# Chapter 2
# Visual Health Nanocomposites: Present and Future


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**Abstract Background**: In recent years, the therapeutics for eye diseases as retinopathy diabetic, dry eye, glaucoma and contact lenses fabrication are including nanocompounds as ocular drug delivery systems, biomarkers for detection of eye diseases, copper and silver ions that has been incorporated by means of the nanotechnology for the production of less toxic and more effective alternatives. Several compounds such as silver nanoparticles, turmeric-based nanocomposites, neovascularization blockers and nanoparticles extracted from the plant *Costus pictus* among others have been researched for this purpose. Those compounds are some of the promising research efforts that are studying and will contribute to preventing vitreous hemorrhages and ocular manifestations that affect large populations, being one of the main causes of blindness in the world. Although, nanotechnology has a lot of contributions which are advantageous for several medicinal areas.

**Objective**: To carry out a bibliographic review of the latest advances and clinical or toxics findings in nanotechnology for the therapeutic treatment for visual health.

**Method**: The review was undertaken in the next databases: Google Scholar, Science Direct, Scopus, Elsevier, Springer and PubMed using the keywords: nanotechnology in diabetic retinopathy, nanotechnology and visual health. 75 papers

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were reviewed with the keywords “nanotechnology”, “visual health”, “diabetic retinopathy”, “glaucoma” and “dry eye”. The Boolean Connector used was “and”.

**Results**: The advantage of nanotechnology at the ocular level is that it allows in the treatment and pharmacology to create nanocomposites that allow them to pass through the delicate ocular tissues and reach the posterior segment of the eye, where many traditional drugs fail. The first nanocomposites were the anti-neovascularization agents such as bevacizumab, atorvastatin, and recently they are producing longer release compounds based on nanotechnology as curcumin silver nanoparticles, extract of insulin Plant (*Costus pictus*) leaves and its silver nanoparticle are some of those nano compounds that promise to be an alternative way to treat diabetic retinopathy.

**Conclusion**: Many nanotechnology-based drugs have been obtained from plant extracts although they are used in treatment applications at the systemic level, recently some have begun to be used at the ocular level in nanocomposite presentations. Nanotechnology is an alternative to the control of diabetic retinopathy, which affects a large part of the population. The use of drug delivery systems based on nanoparticles as liposomes, dendrimers, cationic nanoemulsions, polymeric nanoparticles pointing out the advantages of the proposed nanomedicines to target this ocular disease.

**Keywords** Nanocomposites and diabetic retinopathy · Liposomes · Ophthalmic drugs · Diabetes mellitus · Nanoparticles · Nanotechnology · Ocular drug delivery · Retinal neovascularization · Toxicology

## 2.1 Introduction

In recent years, nanotechnology offers new alternatives for the diagnosis and treatment of diabetic retinopathy, dry eye, glaucoma, and retina diseases (Jo et al. 2011; Raju and Goldberg 2008). The first nano compounds was applied for ocular drugs, nanoparticles for avoid ocular infections and recently for diabetes as anti-neovascularization agents such as bevacizumab, atorvastatin, the curcumin silver nanoparticles, and the extract of insulin plant (*Costus pictus*) leaves and its silver nanoparticle are some of those nano compounds that promise to be an alternative way to treat diabetic retinopathy and other ocular alterations (Aruna et al. 2014). Some studies have shown that curcumin reduces the inflammation and delays or prevents obesity-induced insulin resistance and associated complications, including atherosclerosis and immune mediated liver disease. Unfortunately, dietary curcumin is poorly absorbed by the digestive system and undergoes glucuronidation and excretion rather than being released into the serum and systemically distributed. New improved methods developed with nanoparticles and lipid/liposome formulations that increase absorption and bioavailability of curcumin. Development and refinement of these technologies will enable cell-directed targeting of curcumin and improved therapeutic outcome (Maradana et al. 2013).

The nanocomposites reduce the side effects of traditional drugs and have been used for more than two decades in pharmaceutical formulations, making them more hydrophilic. Drugs at the ocular level can be absorbed in the conjunctiva through the blood vessels and from there go to the choroid and the vitreous, therefore very small particles are required for better absorption and distribution in the tissues (Card and Magnuson 2011; Rupenthal 2020).

When there is an alteration in the retina, the product of a systemic damage caused by diabetes diagnosed in a patient, there is a reduction in the retinal vascular flow which produces ischemia and leads to a decrease in oxygenation at the cellular level in the retina. The retina is the tissue that consumes more oxygen in relation to weight, throughout the human body. Causing a breaking the hemato/retinal barrier and producing plasma exudates and lipids in retinal cells which ends up producing an edema in the whole tissue affected. In diabetic retinopathy the small capillaries of the retina present rupture and obstruction so hemorrhages appear, edema (accumulation abnormal fluid) and important areas of ischemia (total lack of blood) retinal that will carry over time and if they are not treated well, to the loss progressive vision (Campos et al. 2017). The dependence type of diabetes suffered by the patient, the age of the same, the time of evolution since the diagnosis of the disease for the first time base, metabolic controls, and other pathologies such as arterial hypertension or hyperlipidemias, impact directly on the degree of severity of diabetic retinopathy (Farkaš and De Leeuw 2020; Ghafoorianfar et al. 2020).

