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REVIEW ARTICLE

Fouling in ocular devices: implications for drug delivery, bioactive surface immobilization, and biomaterial design

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Abstract

The last 30 years has seen a proliferation of research on protein-resistant biomaterials targeted at designing bio-inert surfaces, which are prerequisite for optimal performance of implantable devices that contact biological fluids and tissues. These efforts have only been able to yield minimal results, and hence, the ideal anti-fouling biomaterial has remained elusive. Some studies have yielded biomaterials with a reduced fouling index among which high molecular weight polyethylene glycols have remained dominant. Interestingly, the field of implantable ocular devices has not experienced an outflow of research in this area, possibly due to the assumption that biomaterials tested in other body fluids can be translated for application in the ocular space. Unfortunately, progression in the molecular understanding of many ocular conditions has brought to the fore the need for treatment options that necessitates the use of anti-fouling biomaterials. From the earliest implanted horsehair and silk seton for glaucoma drainage to the recent mini telescopes for sight recovery, this review provides a concise incursion into the gradual evolution of biomaterials for the design of implantable ocular devices as well as approaches used to overcome the challenges with fouling. The implication of fouling for drug delivery, the design of immune-responsive biomaterials, as well as advanced surface immobilization approaches to support the overall performance of implantable ocular devices are also reviewed.

Keywords Biomaterials · Ocular · Fouling · Protein adsorption · Implantable device · Drug delivery · Immune responsive

Abbreviations

MEMS	Microelectromechanical systems
DME	Diabetic macular edema
AMD	Age-related macular degeneration
FBR	Foreign body response
GDD	Glaucoma drainage device
TF	Tissue factor
PMN	Polymorphonuclear leucocytes
ACAID	Anterior chamber-associated immune deviation
ROS	Reactive oxygen species
TLR	Toll-like receptors
PRR	Pattern recognition receptor
HMGB 1	High mobility group box 1
MCP	Monocyte chemotactic protein
MIP 1β	Macrophage inflammatory protein 1β
DC	Dendritic cells
CLs	Contact lens
IPN or ipn	Interpenetrating polymer networks
MPC	2-Methacryloyloxyethyl phosphorylcholine
PMPC	Poly(2-methacryloyloxyethyl) phosphorylcholine
PSiMA	Poly(bis(trimethylsilyloxy)methylsilylpropyl glycerol methacrylate)
IOL	Intraocular lens
ACO	Anterior capsular opacification
PCO	Posterior capsule opacification
FGF	Fibroblast growth factor
LBL	Layer by layer
ASC	Anterior subcapsular cataract
MIGS	Minimally invasive glaucoma surgery
TBO	Trabeculoctomy
TBE	Trabeculectomy
GFS	Glaucoma filtration surgery
MMPC	2-(Methacryloyloxy)ethyl-[N-(methacryloyloxy)ethyl phosphorylcholine
BSA	Bovine serum albumin
FIH	First in humans

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Introduction

Ocular implants have been promoted as being able to overcome patient compliance issues and other limitations with chronic topical ocular drug administration [1]. The physiological and anatomical structures of the eye maintain a formidable barrier to prolonged contact and drug release from topical eye drops and hence have become a trade-off for invasive implantable devices [2, 3]. It is therefore not surprising that the current landscape for ocular drug delivery comprises a host of implantable devices (Table 1) that ranges from simple contact lenses to advanced electroscope/cameras that can aid the blind eye. Such devices also include platforms for ocular fluid drainage in glaucoma, punctal plugs, polymeric drug reservoirs, microfluidic devices, microelectromechanical systems, scleral buckles, and diagnostic devices. These devices are becoming increasingly common for treating a variety of difficult-to-treat (due to anatomical and physiological barriers) anterior and posterior segment eye diseases and disorders [4 5]. Incidentally, the demand for such devices will continue to increase with the steady increase in the life expectancy of patients since most chronic eye diseases such as age-related macular degeneration (AMD), cataract, diabetic macular edema (DME), and retinopathy are age related [6]. Consequently, the demand for newer biomaterials that are ocular compatible has also increased.

The advanced ocular implantable technologies available today began a journey over 100 years ago, with the first device consisting of horse hair implanted in 1906 by Rollet [7] and an intraocular lens in 1949 by Ridley [8]. Continuous innovation has led to the development of a wide range of synthetic, semi-synthetic, and natural biomaterials and bioadhesives (including nano-enabled systems) for use as ocular implants [9]. Hence, ocular devices have become routine as part of treatment modalities provided by ophthalmologists [6].

Nevertheless, the available ocular biomaterials are not without application constraints in terms of mechanical appropriateness, ocular toxicity, biodegradability profile, and desirable surface properties such as their bio-inertness or anti-fouling features. Several researchers have produced disruptive innovations to overcome these challenges, particularly for implantable ocular devices.

Fouling is the accumulation of cellular matter or bio-organisms on non-biological surfaces (biomaterials) when such biomaterials are found in contact with fluids or tissues in an environment. The ocular space as a biological environment is discussed in this review. Fouling is initiated within seconds of implanting a device in the body. The first step in fouling is the non-specific protein adsorption onto the surface of device closely followed by the cascade of scarring,

Table 1 Ocular implants in the horizon

Implant	API	Company	Drug development phase	Ocular site	Ref
BIM ring	Bimatoprost	ForSightVISION5	II	Fornix	[1]
iDose™	Travoprost	Glaukos Corp	III	Intracameral	[2]
OTX-TP	Travoprost	Ocular Therapeutix	IIb	Intracanalicular	[3]
Dextensa	Dexamethasone	Ocular Therapeutix	III	Intracanalicular	[4]
Implant	Dexamethasone		Preclinical development	Suprachoroidal	[5]
Magnetic micropump	Ranibizumab	Replenish Inc	I	Subconjunctival	[6]
Triggerfish®	Sensor	SENSIMED	IV	Corneal	[7]
Port delivery system	Ranibizumab	Genetech	II	Vitreous	[8, 9]
LipoLat CS202	Latanoprost	Peregrine Ophthalmic	IIb	Subconjunctival	[10]
Eye-D VS10	Latanoprost	BioLight Lifesciences	IIa	Subconjunctival	[11]
L-PPDS	Latanoprost	QLT	II	Punta	[12]

blockage, and possible failure of devices to function as expected [10]. When micro-organisms are the foulants, this is termed biofouling [11]. Fouling is an integral part of the self-preservation, foreign body response cascade by which a surface (perceived by the body as intruding) is cordoned off in a collagenous capsule [12]. Fouling presents a significant challenge in terms of device and treatment failure as well as the potential for life threatening complications to the patient [13]. With certain devices such as the contact lens, proteins are the only foulants and the effect of fouling may be limited to diminishing lens performance, whereas with other ocular devices, it can progress to a full foreign body response (FBR) resulting in device failure. Therefore, the development of biomaterial surfaces that are resistant to protein adhesion, being the first and limiting step to fouling, is critical to ensure optimum device performance [13] and often presents a clue to device bio-inertness and biocompatibility [14].

Prior to the prolific use of polymers for designing implantable devices, metals and their alloys, such as gold, silver, stainless steel, platinum, and cobalt, were used in the bio-fabrication of such devices. Others that followed include ceramics, pyrolytic carbon, and composites [15]. However, polymeric biomaterials are now predominantly used due to their bio-mimetism, relative light weight and flexibility, processability, versatility, tunable physical properties, and amenability to functionalization for advanced ocular drug delivery. In addition, continuous innovation has yielded biomaterials that can elicit a stimuli-responsive function in the ocular space [16 17].

