the use of partial cover porous orbital implant, such as aluminium oxide

(Bioceramic), with the patient’s sclera during enucleation. It allows the movement of the external prosthesis because the four rectus muscles are sutured to the posterior Tenon’s fascia and because of this technique the orbital volume is completely filled. Increasingly research from nanotechnology and bio-nanotechnology mixing chips with genetic engineering there are new alternatives to prevent postoperative rejection of the implant and have greater biocompatibility with the ocular tissues and better resolution for restore visual function [15].

Many implants are being studied around the world, and some patents, and other humans have been implanted to help to the visual rehabilitation, Figure 6. Some of these examples are divided in two categories according of designs or operation’s principles: some using an external camera and image processing to drive implanted electrodes. Another use 1500 small units in microphotodiode arrays (MPA by Retina Implant AG) and Stanford retinal prosthesis, some required external energy to drive the stimulators, others will be wireless. The Stanford array projects a high-intensity infrared image on the implanted photocells and generates sufficient current to excite the secondary neurons. In addition, the classification must be made according the implant site: on the inner of the retina (epiretinal) or outer (subretinal) retinal surface, if the implant is inserted below the choroid plexus (suprachoroidal) or if the implantation take place outside the sclera (episcleral) [16].

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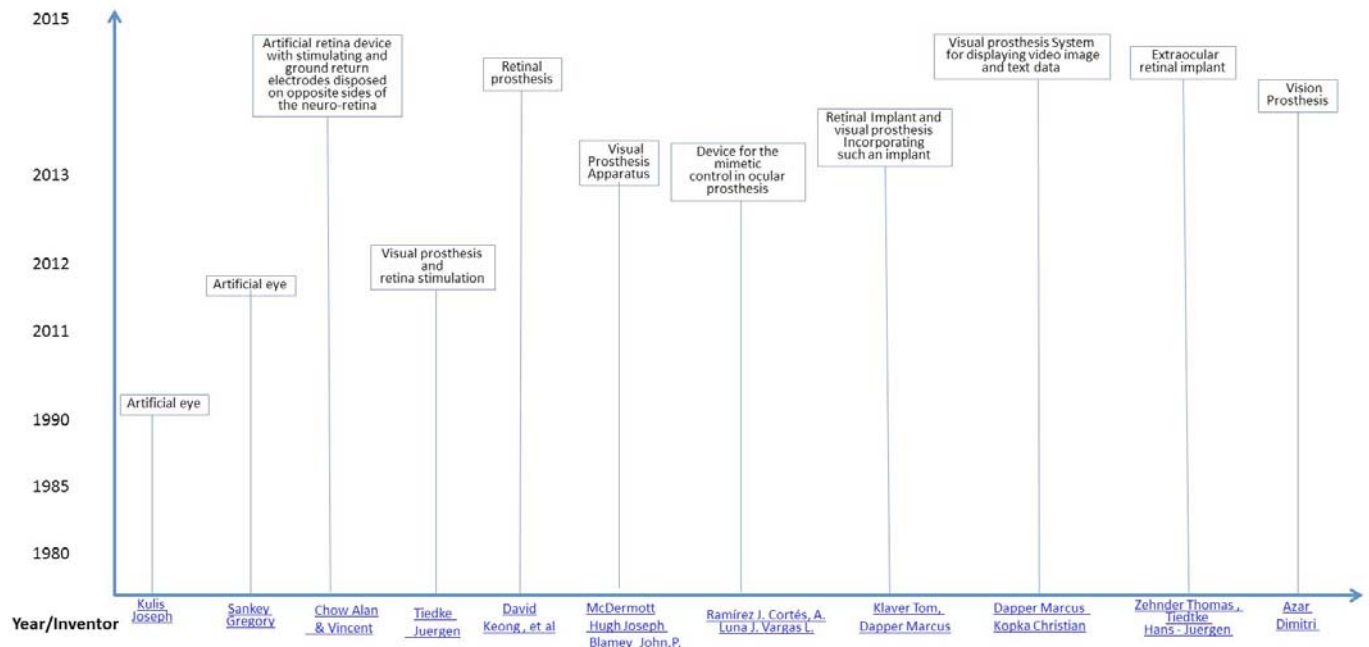


Figure 6: Visual and ocular implants patents. Source: Spacenet & Google Patents.