A complete assessment of the fundus of the eye, supported in addition to complementary exams such as fluorescein angiography and/or tomography of optical coherence is important for the early detection. The diabetic retinopathy does not produce symptoms in the early stages of its evolution and when it manifests, it is usually in a phase advanced. Hence the importance of its early detection with the background examination of the eye, under pupillary dilation. Among the clinical manifestations, the changes are mild, with the presence of microaneurysms, microhemorrhages or subclinical macular edema. Once the pathology starts its progression, it is common to observe abnormal vessels, with irregular calibers, the greater amount of microaneurysms and exudates in the posterior pole. Macular edema is the initial cause of the progressive decrease in central visual acuity. In the phase of proliferative diabetic detinopathy, ischemia is evidenced, the retina compensates for its hypoxia by forming new vessels. These new vessels (neovessels) are abnormal, fragile so they break easily producing hemorrhages (intraretinal, subhyaloid or vitreous), which ends up being the main cause of central and peripheral retinal detachments. Traditional treatment, as photocoagulation laser, can be initially indicated (Samuel et al. 2011). In cases where there is an extensive hemorrhage inside the eye, by bleeding from the retinal vessels, is performed a surgical procedure called vitrectomy, eliminating the blood that is located in the sub vitreous spaces, allowing the use of laser in the retina, minimizing the risk of continuing with visual loss. Other treatments alternatives, include therapy with stem cells, where their effectiveness is not highly proven, and is also found antiangiogenic therapy, which its main objective is to attack the endothelial growth factor, decreasing the likelihood of new vessel formation (Xu et al. 2011).

## 2.2 State of Art of Nanotechnology Applied to Visual Health

The nanotechnology and the artificial intelligence (AI), also called computational intelligence, at the early stages was displayed by machines, and at these time health technologies are based on it. In computer science, an ideal "intelligent" device is a flexible rational agent that perceives its environment and performs actions that maximize its chances of success in some objective or task. The term artificial intelligence applies when a machine imitates the "cognitive" functions that humans associate with other human minds, such as "learning" and "solving problems". As devices become increasingly capable, a technology that was once thought to require intelligence is removed from the definition (Samuel et al. 2011). For example, optical character recognition is no longer perceived as an example of "artificial intelligence" becoming a conventional technology. Technological advances still classified as artificial intelligence are systems capable of playing chess and self-handling. It is to improve it at the surgical room or to avoid malpractices for ethical and moral purposes (Rhoads 2020).

In 1956, John McCarthy coined the term "artificial intelligence", and defined it as: "the science and ingenuity of making intelligent machines, especially intelligent computer programs"(Durán Ospina et al. 2014). For Nils John Nilsson, there are four fundamental pillars on which artificial intelligence is based on:

A search of the required state in the set of rules produced by the possible actions. Genetic algorithms (analogous to the process of evolution of DNA strings). The nanotechnology and the artificial neural networks (comparable to the physical functioning of the brain of animals and humans). Reasoning through a formal logic similar to human thought (Zerfass et al. 2020). There are also different types of perceptions and actions that can be obtained and produced, respectively, by physical sensors and mechanical sensors in machines, electrical or optical pulses in computers, as well as by inputs and outputs of software and its software environment. Several examples are in the area of systems control, automatic planning, the ability to respond to diagnostics and consumer queries, writing recognition, speech recognition, and pattern recognition. The systems based on artificial intelligence are currently part of the routine in fields such as economics, medicine, engineering, and the military, and have been used in a variety of software applications, strategy games, such as computer chess, and other video games (Ting et al. 2020).

Ophthalmology, within medicine, has always been characterized as one of the fields that uses the most significant technology for diagnosis of pathologies and innovation in new surgical techniques. For decades, the incursion of refractive surgery, assessment of optical coherence tomography, new designs of sophisticated surgical microscopes and the incorporation of intraocular lenses with multifocal designs have allowed improving the quality of life of patients. However, some of these advances still have very high costs and are not accessible to all users. Recently, artificial intelligence has been incorporated into ophthalmology operating rooms to provide the surgeon with new diagnostic and treatment alternatives for different surgeries. At first glance, stem cells, the implementation of artificial corneas in

**Table 2.1** Applications of nanotechnology in visual health

| Applied | Nanotechnology in visual Health |
|---|---|
| Glaucoma | • Nanocompounds for new ocular drug delivery<br>• Implant to detect PIO early |
| Ocular Antibiotics | • Copper, cobalt, gold, polyethilenglicol (PEG), graphene and silver nanoparticles<br>• Nanocarriers |
| Retina<br>Conjunctiva<br>Ocular Pharmacology<br>Diagnosis and treatment | • Retina implants<br>• Pharmacology Nanocompounds<br>• Intravitreal injections as liposomes encapsulating an angiogenesis inhibitor to avoid neovascularization<br>• Nanocompounds against COVID-19 on eye surface<br>• Develop new molecules as nanosuspensions, nanospheres, liposomes, and microemulsions<br>• New biomarkers for detect deseases and improve treatments |

biopolymers and new retinal implants that in one look like science fiction, but today they have become tools for ophthalmologists and visual health professionals (Durán Ospina 2013). Nanotechnology and its applications in medicine require multidisciplinary teams among ophthalmologists, researchers, biomedical engineers, molecular biologists, robotics engineers, research managers and even financial and marketing experts to make these developments go beyond an operating room and patents can be achieved to improve patients life quality (Fangueiro et al. 2015).

Otherwise, in the recent years, the stem cell technology has recently become an ally of nanotechnology many advances have been made in the stem cells field for eye surgery purposes, especially at the level of minor conditions, such as myopia (Sheng et al. 2016). However, getting back those who do not have it, either from birth or from a later problem, remains a difficult obstacle to overcome. Stem cells have much to offer in these investigations, as they can transform into different cell types, so it is not unreasonable to regenerate damaged eye tissues with their help. Precisely this is what a group of scientists, who have used "Isogenic pairs of wild type and mutant induced pluripotent stem cell (iPSC)," based on one of the most recent advances in stem cells, have thought to obtain all components of the ocular tissues. Although at the moment they have only done so in rabbits, the results are very hopeful for the extrapolation to humans (Chichagova et al. 2020). Although they can be obtained from many sources, the most common are embryonic stem cells, and therefore have a large number of ethical disadvantages by those who oppose the use of research embryos (Prasad et al. 2019).

Two hundred fifty genes to date have been identified or associated with the development of retinal diseases, and numerous more have been implicated in diverse corneal genetic dystrophies. A genetic condition affects vision and also can significantly impact the patient quality of life. Gene therapy seeks to slow the progression of these diseases by treating the underlying etiology at the level of the genome (Lane et al. 2020). The Table 2.1 summarize the applications of nanotechnology in visual health.