Biopolymers used for intraocular drug delivery can be broadly classified as either biodegradable or non-biodegradable. The process of fouling has more significance for non-biodegradable devices than biodegradable systems. Whereas biodegradable polymers are inherently biodegraded in concert with the mechanisms of drug release, non-biodegradable polymers remain intact representing a continuous "threat" and therefore, a focus of attack by the body's defense mechanism. Paradoxically, bio-fabricated scaffolds and implants used in tissue engineering applications such as those for corneal transplantation must support protein adhesion, cell proliferation and integration for efficacy. In keratoplasty, a biodegradable biomaterial is used to replace, repair or regenerate a diseased or destroyed cornea. The biomaterial used in keratoplasty must, therefore, support the attachment, migration, and proliferation of corneal cells so as to enable the integration of the newly placed biomaterial into the ocular surface [18].

Ocular implantable devices vary with respect to their application, i.e., either for diagnostics, drug delivery, or tissue replacement. Some have overlapping function such as theragnostic devices [19]. Contemporary drug delivery devices may be made up of various components depending on the application. The components of such devices that make direct contact with the ocular environment needs to be rendered biocompatible. Hence, polymers such as polyvinyl alcohol (PVA), poly(1–2-vinyl pyrrolidinone) (PVP), polymethyl methacrylate (PMMA), poly(hydroxy ethyl methacrylate) (PHEMA), ethylene–vinyl acetate (EVA), poly(propylene), and silicone have been used extensively in the production of many commercially available ocular devices. Also, studies have shown that these polymers can be made anti-fouling in laboratory experiments [20]. However, multiplicity of issues that have hindered the translation of biomaterials developed on a lab scale to clinical use have been compounded by the relative lack of harmonized experiments and disease models. For instance, Ronbeck and colleagues (2014) compared the posterior opacification outcomes in different intraocular lenses, namely round edge heparin surface-modified PMMA, round edge silicon, and sharp edge hydrophobic acrylic [21]. Despite having three different biomaterials, all also had three different modifications effectively making objective comparison difficult. This means that it may not be clear whether the best performing intraocular lens is as a result of specific modification or material properties. In addition, many biomaterials that have been developed to inhibit the protein adhesion step of fouling have performed well under in vitro test conditions (i.e., in the presence of one or two proteins) but perform poorly under more complex in vivo test conditions. This reflects the relative lack of optimal models for in vitro experimentation [22].

The ocular space is uniquely different from other confined areas of the body in many aspects. It is an immune privileged environment and therefore, the inflammatory response differs. This requires modifications to intraocular devices that are customizable to either the anterior or posterior segment of the eye [12] as there are reported instances of failed performance of biomaterials or devices within the ocular environment that performed well in other areas of the body as an implant. Ayyala and coworkers evaluated a biomaterial, Vivathane, developed and tested for heart valve function [23], as a glaucoma drainage device [24]. Its performance in the eye was abysmal relative to results obtained in the heart. It may be possible that fouling played a significant role in the failure of the biomaterial or device for intraocular application.

Therefore, this review provides a concise incursion into the phenomenon of fouling applied to ocular implantable devices to achieve bio-inertness and biocompatibility. It examines different devices such as topical vision correcting contact lenses as well as intraocular lenses, telescopes/camera devices, glaucoma drainage systems, punctal plugs for treating dry eyes, scleral buckles for correcting retinal detachments, and ocular inserts for advanced drug delivery to the posterior and anterior segments of the eye. In each of

these areas, emphasis is placed on the influence of fouling on device performance and its implications for drug delivery and the future development of ocular biomaterials.

The impact of fouling in the ocular environment

The response of the eye to an implanted device generally comprises two phases. The first phase is an inflammatory response involving acute and chronic stages and aimed at repairing the surgical wound from implant insertion. The second phase is an immune response to ''eliminate'' the implant. Each phase is preceded by the adsorption of proteins from the injured blood vessels, ocular fluids and tissues to form a film, which constitutes the foulant, on the implanted device [25]. Usually, the device surface is enclosed within a complex fusion of adsorbed proteins based on affinity for the biomaterial. According to the Vromans effect [26], even though the types of adsorbed proteins may transition over time, the quantity remains stable due to the inability of proteins to absorb non-specifically to the monolayer. The properties of the device such as surface charge, matrix stiffness, rugosity, physiochemical characteristics, and topography play a significant role in determining the quantity and composition of the protein biofilm during fouling [27]. Figure 1 depicts the activation of the coagulation cascade, compliment, and platelet adhesion through different but interconnected pathways in response to an implanted device. Factors XII, XIIa, and tissue factor (TF) work concurrently in the coagulation cascade to release thrombin, followed by platelet activation to form a transient blood cloth matrix from fibrin deposition. Complement proteins such as polymorphonuclear leukocytes (PMN) and monocytes activated through pathways C1 to C5 can sense fibrinogen adsorbed onto the surface of devices (biomaterials) and induces platelet activation as well as cell adhesion that leads to a coagulation cascade. The extracellular matrix (ECM) releases fibronectin and vitronectin that regulates the inflammatory process and facilitate the fusion of macrophages to foreign body giant cells on the device. This either increases inflammation or assists in wound healing. Persistent stimuli will lead to the chronic inflammatory stage with the release of T lymphocytes and natural killer cells (NKCs). The implanted device becomes engulfed in a collagenous sheet which stimulates angiogenesis or neovascularization [29 30]. The foreign body response to implanted devices (or biomaterials) varies in different regions of the eye. A more detailed description of the processes is provided in other reviews of the literature [31 28]. The eye is a regionally immune privilege organ and when the blood-ocular barriers are intact, the inflammatory immune response is limited to the anterior chamber, vitreous, and subretinal space, while the cornea, iris, ciliary body, retina, and subconjunctival space are prone to tightly regulated immune functions [32]. T regulatory cells secreted by the anterior chamber-associated immune deviation (ACAID), corneal endothelial cells, and retinal pigment epithelial cells are together responsible for maintaining the immune privilege status of the ocular micro-environment [33]. In any case, the degree of immune privilege of any part of the eye can be compromised by factors such as the disease state and surgical invasiveness.

The extent and implications of fouling in implanted ocular devices

Several anatomical sites in the eye are amenable to the implantation of ocular devices ranging from contact lens devices for vision correction and drug delivery, intraocular lenses, glaucoma drainage devices, and predominantly intravitreal devices for sustained and site-specific drug delivery [34] (Fig. 2). The extent of fouling associated with these devices is critical in order to evaluate device performance and varies with implantation site and in severity of adverse outcomes. Excessive fibrosis in the formation of bleb for certain glaucoma drainage devices has been shown to be responsible for up to 50% of resulting complications [35]. Outcomes of protein adsorption on contact lenses have been shown to depend not only on the quantity of adsorbed protein, but also on the quality, speed of adsorption, and the location [36]. Adsorbed protein denatured by interaction with contact lens biomaterial can lead to discomfort, may trigger immune reactions such as contact lens papillary conjunctivitis, and may lead to dry eyes as an inflammatory outfall [37]. Likewise, biofilm formation with consequent bacterial adhesion also results in inflammatory response such as contact lens induced red eye and peripheral ulcers [38]. These adverse events lead to approximately 50% drop out in contact lens wearers [39].