A REVIEW OF SOME PATENTS OF VISUAL IMPLANTS

Ocular prosthesis materials and visual implants are not a recent innovation. It has been around for several years, however the innovation of the recent years involves more patents for visual implants, Figure 6. Below summarizes some of the patents are two innovations in recent years.

DISCUSSION

The overall trend in the present and also in the future for ocular prostheses and visual implants will be the organ 3D print known as bio-printing. The fusion between ophthalmology and nanotechnology will continue rising. The scanning and modeling software innovation and the use of biopolymers, and mixture between them, will improve the quality of vision in the case of visual implants and the production of ocular prostheses with more technology, greater protection against microbes and less handmade. Likewise, the search for new electronic integrating chips and biomaterials together with the visual health, is another finding to improve new prototypes as the same way, simulation and modeling remain the most important aspect to achieve support on this field.

The Challenge of New Visual Innovation

There are multiple challenges that must continue to be improved for these new global developments in ocular prosthesis and visual implants.

In order to make these implants accessible to patients it is required a good transfer of technology, training and meet some challenges mainly in the following points:

1. Research: strengthening the global researchers' mobility, and internships among researchers of visual health-electronical engineering groups around the world to be training in transdisciplinary teams about the new surgical technique and developments in electronic engineering and their applications to visual health. It must include developments for other healthcare artifacts.

2. Financial: search financial resources from governments and public and private entities to developing policies for technology transference

3. Create a database of target population in visual implants: a global database of possible patients that can be benefit with these innovations is a priority in each country and make us think in plans for monitoring

and check the progress in the new implanted patients, to verify the recovery rates and design a project of the improvement thereof.

4. Challenge for IRB: the Institutional Review Boards of universities around the world, should share global protocols around implantation, care of the visual implants, informed consent in the use of these new innovations, provide mechanisms for timely and appropriate communication to users, investors and inventors, reporting the cost - benefits of these new alternatives.

5. Marketing: The other challenge is distribution's channels: it requires a highly qualified medical and rehabilitation staff after implantation: a team of psychological support, visual rehabilitators, low vision experts around the world and the most important the family support for the real success of visual recovery.

Specifically, in the case of ocular prosthesis, the personal cleaning regime requires a periodic professional care, some authors have proposed the three phases model of wear according to the discharge associated with prosthetic eye wear. An initial period: new (or newly-polished) prosthesis when homeostasis is being established (or re-established); a second period: equilibrium phase where beneficial surface deposits have built up on the prosthesis and wear is safe and comfortable, and a third period: breakdown phase where there is an increasing likelihood of harm from continued wear. New covers such as nanofilms or new biopolymer can reduce the deposits another way is the traditional surface polish. There is not too much published literature about maintenance care of visual prosthesis, electrodes and microarrays.

Research in the development of artificial organs and ocular prosthesis is focused towards inclusion of new biomaterials, with graphene or nano-coatings against biofilm and microorganisms, creating prototypes digitized and customized for each patient, using the new technology and working with organs 3D printers. Some advances have been developed in the United Kingdom in partnership with Fripp Design and Research and Manchester Metropolitan University, using the Spectrum Z-Corp 510 3D printer.

The main reason for inclusion of graphene as a ocular biomaterial is because this material serves as a photovoltaic semiconductor which, unlike the metal or silicon-based materials used until now for such biotechnological interfaces. The graphene is soft, light and flexible and highly biocompatible and naturally

sensitive to visible light, is a photovoltaic material, and this characteristic not require an external electrical source to function.

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