This shows that nanotechnology will not only be an application science in the fields of engineering, agriculture and medicine and more specifically in ophthalmology and visual health.

People affected with ocular diseases will significantly increase over the next decades, and, consequently, a substantial increase in health costs is expected. Diabetic retinopathy is the most common chronic complication of diabetes. The treatment of eye diseases affecting the posterior segment, such as diabetic retinopathy, is quite challenging due to the anatomy, physiology, and biochemistry of the eye. Therefore, the development of new therapeutics for posterior eye diseases has been a major focus of pharmaceutical research in the area of vision sciences. Several nanosystems already offer efficient solutions for ophthalmological conditions, targeting internal eye tissues, as the retina, and many novel products are expected to appear hereafter (Weng et al. 2017), and Syed (2017) developed fluocinolone acetonide intravitreal implant 0.19 mg is a useful option for the treatment of DME in these patients. This review provides an insight into nanoparticle-based solutions for therapies directed to the posterior segment of the eye diseases, particularly diabetic retinopathy, the present scenarios, and the demands and expectations for the future or toxic effects (Jo et al. 2011).

Therefore, it is important to carry out a good review and vigilance strategy regarding not only the benefits but also the possible toxic effects or interactions with other drugs. Nanotoxicology represents a new and growing research area in toxicology. It deals with the assessment of the toxicological properties of nanoparticles (NPs) with the intention of determining whether (and to what extent) they pose an environmental or societal threat (Jo et al. 2011). Inherent properties of NPs (including size, shape, surface area, surface charge, crystal structure, coating, and solubility/dissolution), as well as environmental factors (such as temperature, pH, ionic strength, salinity, and organic matter), collectively influence NP behavior, fate and transport, and ultimately toxicity (Durán Ospina and Zapata 2016; Prasad et al. 2019). The mechanisms underlying the toxicity of nanomaterials (NMs) have recently been studied extensively (Prasad 2019). Reactive oxygen species (ROS) toxicity represents one such mechanism. An overproduction of ROS induces oxidative stress, resulting in an inability of the cells to maintain normal physiological redox-regulated functions. In context, this chapter includes topics pertaining to chemical and physical properties of NMs and characterization for proper toxicological evaluation, exposure, and environmental fate and transport and ecological and genotoxic effects (Campos et al. 2017). The purpose of this chapter is to review the available research pertaining specifically to NMs in the aquatic environment (implants, aquatic invertebrates, and fish) and their use in biomarker studies. Artificial intelligence and nanotechnology are closely intertwined to allow image visualization and simulated models required for the construction of the nanocarriers and nano compounds (Xu et al. 2011).

Those Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR-Cas) therapies in ophthalmology must be incorporated in the targeting of autosomal dominant pathogenic alleles as well as the knockdown of specific wild-type genes that produce pathogenic phenotypes in particular locations, such as vascular

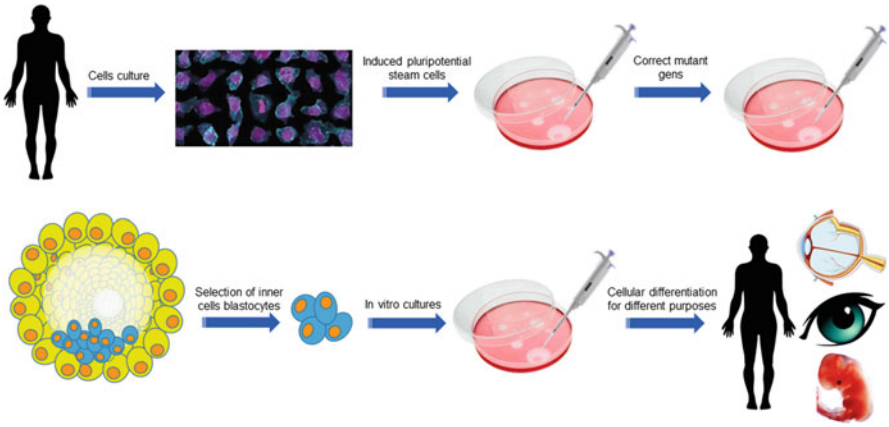


**Fig. 2.1** Schematic of the steam cells culture

endothelial growth factor (VEGF) in causing neovascularization of the choroid. Do not require a donor DNA sequence for homologous recombination, reducing the size requirements of the delivery vector. Further development to differentiate CRISPR-Cas modified iPSCs into retinal, corneal and other cell types, as well as methods for autologous transplantation, could make sight-saving advances in numerous genetic diseases of the eye possible (DiCarlo et al. 2017).

Genome surgery: the process of selection of somatic cells from patients, reprogramming to iPSC and implanting through autologous transplantation. The generation of embryonic stem cells by a selection of inner cell mass from a blastocyst, culture, and then reprogramming/genome editing for different purposes. See Fig. 2.1.

The CRISPR and CRISPR-associated systems(Cas) represent one of the powerful tools for studying diseases through the creation of model organisms generated by targeted modification and by the correction of disease mutations for therapeutic purposes. CRISPR-Cas systems have been applied successfully to the visual sciences and study of ophthalmic disease. As a modification of zebrafish and mammalian models of eye development and disease, to the correction of pathogenic mutations in patient-derived stem cells. Recent advances in CRISPR-Cas delivery and optimization boast improved functionality that continues to enhance genome-engineering applications in the eye. This review provides a synopsis of the latest implementations of CRISPR-Cas tools in the field of ophthalmology. It meant for many years, the search for a way to obtain large quantities of these cells without having to use human embryos. Finally, in 2006, this process was successful with the discovery of induced pluripotency stem cells known as iPS, Takahashi and Yamanaka obtained those cells, and to generate iPS, those researchers took cells from adult tissues, which induced the expression of four genes capable of de-differentiating and transforming them into stem cells, similar to those found in embryos (Chichagova et al. 2020). It marked the beginning of a new era in the field

of regenerative medicine, since they offered a range of immense possibilities and, also, successfully surpassed the barrier of ethics (Peng et al. 2017).