CL devices

Contact lens (CL) devices are designed to be inserted onto the tear fluid layer covering the cornea, were originally intended for vision enhancement, but have morphed to include cosmetic applications and for therapeutic drug delivery. CLs are not considered as implantable devices [15], but its intimate contact with the eye surface and increasing propensity to be used as a drug delivery device has necessitated its inclusion in this review. Although fouling does not proceed further than the initial protein adhesion step in CL devices, changes in the secondary structure of proteins adsorbed on the CL device lead to changes in the tear fluid, causes possible dehydration of the cornea, and may reduce visual acuity. Incidentally, the

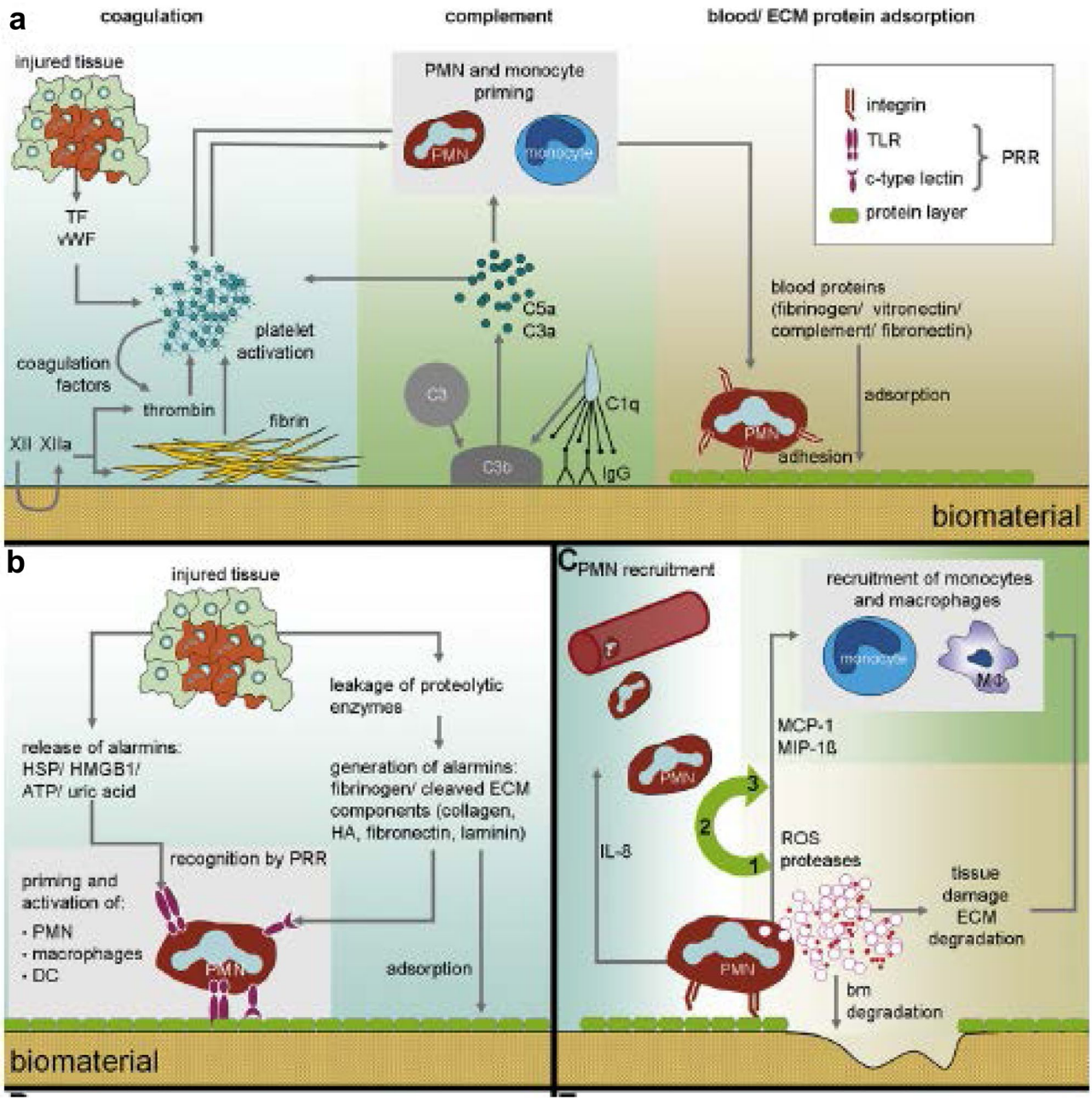

Fig. 1 **a** Protein adhesion, coagulation cascade, and complement activation with consequent release of PMN and macrophages. **b** Damaged tissue releases which leads to further immune response. **c** Continued inflammatory response leads to release of proteolytic enzymes and reactive oxygen species (ROS) which may damage the biomaterial surface. Adapted from Biomaterials, vol.32, no. 28, S. Franz, S. Rammelt, D. Scharnweber, and J. C. Simon, "Immune responses to implants—a review of implications for the design of immunodulatory biomaterials," Copyright (2011) with permission from Elsevier [28]

tear fluid is very rich (though in varying proportions) in simple and complex proteins such as lysozyme, lactoferrin, albumin, fibronectin, and vitronectin [38]. Once in contact with the tear fluid, these proteins adsorb to the CL device surface and this interaction causes changes in the adsorbed protein's secondary structure [41]. These denatured proteins can trigger an inflammatory immune response which contributes to the 12–15% adverse events in properly fitted CLs [41]. On the other hand, adsorption of certain proteins such as lysozyme and lactoferrin can lead to a reduction in the viable bacterial count and an improvement in the antimicrobial properties of the adsorbed proteins [38]. This effect, however, depends on the coadsorption or otherwise of other competing proteins. In the case of

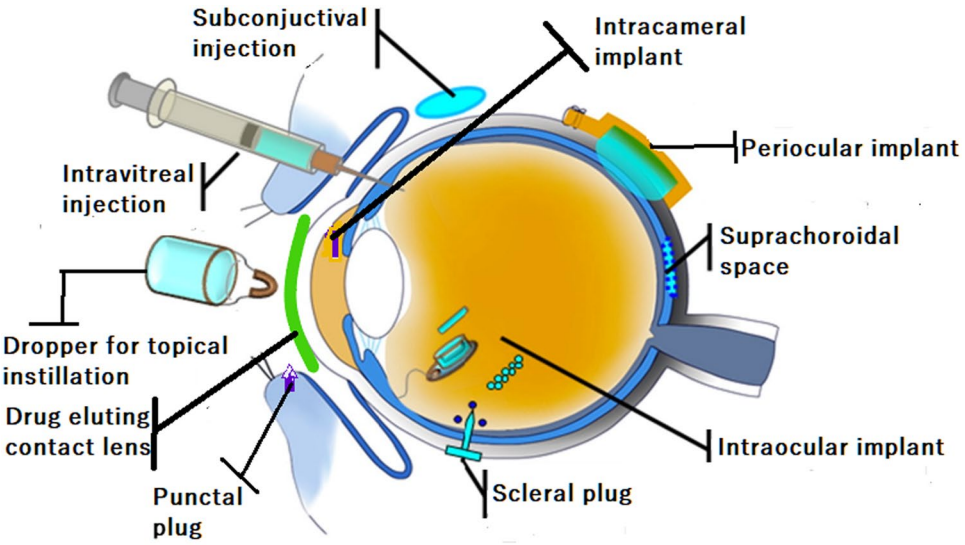

Fig. 2 Possible sites of ocular implant placement. Adapted from *Adv. Drug Deliv. Rev.*, vol. 128, pp. 148–157, H. Kaji, N. Nagai, M. Nishizawa, and T. Abe, "Drug delivery devices for retinal diseases," Copyright (2018) with permission from Elsevier [40]

lactoferrin and lysozyme, the effect of adsorbed lysozyme on *P. aeruginosa* depends on the amount of lactoferrin coadsorbed [38]. It is worthy of note that the nature of the interaction with the biomaterial surface [36] greatly determines the outcome of such interactions.

CL devices were introduced over 50 years ago by Wichterle and Lim [42]. Since then, there has been a continuous improvement on the biomaterial properties to optimize functionalities that limit the perceived drawbacks over time. The early approaches to incorporating drugs into CLs involved immersion into drug solutions that resulted in bursts of drug release [43]. As nanotechnology emerged, so did CLs containing drugs dispersed as nanoparticles [44 45], nanomicelles [46], nanoliposomes [47], and nanoemulsions [48]. However, these nanocolloidal systems affected the transparency of CLs and modified the properties of the pre- and post-lens tear fluid [49]. In order to overcome this challenge, different archetypes of CL inserts such as rings [50] and sandwiches [43] emerged. Goda and colleagues also improved the surface properties of PDMS with 2-(methacryloyl)ethyl-[N-(2-methacryloyl)ethyl]phosphorylcholine (MMPC) crosslinked 2-methacryloyloxyethylphosphorylcholline (MPC) and showed that it minimized protein adhesion in the ocular environment [51]. Also, Maulvi and coworkers developed a CL loaded with hyaluronan formed as a ring outward from the center to prevent vision obstruction (Fig. 3) [52].

Other researchers designed CLs in the form of nanowafers containing an array of nanoenabled drug reservoirs for sustained drug delivery [53]. Ciolino and colleagues demonstrated that careful choice of components can minimize the effect of drug loading on the transparency of drug-loaded CLs [54]. The continuous improvement of biomaterials has seen a comparative exponential progression in the number of CL users and serves as a catalyst for the design of newer biomaterials with properties that can improve CL platforms for drug delivery [55]. Figure 4 depicts the progressive market shift of various types of CL biomaterials in the USA for 2018 and 2019 [56].

In addition, the limitations of topical eye drops and the invasiveness of intravitreal implants for treating posterior segment eye diseases have positioned CLs as the ocular drug delivery device of the future. This limitation, for topical instillation, arises because the bioavailability of topically administered drops rarely exceeds 5% due to the short residence time and rapid tear turnover [57]. On the other hand, this limitation for intravitreal implants arises due to the corneal enforced, limited accessibility of topically administered drugs to the posterior segment. Peng and coworkers demonstrated that the CLs device can be used as a platform to extend the release and by extension, the bioavailability of a topically administered timolol in beagle dogs [58]. Studies by Ross and colleagues showed that the contact lens device can be used to overcome the formidable corneal barrier and deliver dexamethasone, over several weeks, to the retina in a non-invasive application [59]. Byrne and coworkers developed a CL device based on a silicon hydrogel in which receptor sites are embedded for commonly used ocular drugs, particularly antibiotics and anti-inflammatory agents via molecular imprints. These sites create a strong affinity between the drug and the CL thereby achieving sustained drug release [60].

The prediction that CLs can do more than correct vision is also witnessed in the design of the Triggerfish® device [61]. Triggerfish® is a CL device made up of a sensor designed to detect changes in the cornea that arises from the constantly changing aqueous humor volume in glaucomatous eyes over a 24-h period. This platform could also be used as a micro-electro mechanical system (MEMS) as proposed by Lee and coworkers [62] for drug delivery. Similarly, in pursuit of more

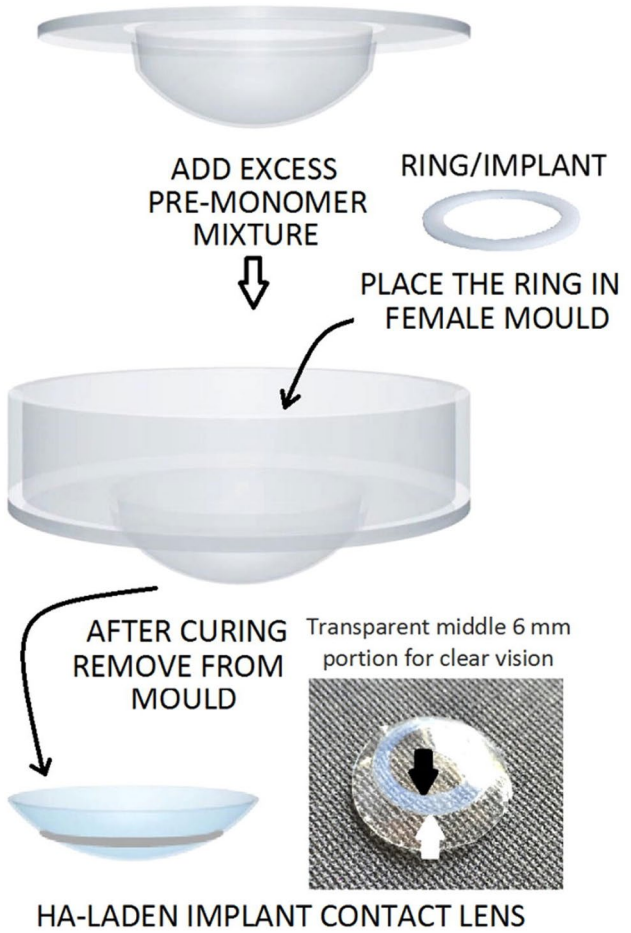

Fig. 3 Contact lens with hyaluronan ring prepared by cast molding. Reprinted from *Acta Biomater.*, vol. 53, no. 15, F. A. Maulvi, A. A. Shaikh, D. H. Lakdawala, A. R. Desai, M. M. Pandya, S. S. Singhania, R. J. Vaidya, K. M. Ranch, B. A. Vyas, D. O. Shah "Design and optimization of a novel implantation technology in contact lenses for the treatment of dry eye syndrome: *in vitro* and in *vivo* evaluation". Copyright (2017) with permission from Elsevier [52]

non-invasive ocular technologies, Badugu and coworkers developed a CL device comprising a silicon hydrogel interpenetrating network (IPN) that was conjugated with glucose sensitive fluorophores (Quin C18) that fluoresced in inverse proportion to the concentration of glucose absorbed [63]. With an appropriate UV detection device, the concentration of glucose in tear fluid was accurately measured from the CL under conditions of minimal disturbance of the tear fluid to enhance the reliability of measurements.

It should be noted that the insertion and the prolonged wearing of CL devices has not always been comfortable for patients and had led to instances of poor compliance. Approximately 50% of contact lens wearers experience some form of discomfort till date [64]. Proteins and lipids are the main foulants in CLs, and this fouling constitutes the major source of discomfort experienced with the wearing of CL devices. These foulants are adsorbed from tear fluid and results in conformational changes in cationic lysozymes and lactoferrin that are predominantly present [65]. In addition, certain forms of keratitis, dry eye syndrome [66], and even blurring of the lens [43 67] can result.

The surface modification of biomaterials has been a predominant method of limiting fouling in silicon hydrogels used in the design of CL devices. The surface modification has been shown to only temporarily reduce the protein adhesion step [15] due to the fluid dynamics involved. The major categories of soft contact lens biomaterial currently in use were classified by the International Organization for Standards, ISO. These are predominantly silicone hydrogels and hydrogels and their susceptibility to protein or lipids adsorption is illustrated in Fig. 5. According to ISO, group II materials conventionally contain silicone and represented by non-ionic hydrogels with medium to high content water. Group IV materials are ionic and contain fluorine rather than silicone. It can be seen from Fig. 5 that both group II and IV materials attract a high level of proteins.

Shimizu and colleagues developed a CL polymeric biomaterial based on random block copolymers, poly(MPC-co-SiMA) and an IPN (MPC-ipn-PSiMA) of silicone base material, (bis(trimethylsilyloxy)methylsilylpropyl glycerol methacrylate) (SiMA), and poly(2-methacryloyloxyethyl phosphorylcholine) (MPC). Figure 6 shows the result of protein adsorption studies of the IPN (MPC-ipn-PSiMA), the block copolymers, poly(MPC-co-SiMA), and a commercially available CL device. MPC-ipn-PSiMA and poly(MPC-co-SiMA) containing 30% and 39% of MPC, respectively, had the least protein adsorbed indicating a reduction in fouling [68].