The surgical procedures and some techniques currently used for ocular surgery are described below, which has been coming in for decades to benefit patients. Some of them are already used, and others are still in the experimental phase before they can be marketed or approved by bioethics committees and implemented. The progress has been classified according to the most used eye surgery.

### *2.2.1 Laser Eye Surgery*

Of the ocular surgical techniques that have incorporated nanotechnologies and artificial intelligence techniques, is Laser assisted in Situ Keratomileusis (LASIK) computerized surgery has been describing as one of the eldest, with the incorporation of mathematical algorithms for the postoperative prediction and although not known as artificial intelligence, have been the most accurate calculations involving mathematical formulas. The recent inclusion of robotic surgery and monitors inside operating rooms are some of the challenges for eye surgery shortly. A group of equations that have contributed mainly concerning the previous ones is the inclusion of more predictive values. Olsen was the one that in addition to predictive values of axial length and keratometry, added the preoperative anterior camera deep (ACD) and the crystalline thickness. Later, Holladay developed a new formula, Holladay II, increasing the number of predictive values to seven (axial length, keratometry, ACD, white- white, crystalline thickness, preoperative refraction, and patient age) (Srivannaboon et al. 2013).

Although the author before the development of the formula Holladay II, developed strategies to improve clinical results by adding diopters to the power of the lens calculated with the formula Holladay I, the publication of his new formula was a before and after in terms of said formula, especially in short eyes, offering the possibility to improve refractive results. Indeed, authors such as Fenzl (Fenzl et al. 1998) state that with this formula 90% of patients can be achieved within a range of (positive and negative Dioptrias) $\pm$1D of the desired refraction and 100% in the field of $\pm$2D.

Another of the fourth generation formulas for LASIK surgery was the one developed by Haigis et al., which uses the axial length, keratometry, and depth of the anterior chamber for the calculation of intraocular power. Three constants characterize the difference of this formula: constant provided by the manufacturer ($a_0$), associated to the ACD ($a_1$) and constant ($a_2$) associated with the axial length and calculated by regression methods using data from multiple surgeons (Whang et al. 2020). Another essential feature of this formula is its usefulness in the calculation after refractive surgery, since for the estimation of the effective lens position (ELP), it does not use the keratometry, is the one known with Haigis-L (Kim et al. 2015). Corneal essential to think about, the conceptions of regulation, around the world, and know all the new technologies to research is demonstrating that the

incorporation of exogenous recombinant human stromal cell-derived factor-1 alpha (SDF-1 alpha) with thermosensitive chitosan-gelatin hydrogel (CHI hydrogel) accelerated corneal epithelium reconstruction with more native structural and functional properties and increased local expression of growth factors that are essential for corneal epithelium repair. The mechanism by which the exogenous SDF-alpha promotes corneal repair may involve in inducing proliferation and migration of chemokine stromal-cell derived factor-1 known as CXCR4-expressing in limbal epithelial stem cells (LESCs) and mesenchymal stem cells cells (MSCs) to the injury site via the SDF-1/CXCR4 chemokine axis. Therefore, SDF-1 alpha/CHI hydrogel complexes could be a benefit to the future application. As a biosecurity way, to prevent pre and post-surgery infections, novel hydrogels as a chitosan/$\beta$-glycerol phosphate solution can be administered as an eye drop that will form a transparent dressing on the front of the eye. The dressing will deliver a sustained release of antibiotics, killing bacteria, but not harming the cells in the cornea (Tang et al. 2017).

For precision surgery, an early detection of ectasia the tomographic and biomechanical index, which combines scheimpflug-based corneal tomography and biomechanics for enhancing ectasia detection. The detection of mild or subclinical forms of ecstatic corneal diseases has gained relevance because these cases are at high risk for developing iatrogenic progressive ectasia (keratectasia) after corneal laser vision correction. Ectasia progression occurs due to the biomechanical decompensation of the corneal stroma, which is related to the preoperative predisposition or biomechanical status of the cornea and to the structural impact from the surgical procedure itself and after surgery. The effect from the procedure may be evaluated using parameters such as the residual stromal bed and the percent of tissue altered. Although different artificial intelligence methods are available, the random forest method provided the most efficient strategy for developing the TBI (Ambrósio et al. 2017). As for any machine learning method, it is fundamental to include a cross-validation method to infer or presume external validity of the model. The current study chose the leave-one-out cross-validation (LOOCV). This method increases computational time and complexity, but also significantly increases the reliability or robustness of the model in classifying new data. A possible study for assessing ectasia susceptibility involves the analysis of the preoperative state of cases that developed ectasia after laser vision correction along with the surgical parameters that represent the impact from surgery on the cornea. Another possible approach is to integrate finite element simulations with the corneal structural and shape analysis. Also, adding longitudinal study for a retrospective evaluation of patients who progressed to clinical ectasia would further improve criteria to define such a group as simulation models very useful also in nanotechnology for design nanocompounds.

### 2.2.2 Cataract Surgery

As a field of regenerative medicine and nanotechnology, the repair and regeneration of tissues using endogenous stem cells represent an ultimate goal. Currently, the only treatment for cataracts, the leading cause of blindness worldwide, is to extract the cataractous lens and implant an artificial intraocular lens. However, this procedure poses notable risks of complications; they isolate lens epithelial stem/progenitor cells (LECs) in mammals and show that Pax6 and Bmi1 are required for LEC renewal. A new surgical technique of cataract removal that preserves endogenous LECs and achieves functional lens regeneration in rabbits and macaques, as well as in human infants with cataracts was proved on China. The method differs conceptually from current practice, as it preserves endogenous LECs and their natural environment maximally, and regenerates lenses with visual function. This approach demonstrates a novel treatment strategy for cataracts and provides a new paradigm for tissue regeneration using endogenous stem cells (Sharma et al. 2016). Researchers have developed a surgical technique with stem cells to eliminate the cataract. The method developed by scientists at Sun Yat-sen University (China) and the University of California, San Diego (USA) removes the cataract from the inside of the lens through a small incision. This structure is coated with epithelial crystalline stem cells, which usually repair the damage. Before the tests, scientists estimated that this procedure would regenerate the lens. The team reported that tests with rabbits and monkeys were successful, so the method was then tested in 12 children. Otherwise, the intraoperative optical coherence tomography (iOCT) is a noninvasive imaging modality that provides real-time dynamic feedback of the various surgical steps. The use of iOCT as an aid to decision-making has been successfully reported in cases undergoing keratoplasty, implantable collamer lens (ICL) implantation as well as cataract surgery. iOCT helps to assess the graft-host relationship in penetrating keratoplasty, to detect subclinical big bubbles and guide layer by layer stromal dissection in cases of deep anterior lamellar keratoplasty. It acts as a guide during crucial surgical steps in endothelial keratoplasty, right from the scoring of the descemet membrane to ensuring graft apposition at the end of surgery. The morphological features of the corneal incision in phacoemulsification may be assessed cells (Ehlers et al. 2014).

The iOCT is a useful tool in assessing the status of the posterior capsule and may help identify preexisting posterior capsular defects during cataract surgery in various clinical scenarios such as posterior polar cataract, traumatic cataract, and vitrectomized eyes. It allows on-table assessment of the Implantable Collamer lens (ICL) vault and potentially facilitates the exchange of ICL in the same sitting in extremes of the vault. Ocular surface disorders such as ocular surface squamous neoplasia, pterygium, and dermoid may find an application for iOCT, wherein an iOCT-guided stromal dissection will ensure adequate depth of dissection. Further technological advancements may allow for automatic centration and tracking and address the present limitation of instrument-induced shadowing. Intraoperative OCT is a useful tool in assessing the status of the posterior capsule during cataract surgery

in various clinical scenarios. In cases with posterior polar cataract, it may help detect cases with an actual posterior capsular defect.

The tools exposed before may allow the surgeon to exercise extra caution in such cases, thus reducing the incidence of complications. It may also help ascertain the posterior capsule status in cases with traumatic cataract. Patients with posterior segment pathology often develop cataract during treatment, which may be associated with the iatrogenic posterior capsular defect. Intraoperative Optical coherence tomography (OCT) aids in decision-making in various anterior segment surgeries and has the potential to decrease surgical time as well as postoperative complications. Technological advancements have led to the replacement of handheld and microscope-mounted OCT devices with microscope-integrated iOCT that seamlessly integrates image acquisition with the various surgical steps. A prototype automated stereo vision surgical instrument tracking system developed automatically centers the iOCT scan-field on the surgical instrument tip and allows for continuous visualization of instrument-tissue interactions over a 2500 $mm^2$ field. Widespread use of this technology will further enhance the advantages of iOCT. One of the significant limitations of microscope-integrated iOCT is the shadowing induced by the surgical instruments, obscuring the underlying cross-sectional view. Further advances technology may help overcome these obstacles shortly and enhance the safety of various surgical procedures (Ehlers et al. 2014).

### *2.2.3 Glaucoma Surgery*

Stem cells derived from tissues of healthy adults such as skin, brain, bone marrow, nasal mucosa and are recently used to glaucoma treatment for their high potential to protect the optic nerve from further damage and slow the progression of vision loss due to glaucoma. It can replace the ocular tissues and include regeneration of trabecular meshwork. Also, it can be implanted inside the eye to be functional and establish working connections with the brain. The challenge for researchers and experts in nanotechnology and ophthalmologists now is to reliably differentiate into the specific ocular tissues that are damaged in glaucoma and following for any side effect (Squillaro et al. 2018; Fangueiro et al. 2015).

To avoid the fibrosis and hence capsule formation around the glaucoma implants, two of the main reasons for glaucoma implant failure. To address these issues, researchers have designed a microfluidic meshwork and tested its biocompatibility in a rabbit eye model. The amount of fibrosis elicited by the microfluidic meshwork was compared to the amount obtained by the plate of the conventional glaucoma drainage device. The microfluidic meshwork got minimal fibrosis and capsule formation after 3-months implantation in a rabbit model. It provides promising evidence to aid in the future development of a new glaucoma drainage implant that will elicit minimal scar formation and provide better long-term surgical outcomes. The drainage devices were fabricated using photolithography techniques similar to those presented previously. The fabrication was done on silicon wafers

with a nickel-releasing layer. Briefly, microchannel walls were patterned with negative photoresist SU-8, and the microchannels were formed by sacrificial photoresist (LOR 5A and AZ1505, Microchem, Westborough, MA). The meshwork had an overall area of 7 mm × 7 mm and a grid period of 100 μm. The thickness of the meshwork was four μm. The microfluidic channels had outer diameters of 20 μm and inner diameters of 8 μm. These parameters were determined according to finite element simulations to provide sufficient AH outflow (2 μL/min at 10 mmHg). After being released from the substrate, the meshworks were washed and stored in a buffer solution before autoclave and implantation (Amoozgar et al. 2017), as glaucoma drugs, the atorvastatin as a statin based on solid lipid nanoparticles has been studying as eye drops for the treatment of the age-related macular degeneration (AMD) (Yadav et al. 2020).