IOL devices

Intraocular lens (IOL) replacement following phacoemulsification has been the standard of cataract treatment as the most common lens disorder [69]. Cataract is the leading cause of reversible blindness. With over 20 million surgeries annually, cataract surgery is the most commonly performed procedure not requiring hospitalization [6] [70]. Before the introduction of phacoemulsification (that reduced the time spent in surgery and utilizes minimal 2.8 mm incisions) by Kelman and coworkers, cataract extraction involved creating large incisions that resulted, in addition to other complication, astigmatism [69 71]. Despite advanced micro-incisive phacoemulsification, the prospects of complete success in cataract surgery remains limited by the posterior and anterior capsule opacification (PCO and ACO). These usually necessitate a second procedure (Nd-YAG laser capsulectomy) causing further complicated and serious adverse events [72].

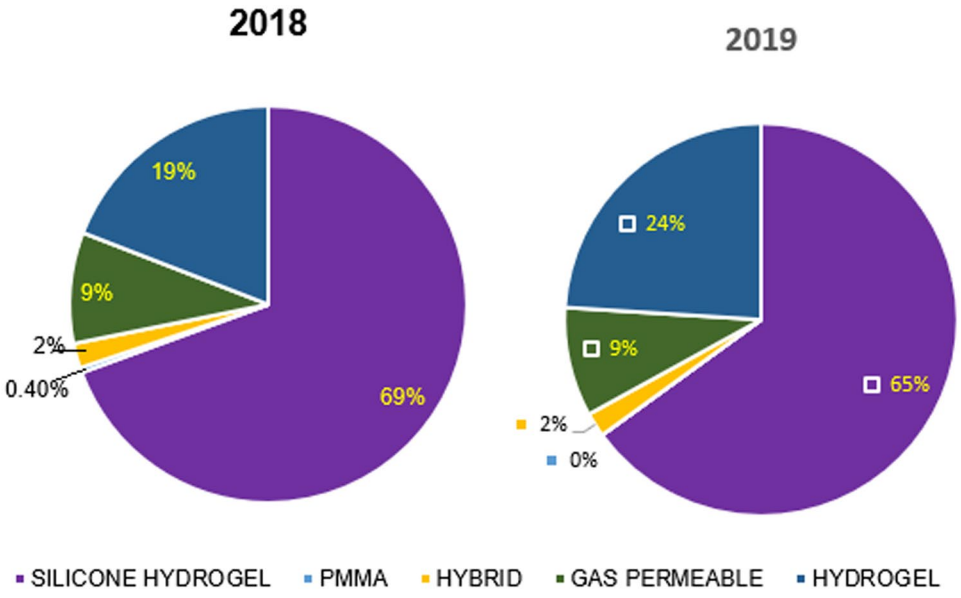

Fig. 4 The 2018 (**a**) and 2019 (**b**) prescription of CL by material in the US courtesy of Jason J. Nichols, OD, MPH, PhD. Adapted and Reused with permission from the January 2019 and January 2020 issues of *Contact Lens Spectrum* [56]

Although the anterior chamber of the eye is an immune privilege site, the injury caused by the surgical incision (however minimal) leads to the disruption of the blood-aqueous barrier and influx of inflammatory cells that will eventually lead to PCO and ACO. ACO is often, initiated by protein and lens epithelial cell adhesion (mediated by integrin) while migration and proliferation (mediated by fibroblast growth factor, FGB) leads to PCO. Simultaneously, the presence of inflammatory cytokines in the aqueous humor with the surgical incision promotes opacification of the newly implanted lens [73]. Fibronectin and fibrin have been identified as the major proteinaceous adsorbing components on rabbit eyes implanted with IOL devices [74] and may contribute to the formation of fibrinous uveitis after phacoemulsification [75]. While ongoing efforts such as the use of antioxidants are targeted at the prophylaxis of cataract, there is an immediate need to improve the outcomes of surgical treatment for approximately 40% of adults and 100% of children patients affected by cataract surgery complications annually [15 76].

It has been established that the most important factors predisposing to PCO and ACO are the surface properties of the biomaterial used and the design of the IOL device [77 78]. These remain a recurring challenge in determining the outcome of cataract surgery. In order to reduce PCO, cataract surgery is always followed by the administration of topical drops containing proliferation inhibitors and antibiotics [75]. From topical drops, ophthalmologists began immersing IOL devices into drug solutions of proliferation inhibitors before insertion. However, drug-loaded IOL devices afforded drug release as a bolus over a short period of time [79] and efforts

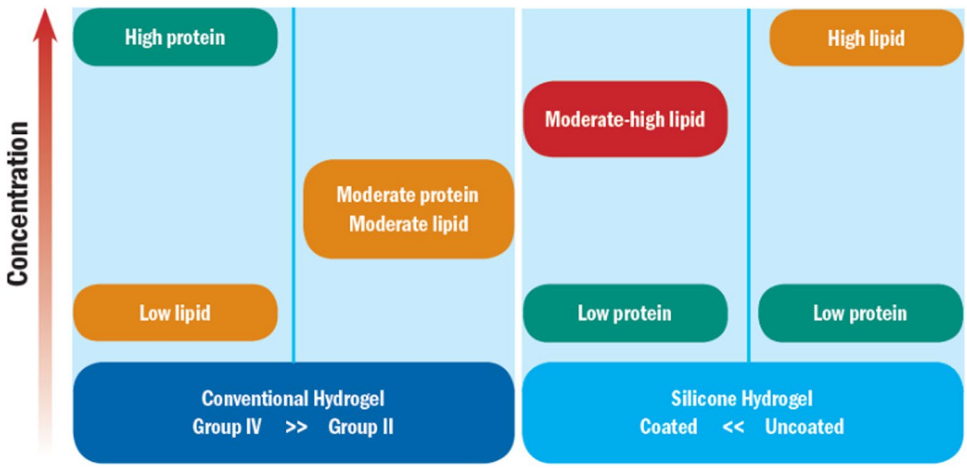

Fig. 5 Schematic illustration of trends in lipid and protein deposits on different contact lens materials Adapted from [37]. Mann A and Tighe B. Contact lens interactions with the tear film. Experimental Eye Research, 2013;117:88–98) with permission from Elsevier

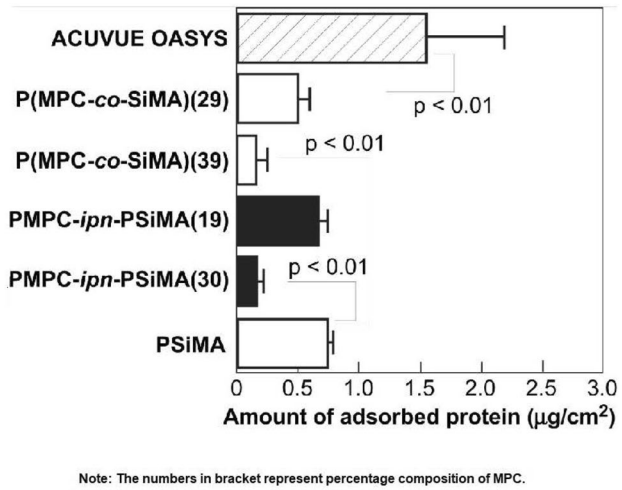

Fig. 6 Quantity of protein adsorbed on modified silicone; (MPC-ipn-PSiMA), poly(MPC-co-SiMA), and marketed ACUVUE OASYS. Reprinted from *Biomaterials*, vol. 31, no. 12, T. Shimizu, T. Goda, N. Minoura, M. Takai, and K. Ishihara, "Super-hydrophilic silicone hydrogels with interpenetrating poly (2-methacryloyloxyethyl phosphorylcholine) networks," Copyright (2010) with permission from Elsevier [68]

geared towards the use of drug-loaded IOL devices for site-specific drug delivery to minimize post-surgical inflammation have continued.