### *2.2.4 Vitreo Surgery*

Since they were first derived more than three decades ago, embryonic stem cells have been proposed as a source of replacement cells in regenerative medicine, and this science includes the nanotechnology field. Their plasticity and unlimited capacity for self-renewal raises concerns about their safety, including tumor formation ability, potential immune rejection, and the risk of differentiating into unwanted cell types. The authors report the medium-term to the long-term safety of cells derived from human embryonic stem cells (hESC) transplanted into patients. The human embryonic stem cells hESC and hESC-derived retinal pigment epithelium cells were generated as previously described. Briefly, vials of hESC-MA09 were thawed, expanded, and differentiated into pigmented retinal pigment epithelium patches by the current good manufacturing practices. The hESC-retinal pigment epithelium cells were assessed for safety and characterized for retinal-pigment-epithelium-specific attributes at various times. Vials of cryopreserved hESC-retinal pigment epithelium cells were thawed, formulated, Gramstained, and delivered to the operating room. Pars plana vitrectomy, including the surgical induction of posterior vitreous separation from the optic nerve anteriorly to the posterior border of the vitreous base, was done in the eye with the worst vision. 150 μL of retinal pigment epithelium was injected through a MedOne PolyTip Cannula 23/38 or 25/38 (MedOne Surgical, Sarasota, FL, USA) to deliver the targeted dose of viable retinal pigment epithelium cells into the subretinal space in sites with a preselected transition zone (the area between atrophic photoreceptor, retinal pigment epithelium, and choriocapillaris and fairly healthy post-equatorial retina) as the centre is assessed with autofluorescence and optical coherence tomography imaging. Transplantation sites were chosen carefully based on the presence of native, albeit compromised, retinal pigment epithelium and similarly compromised overlying photoreceptors to optimize the chances of transplant integration and potential for photoreceptor cell rescue. Three dose cohorts were treated for each disorder: cohort 150,000 cells (three patients with Stargardt's macular dystrophy and three with age-related macular

degeneration); cohort 2, 100,000 cells (three patients with Stargardt's macular dystrophy and three with age-related macular degeneration); and cohort 3, 150,000 cells (three patients with Stargardt's macular dystrophy and three with age-related macular degeneration). The oral-systemic immunosuppression regimen included tacrolimus and mycophenolate mofetil 1 week before the surgical procedure and continued for 12 weeks. Researchers found that hESC-derived cells were well tolerated for up to 37 months after transplantation in individuals with atrophic age-related macular degeneration and Stargardt's macular dystrophy. So far, in the two clinical trials, there were no serious adverse safety signals attributed to the transplanted cells. Potential safety concerns about the use of hESC in people, including the possibility of teratoma formation, immune reactions, and the risk of cells differentiating into unwanted ectopic cell types were not noted. According to literature reports, teratoma formation was expected to arise within the first few months after transplantation, but this was not the case in our patients who have been followed up for a median of 22 months. To the best of our knowledge, this is the first report of the results of medium- term to long-term safety and tolerability after transplantation of cells derived from pluripotent stem cells in individuals with any disease (Schwartz et al. 2015).

On the other hand, the intravitreal implant of fluocinolone acetonide 0.19 mg (ILUVIEN) is one of the recent corticosteroids implants for the treatment of diabetic macular edema (DME).

### *2.2.5 Retina Surgery*

The artificial soft retina developed used rigid and hard material. In 2017, a Colombia student of Post-Doctoral study at Oxford University at the Chemistry Department can successfully obtain a biological artificial retina tissue developed in the laboratory. It will be a revolutionary innovation for bionic implants and future surgeries and a new alternative for patients with retinosis pigmentaria. They are using light into electrical signals that travel through the nervous system, triggering a response from the brain, ultimately building a picture of the scene on. This new development of a new synthetic, double-layered retina which closely mimics the natural human retinal process immerse in soft water droplets (hydrogels) and biological cell membrane proteins. Designed like a camera where the cells act as pixels, detecting, and reacting to light to create a greyscale image (Schild 2020). See Fig. 2.2.

In 2015, Steven Schwartz and colleagues reported the results of treatment of 18 patients with advanced dry age-related macular degeneration and Stargardt's disease (juvenile macular degeneration) using stem cells. Transplantation of stem-cell derived retinal pigment epithelial cells cannot restore vision but might be able to prevent further disease progression; low vision is one of the challenges for surgeons in recent years. With a micro fundus perimeter, which allows visualization of the retina and where a person fixes a target, they identified that the eyes that improved were unable to move the fixation target out of the scotoma onto seeing the retina at

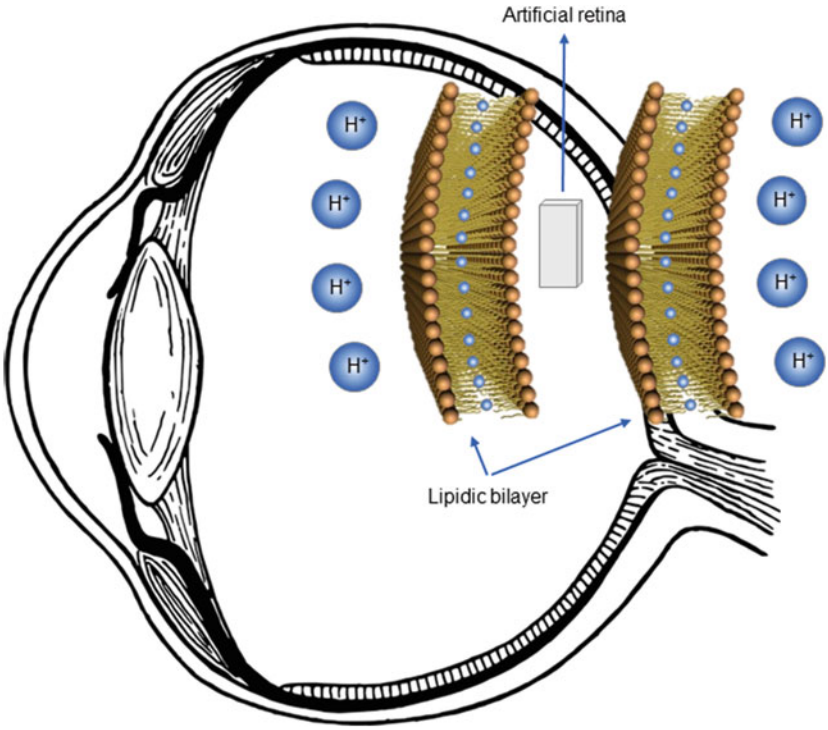


**Fig. 2.2** Schematic retina implant

baseline. This improvement of vision in the worse eye inevitably comes into play when interest focuses on repeated testing or administration of treatment to that eye pre and postsurgical.

Otherwise, to creating an automatic system to locate and segment the optic nerve head (ONH) in eye fundus photographic images using genetic algorithms, the diagnosis and surgical procedures will have more certain pictures of the optical nerve. It is called "Domain knowledge," and it is used to create a set of images' guide. Initially, using an eye fundus color image as input, a collection of hypothesis points was obtained that exhibited geometric properties and intensity levels similar to the ONH contour pixels. Next, a genetic algorithm was used to find an ellipse containing the maximum number of hypothesis points in an offset of its perimeter, considering some constraints. The curve thus obtained is the approximation to the ONH. This study was performed with the database belonging to the Ophthalmology Service at Miguel Servet Hospital, Saragossa (Spain). Researchers report that those algorithms can reinforce when it is applied to a different image base to predict the changes in the contour of the papilla and see pixels with geometric characteristics and intensity levels using MATLAB software (Schwartz et al. 2015).

### 2.2.6 *Oculoplasty*

Various techniques of autologous fat grafting have been described and are becoming increasingly popular as a primary surgical procedure and as an adjunct to other processes; for example, the use of periocular fat grafting and fillers in their approach to rejuvenation of the periocular aesthetic unit and management of cicatricial ectropion. The surgical techniques suggest a real benefit from combining autologous fat grafting with traditional lifting techniques as a substitute for using a posterior spacer graft in the management of the retracted lower eyelid after blepharoplasty. The method consists of autologous fat harvesting that was performed using a Coleman-type method. Fat grafting was performed in combination with various lifting procedures, as a substitute to a posterior spacer graft, to function as a scaffold that provides additional vertical support to the eyelid. The fat harvesting and preparation are performed under intravenous propofol anesthesia with supplemental local anesthesia and nano compounds will be a good alternative for better penetration. Two percent of Xylocaine with 1:100,000 epinephrine was injected around the lower eyelids and in the submental area with a 30-gauge needle. The tumescent anesthetic agent was infiltrated in the outer thigh or suprapubic area where liposuction was performed. A 2-hole Coleman harvesting cannula with a blunt tip was attached to a 10-mL Luer- Lok syringe, enabling manual aspiration of the fat. Fatwas manually filtered and then placed into 3-mL syringes and then placed upright in a sterile bowl to allow separation of the fat. Once the fat settled, the infra- and supernatant were decanted out, leaving the pure yellow fat. The purified fat was transferred to 1-mL syringes via a Luer-Lok connector (Al Fayez 2013).

The principal role of fat grafting in the setting of post blepharoplasty ectropion is to push/stretch the anterior and middle lamellae up across the entire horizontal length of the retracted lower eyelid while the posterior lamella is being released. At the same time, retractor release and lateral tightening necessary to elevate further and stabilize the retracted eyelid. Fat stem cells may also improve internal scarring and reduce further cicatrix formation. This technique provides significant improvement in eyelid position while avoiding the use of a posterior lamellar spacer graft. The authors have not used posterior lamella spacers in the surgical management of blepharoplasty-induced lower eyelid retraction for some years. In conclusion, the authors' experience suggests that for management of blepharoplasty-induced lower eyelid retraction, autologous fat grafting plays a useful role in optimizing both the functional and aesthetic rehabilitation, in combination with standard lifting techniques. It is the first case series demonstrating the use of autologous fat grafting as an adjunct procedure for the correction of post blepharoplasty lower eyelid retraction.

Otherwise, the use of monoclonal antibodies has been described in the treatment of orbital vascular lesions, lymphoma, and squamous cell carcinoma. Inflammatory conditions treated with monoclonal antibodies include thyroid eye disease, IgG4 disease, and granulomatosis with polyangiitis. Immunotherapy with checkpoint inhibitors has also found applications to orbital disease. Use of small molecule inhibitors has been described in the treatment of basal cell carcinoma, squamous

cell carcinoma, and Erdheim–Chester disease. There are many orbital, lacrimal, and eyelid side effects of molecular target agents (MTAs) with which the oculoplastic surgeon should be familiar, including hypertrichosis, edema, and orbital and eyelid inflammation. Small molecule inhibitors (SMIs) block a metabolic or enzymatic step in the target cell, which halts the growth of the cell. As opposed to monoclonal antibodies, small molecule inhibitors can often cross the blood–eye, and blood-brain barrier. The name of the molecule describes the targeted metabolic or enzymatic step. Ending in -tinib,—zomoib,—ciclib, or -parib denotes a tyrosine kinase, proteasome, cyclin-dependent kinase, or poly-ADP-ribose polymerase inhibitor, respectively. Thus, ibrutinib, an inhibitor of Bruton's tyrosine kinase, (BTK) is a tyrosine kinase inhibitor (-tinib). Straddling oculoplastic surgery and external disease and success of the treatment of vernal keratoconjunctivitis and mucous membrane pemphigoid has been investigated with monoclonal antibodies. Omalizumab, an anti-IgE antibody that binds to circulating IgE has been reported to be effective in the treatment of severe refractory vernal keratoconjunctivitis. Treating refractory mucous membrane pemphigoid with nanocomposites of rituximab has also shown promises for recovery postsurgical inflammation (Allen 2017).