Adjunctive therapy with anti-inflammatory agents (and antioxidants) has also effectively brought to the fore the possibility of using IOL devices for vitreo-retinal drug delivery [75]. Han and coworkers developed a drug-eluting IOL device by condensing doxorubicin (DOX) into chitosan nanoparticles prepared by polyelectrolyte condensation between cationic chitosan and tripolyphosphate [75]. The DOX-loaded chitosan nanoparticles were loaded into the IOL device using layer-by-layer (L-b-L) assembly to achieve a multilayered IOL device. The DOX concentration increased as the layering increased. Previously, high-dose dexamethasone-loaded devices (such as Ozurdex®) were implanted into the posterior chamber in an additional surgery that led to cataract development in pristine lenses due to the multiplicity of surgical invasions in the ocular space particularly in patients with coexisting morbidities such as glaucoma [17].

Rugose device surfaces (comparatively sharp and rounded device edges) have also been shown by several researchers to retard protein adhesion as the first step to limit fouling [80]. Auffarth and coworkers evaluated the effect of edge design of IOL devices on PCO development [81] and found a close correlation between the edge type and development of PCO. Findl and coworkers also confirmed that the rounded edges preferentially predisposed to PCO than sharper edge designs [82]. Consequently, there has been a concerted effort to improve the design of IOL devices through the development of biomaterials that limit the protein adhesion step in fouling. Early attempts at improving the properties of IOL devices involved the use of coating materials such as Teflon [83], F+ ion [84], and titanium [85]. Current modifications focus on using super hydrophilic polymers and heparin [86] as coating materials. Xu and coworkers examined the effect of pegylation on the biocompatibility of a silicon hydrogel-based IOL device in rabbits [74]. In their study, a commercially available silicon hydrogel-based IOL device was compared against a polydimethylsiloxane (PDMS)-based device designed in their lab. Although statistically weak, there was claimed difference in posterior capsule hyperplasia from histology studies between the pristine and pegylated IOL device as shown in Fig. 7.

Similarly, Tan and colleagues demonstrated the uveal and capsular biocompatibility of surface modified hydrophobic IOL devices. They modified the surface by plasma grafting of copolymers of MPC and methacrylic acid with the aim of utilizing the expected synergistic action between the negatively charged hydrophilic polymers to minimize the interaction between adhering protein and the IOL devices thereby reducing inflammatory response [87]. Qin and coworkers (2017) elucidated the role played by syndecan-4 in the signaling pathway of integrin and fibroblast and

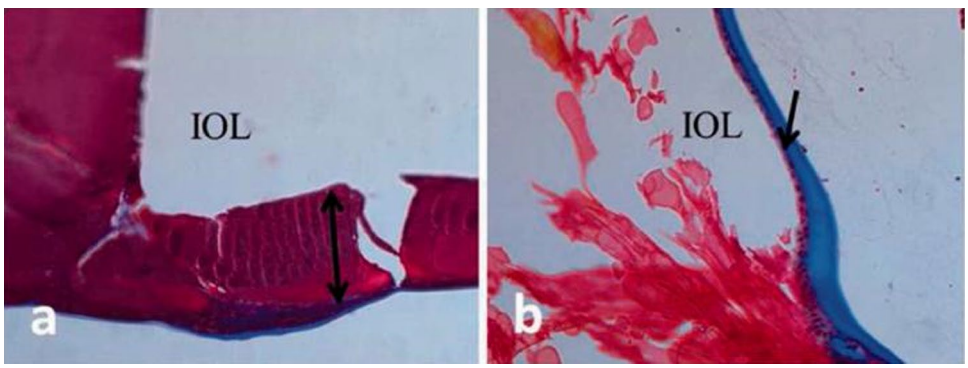

Fig. 7 Light photomicrograph of the (**a**) pristine and (**b**) pegylated IOL. The arrow shows the magnitude of posterior capsule hyperplasia. Reproduces with permission from [74]

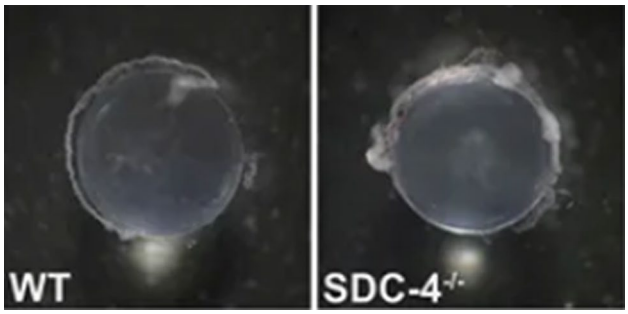

Fig. 8 The effect of syndecan-4 in the development of ASC. Reprinted from [76]

hence a possible therapeutic target for limiting capsular opacification [76]. They induced injury in the lens capsule and monitored anterior subcapsular cataract (ASC) formation in both wild-type rats (WT) and syndecan-4 (SDC-4)-deficient rats. The wild-type rats developed ASC within 3 days while syndecan-4-deficient group barely exhibited ASC as shown in Fig. 8. This could be charting a course for ocular biomaterials conjugated or ligated with syndecan-4 inhibitors as immunomodulatory materials for effective non fouling applications. Molokhia and coworkers also proposed the capsule drug ring—a possible refillable drug reservoir (Fig. 9) that was intended to take advantage of the unfilled space left in the lens capsule after surgery. The group demonstrated the proof of concept using a protein drug Avastin® to achieve the release of the drug in vitro [88].

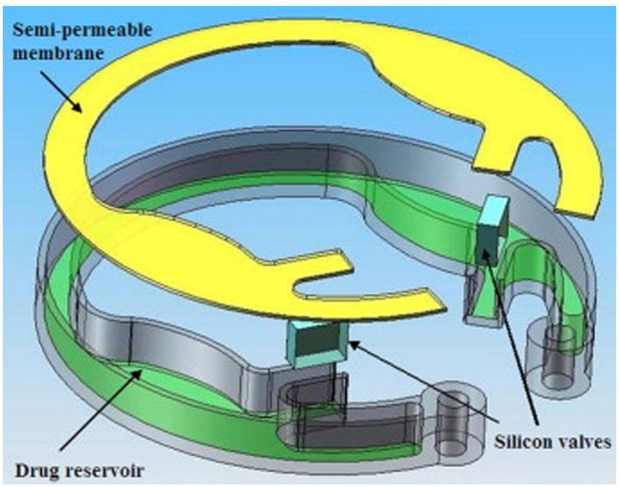

Fig. 9 Schematic representation of the capsule drug ring. Reprinted from *Vision Res.*, vol. 50, no. 7, pp. 680–685, Sarah A. Molokhia, Himanshu Sant, Jacquelyn Simonis, C.J. Bishop, R.M. Burr, Bruce K. Gale, Balamurali K. Ambati "The capsule drug device: Novel approach for drug delivery to the eye," Copyright (2010) with permission from Elsevier [88]

GD devices

Glaucoma is the leading cause of irreversible blindness, and the etiology is based on optic nerve damage resulting from the proliferation of inflammatory cytokines in the presence or absence of chronically elevated intraocular pressure (IOP) [89 90]. It has been shown that elevated IOP leads to the multiplication of the inflammatory cytokines ab initio [91]. The therapeutic management of glaucoma is aimed at lowering IOP either by reducing aqueous humor production or by increasing its outflow through various procedures such as trabeculoctomy (TBO), trabeculectomy (TBE), minimally invasive glaucoma surgery (MIGS), and the use of glaucoma drainage (GD) devices. While β-blockers, carbonic anhydrase inhibitors, α2 adrenergic agonists, and prostaglandin analogues are the first-line drugs for primary open angle glaucoma (which is the most common type) [92], glaucoma filtration surgery (GFS) is reserved for patients in whom the maximum tolerated drug therapy fails to lower IOP [93]. TBO involves the removal of some components of the trabecular mesh in a bid to improve aqueous humor flow. It is the glaucoma filtration surgical procedure of choice [8]. TBE is the creation of an ostium into the interior chamber from under a scleral flap that leads to the formation of a filtering bleb [93]. GD device surgery (also called tube shunts) presents an alternative to TBO as an initial procedure or in the event of failure [94]. GD devices have traditionally been used to physically drain aqueous humor in conditions of high IOP and have the capacity to maintain flow consistency and reduce hypotony [91]. Fouling of GD devices resulting from the foreign body response to the device ultimately causes fibrosis and closure of blebs in GFS and around GD device plates. Currently, antimetabolites such as mitomycin C, 5-fluorouracil [95], and pirfenidone [84] are often used to manage inflammatory response that leads to the fouling of GD devices.