This are recognized companies designing clinical trials for advanced dispositions to include those new technologies based on nanotechnologies to the surgeons service: Stargardt disease, including Advanced Cell Technology®, Acucela®, Alcon (Novartis)®, Alexion®, BioMarin®, Cell Cure®, Genentech (Roche) ®, Intrexon®, Janssen®, Pfizer®, Stem cells®, and Sucampo® and the new innovations ones which are working on patents and improve new techniques to be implemented in surgical environments. One of the innovations was "Argus II," one of the recently approved retina implants has a miniature video camera located in the eyeglasses of the patient who captures a scene. The patient carries a minicomputer that receives and processes the video. These instructions are transmitted wirelessly to the retinal implant. Once there the chip converts the signals into small pulses of electricity that bypass the damaged photoreceptors of the macula and directly stimulate the remaining cells of the retina, which transmit the information through the optic nerve, to the brain creating the perception of patterns of light. A micro camera housed in the patient's glasses captures the images, and these are sent to a small computer that the patient carries on, where they are processed and transformed into instructions. These are transmitted wirelessly to the antenna of the retinal implant. These impulses stimulate healthy cells that remain in the retina and send information to the brain through the optic nerve to create the perception of light patterns, which patients learn to interpret (Schaffrath et al. 2019).

In summary, "Argus II" works as a macular implant that is attached to an external high definition camera and a processor that stimulates the inner retina and ends up generating a visual stimulus in the visual pathways and improves the patient's vision. The user of this chip should wear glasses, which have the camera inserted, and a mini computer on top, which receives the scenes that the camera captures. The computer system transmits the information wirelessly to the implant, and the chip converts the signals into tiny pulses of electricity that stimulate the retina and create

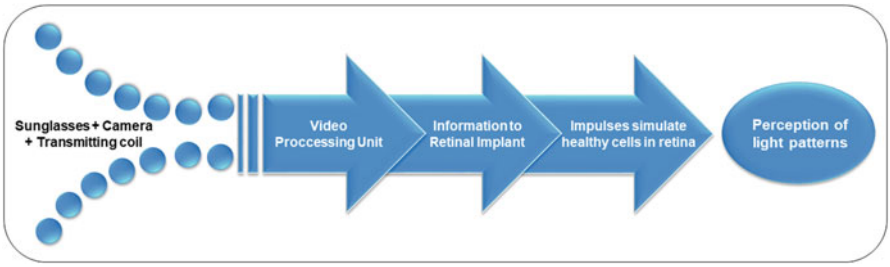


**Fig. 2.3** Functional process of Argus II retinal implant

patterns of light. The dispositive in 2017, cost $US 100.000 approximately. See Fig. 2.3.

## 2.3 Present and Future of Eye Surgery: Nanotechnology, Genomic and Nanorobotics

A recent project named WET: Whole eye transplantation will be the most ambitious. Blindness afflicts ~39 million people worldwide. Retinal ganglion cells are unable to regenerate, making this condition irreversible in many cases. Whole-eye transplantation (WET) provides the opportunity to replace diseased retinal ganglion cells, as well as the entire optical system and surrounding facial tissue, if necessary. Recent success in face transplantation demonstrates that this may be a promising treatment for what has been to this time an incurable condition. An animal model for WET must be established to further enhance our knowledge of nerve regeneration, immunosuppression, and technical aspects of surgery. A systematic review of the literature was performed to evaluate studies describing animal models for WET. In the majority of published research, WET can result in the recovery of vision in cold-blooded vertebrates. There are a few instances in which mammalian WET models demonstrate survival of the transplanted tissue following neurovascular anastomosis and the ability to maintain brief electroretinogram activity in the new host. Mammalian animal models for WET will be the future research for translation to human eye transplantation. Human WET holds promise to restore vision to patients who have blindness. Significant research has been conducted to achieve this goal. However, it was seen as science fiction some decades ago, the first mention of eye transplantation in humans occurred as early as 1885 *Revue Générale d'Ophthalmology*. Dr. Chibret removed the staphylomatous and buphthalmic eye of a 17-year-old girl and placed a rabbit. But what if it is true is that science and advances are promising for these patients. Table 2.2, Summarize the recent innovation of nanotechnology and artificial intelligence for eye surgery.

**Table 2.2** Innovation in nanotechnology and artificial intelligence for eye surgery

| Innovation | Eye surgery | Purpose |
|---|---|---|
| Steam Cells | Cataract, Cornea, Vitreo, Oculoplastic, Glaucoma | Tissue regeneration (Tang et al. 2017) |
| Algorithms for precision measurements | LASIK, Cataract, Keratoplasty | Application of mathematical algorithms for precise surgeries (Sharma et al. 2016) |
| iOCT | Retina, Glaucoma | Glaucoma, retina (Ehlers et al. 2014) |
| Retina Implant and micro-electronic memristors (MEMS) | Retina | Restoration of vision through electrical signals (Schaffrath et al. 2019) |
| CRISPR-Cas systems | Reconstruction of ocular tissues | Regenerative ophthalmology (Lane et al. 2020) |

## 2.4 Conclusions

Advances in nanotechnology, stem cells and the incorporation of robotics and nanotechnology continue to revolutionize surgical techniques and present a challenge to surgeons and institutions that train future visual health professionals to incorporate these new technologies, create protocols and establish mechanisms so that the transfer of technology can reduce costs to benefit patients. Shortly, blindness in the world will be a subject of research and social inclusion, so that these new patents and developments can reach from public policies and foundations people who need it. It requires teams of professionals such as ophthalmologists, engineers, molecular biologists and professionals who in one way or another know about research management to help communities to make these new devices known and can be used by those who need them.

The training of new ophthalmologist surgeons should be viewed from a global perspective not only with medicine, but even their preparation should incorporate engineering, artificial intelligence, robotics, nanotechnology and learn to make stem cell cultures. In developing countries, these devices are not accessible because of the vast sums of money involved in establishing research centers and doctoral training at this level. But you can think of the help of fellows and support through governments to finance these innovative talents. The ophthalmic industry is also changing and incorporating this new equipment, standardizing tests, and making the transition from animal models to humans. Bioethics committees must also be trained to allow and be aware of any changes that may or may not be beneficial to making significant adjustments.

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