Unfortunately, the life span of the most innovative GD device does not exceed 5 years [8] due to fibrosis, scarring, and blockage leading to device failure [96]. An attempt to undo scar-induced blockages of GD devices involved the use of an enzyme injection that dissolved the fibrosistic tissue. However, the sustainability of this approach remains to be tested [97]. The most important factors in the fouling of a GD device are the nature and design of the biomaterial used for the fabrication of the device. Elevated IOP always results in the buildup of proinflammatory cytokines in the aqueous chamber. GD devices by design must be able to withstand the surge of pro-inflammatory cytokines in the aqueous chamber post-insertion of the device. The FBR process can be impeded if there is a way of reducing the level of Transforming Growth Factor β-2 (TGFβ-2) that is induced by the high

IOP and elevating the level of pro-apoptotic FAS-ligand that promote fibrosis resolution. Various attempts have also been made to modify the biomaterials for constructing GD devices in order to minimize fibrosis. Ayyala and coworkers explored Ahmed GD devices (propylene), Baerveldt GD devices (silicone), and a third material Vivathane® developed by the University of South Florida and used in a magnetically actuated left ventricular assist device [24]. Their findings supported an earlier study by the same authors [98] on the comparative inertness of silicone over the other biomaterials. Acosta and coworkers also evaluated the biocompatibility of a novel polymer hybrid polystyrene–polyisobutylene triblock polymer (Quartromer™) as a possible GD device biomaterial. The properties were compared to that of PDMS and found to be superior [99]. Likewise, Choritz and colleagues demonstrated the influence of surface topography on the long-term performance of GD devices [100]. The surface evenness of four commercially available GD devices was studied using scanning electron microscopy (SEM) and cell proliferation studies. Results obtained indicated that the smoother surfaces (through a combination of mechanical stimulation and early cell attachment) were less prone to fibrosis and may be why anti-inflammatory agents are less effective in minimizing GD device fibrosis. Table 2 provides a list of selected commercially available GD devices and their biomaterial of construction.

Historically, the efficiency of most GD devices was measured at 70% with an annual failure rate of 10% predominantly caused by device scarring [101]. With improvement in the design of biomaterials with anti-fouling properties, minimally invasive devices and procedures are now preferred. In 2006, Pan and coworker designed an artificial nanodrainage implant that exploited MEMS miniaturization technology to produce a nanoporous mesh mounted at one end of a polymeric shaft [89] to drain the aqueous humor via the uveo-scleral pathway. The nanopores also prevented bacterial invasion while PEGylation of its silanol grafted surface provided anti-fouling properties (improved bio-inertness). Similarly, Amoozgar and colleagues used the concept of a microfluidics mesh-work to replace the plate in traditional GD devices (Fig. 10) [96]. In 2018, Ahmed and coworkers started first-in-humans trials of a minimally invasive glaucoma surgery (MIGS) device known as MINIjet® and developed by iSTAR medical SA [102]. The injectable device comprises medical grade soft and flexible porous silicone that utilizes the uveo-scleral pathway for draining aqueous humor. The device pores are coated with a loose collagen capsule after bio-integration such that each drainage pore remains viable for a long time. Another MIGS-based stent, Xen45® gel (a gelatin-based stent), was developed by Allergan has also been evaluated [103, 104]. This injectable implant is made from collagen derived gelatin and crosslinked with glutaraldehyde. Studies show that there were no fibrosis for the duration of the study [105].

Intravitreal devices

Intravitreal devices are a group of implants designed from biodegradable and non-biodegradable biomaterials used to target posterior segment eye diseases that often require chronic

Table 2 Marketed GDDs and materials of construction. Reproduced from (*Br. J. Ophthalmol.* "Glaucoma drainage devices; past, present and future,"K. Lim, B. Allan, A. Lloyd, A. Muir, and P. Khaw., Vol. 82, no.9, pp. 1083–1089, Sept. 1998) with permission from BMJ Publishing group LTD. [8]

GDDs	Year introduced	Tube diameter/material	Plate size/material	Resistance mechanism
Molteno	1979	0.63 mm OD 0.30 mm ID Silicone	135 mm^2 polypropylene	None
Baerveldt	1990	0.63 mm OD 0.30 mm ID Silicone	200, 250, 350, 500 mm^2 silicone	None
Krupin with disc	1990	0.58 mm OD 0.38 mm ID Silicone	180 mm^2 silicone	Slit valve
Ahmed	1993	0.63 mm OD 0.30 mm ID Silicone	185 mm^2 polypropylene with silicone	Venturi valve
Optimed Model-1014	1995	0.56 mm OD 0.30 mm ID Silicone	140 mm^2 silicone with PMMA matrix	Microtubules

OD outside diameter, *ID* inside diameter

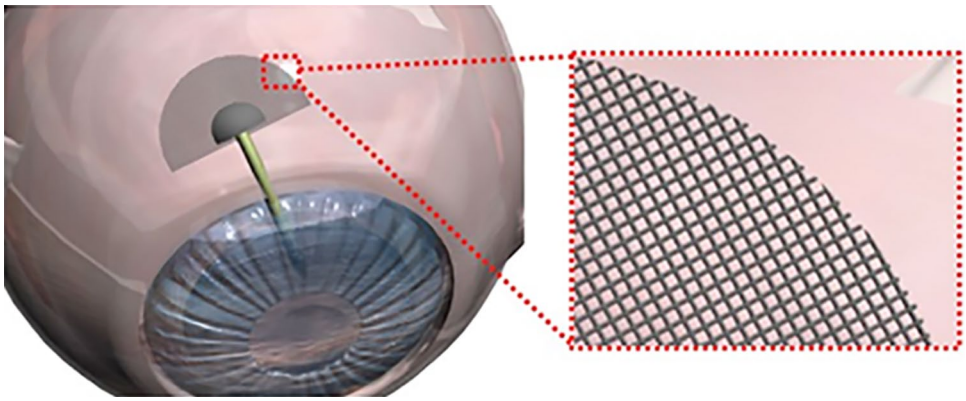

Fig. 10 An illustration of the microfluidic meshwork that replaced the plate of a traditional GDD. Reproduced from [96]

management [4]. Posterior segment eye diseases/disorders being predominantly age related and chronic are on the increase as a result of prolonged life expectancy. Unfortunately, because of the inaccessibility of drug molecules to the posterior segment from current topically administered eye drops or therapeutic inserts, intravitreal injections of drug have become the mainstay of intraocular therapy. To further complicate matters, most bio actives used to treat retinal diseases are macromolecules that are easily degraded and necessitate frequent intravitreal injection and specialized molecular carriers. A selection of FDA-approved retinal inserts is shown in Table 3.

Biodegradable intraocular devices are designed from biomaterials (polymers) that are easily degraded by enzymes in the body. The rate at which drug is released depends on the rate of biodegradation. The predominantly used biodegradable polymers in commercially available intravitreal devices comprise polylactide (PLA), poly(lactic-co-glycolic acid) (PLGA), and hydroxypropylmethyl cellulose (HPMC). For non-biodegradable polymeric devices, polyvinyl alcohol (PVA), ethylene vinyl acetate (EVA), and silicone have been mostly used. PVA is highly hydrophilic and if used alone will result in a rapid drug release. It is therefore frequently used in combination with hydrophobic EVA to control drug release over a prolonged period. For certain devices the biomaterial contributes significantly to an FBR as shown in a study with the intravitreal device Retisert®. The increased incidences of PCO in all phakic patients compared with those treated with drug alone [85] was seen as a confirmation of this

Table 3 FDA-approved drug delivery implants

Implant	API	Company	Material	Size (diameter × length)/ implant style	Approximate duration of release/ strength	Approval year	Reference
Ozurdex®	Dexamethasone	Allergan Inc	PLGA	0.46 mm × 6 mm/0.7 mg	6 months/0.7 mg	2009	[116]
Retisert®	Flucinolone Acetonide	Bausch &Lomb	PVA/Silicon	1.5 mm × 6 mm and (2 mm wide)/surgical insertion	30 months/0.59 mg	2005	[117]
Illuvein®	Flucinolone Acetonide	Alimera Sciences	PVA matrix in Polyimide tube	3,5 mm × 0.37 mm/intravitreal injection with 25-G needle	36 months/0.7 mg	2014	[118]
Vitasert®	Ganciclovir	Bausch & Lomb	PVA/EVA	(Pellets)4.5 mg/surgical insertion	8 months/4.4 mg	1996	[119, 120]
Surodex®	Dexamethasone	Oculex Pharmaceuticals Inc	PLGA/HPMC	1 mm × 0.4 mm/intracameral insertion with 25-G needle	10 days/0.06 mg		[88]
DEXYCU™	Dexamethasone	Eyepoint Pharmaceutical Inc	Durasert ™Technology	Intraocular suspension/ intracarmeral injection	21 days/0.52 mg	2018	[121]
YUTIQ™	Flucinolone acetonide	Eyepoint Inc	Durasert ™Technology	Microinsert/intravitreal in a preloaded applicator	36 months/18 mg	2018	[120]
DURYSTA™	Bimatoprost	Allergan Inc	PLGA/PLA/ PEG	1 mm/Intracameral	6 months/10	2020	[122]

contribution. Another major complication is the dislocation of the drug reservoir posing serious sight-threatening danger [106]. Du Toit and colleagues developed an intelligent intraocular implant as a stimuli-responsive system to deliver ciprofloxacin and indomethacin to the posterior segment [17]. The bio-responsive polymer matrix developed was targeted to be switched on and off in response to inflammation. Even though fouling was not important for the biodegradable implant, the smart response to inflammation elicited could be the basis of engineering non-biodegradable devices that minimize fouling through inflammation prevention.

Several researchers are working on micropump (MP) refillable devices for intravitreal implantation with many granted patents in this regard, although none have been approved by the FDA for commercialization. First-in-human trials of MP devices that reported promising results were undertaken in 2014 by Humayun and coworkers. They aimed at establishing device safety and surgical practicality [107]. MPs are designed to deliver predetermined doses of drug to the retina (posterior segment) or to the anterior segment with each comprising wireless charging (with bidirectional communication with the device) and drug refilling capability (reservoir-based).

Miscellaneous ocular devices

Other devices (or biomaterials) implanted (or used) in the ocular space include scleral buckles, punctal plugs, corneal bandages, and orbital prosthetics. These are considered separately in that their frequency of use is relatively low and their site of implantation (or insertion) is not confined to a single area within the ocular environment. However, these devices may also present with fouling and ultimately lead to device or therapy failure.

Scleral buckles are (drug-free) devices used to reconnect detached retina to sub-retinal tissues [108]. Retinal detachment can result from many ocular procedures such as chronic intravitreal injections or implantation of devices. Scleral buckles are currently made from silicone elastomers and earlier systems comprised of hydrogels but were discontinued due to late stage swelling. Scleral buckles also present an approach that can be used for site-specific drug delivery, although this has rarely been explored. Reabsorbable pigskin gelatin soaked with antibiotics was used at one point, but development of low-grade inflammatory response that can escalate limited its use [109]. In addition, hydrophilic hydrogel materials such as MIRAgel that had great potential for drug delivery was introduced about 40 years ago, but late complications arising from swelling of the matrix also stopped its use [110].

Punctal plugs (similar to canalicular plugs) are small, elongated pellets used to block the lacrimal duct to limit tear drainage [111]. It is used to treat dry eye syndrome and is useful for contact lens wearers. Two categories exist based on their biodegradability profile, i.e., resorbable (collagen-based) or non-resorbable (silicone-based) plugs [112]. A significant challenge with punctal plugs is related to fouling elicited as a result of the constituent biomaterial. This fouling is presented as granular tissue formation [113] and may result to plug migration (with consequent dacryocystitis), excessive tearing and eye infection [111]. Researchers have also explored the use of punctal plugs as drug delivery device for three concentrations of latanoprost and have passed phase 2 clinical trial [114]. Another intracanalicular plug from Ocular Therapeutix Inc., Dextenza®, containing 0.4 mg dexamethasone and delivers the drug for up to 30 days is the first to receive FDA approval [115]. Another punctual plug from the same company, OTX-TP®, containing travoprost is currently in a phase 3 clinical trial [115].

Corneal lens bandages are frequently used during keratoplasties and for keratoprosthesis to treat possible vision loss that can result from corneal injury, lacerations or infection [116]. Usually cadaveric corneas are used, though the process is fraught with challenges such as graft rejection and availability. The paucity of cadaveric grafts has catalyzed research in this direction. However, the biomaterial specifications required complicates the process of developing such grafts. Essentially the biomaterial should have specific anti-fouling properties by supporting cell adhesion at the periphery while resisting protein adsorption at the center [18]. This is a unique requirement since the cornea provides two thirds of the eye's refractive power while doubling as a barrier to environmental assault. The most commonly used artificial corneal replacement is made from PMMA and a titanium lock (the PMMA base plate has been replaced with titanium to eliminate the need for the lock) and a device comprising poly-2-hydroxyethyl methacrylate (PHEMA) [117]. Recent advances include the development of a 3D bio-printable device consisting of collagen and alginate polymers for the production of patient specific corneas [18, 108]. Currently, there is no mention of such corneal bandages to be used as drug delivery devices, though this may be feasible for conditions requiring corneal repair.

Orbital implants are molded biomaterials (mainly silicone, polyethylene, and PMMA) that can be inserted into the eye socket after eye enucleation for volume replacement and aesthetics. These implants have evolved from simple brittle, non-porous spheres to complex multifunctional devices that are available in specific shapes [118]. Fouling and FBR are some of the challenges faced with orbital implants since the underlying tissues remain active after enucleation [118].

Modification of biomaterials as an anti-fouling approach

Ideal ocular biomaterial properties include optical clarity, structural integrity, stability, durability (for non-biodegradable materials), non-toxicity, biocompatibility, and tear film stability for contact lens applications [119]. Modification methods are aimed at maintaining these properties while imparting anti-fouling behavior (resistance to protein adsorption and surface biofilm formation). There is no consensus on the limit of protein adhesion for optimal biomaterial performance and differs for various types of proteins and applications. For instance, the adsorption maximum for fibrinogen has been reported at approximately 5 ng/cm^2 [22 120]. Various approaches have been explored to solve the challenge of fouling. Preference has been given to device surface modifications and involves the use of poly(ethylene glycol) (PEG), poly(2-oxazolines) (poly(2-methyly-2-oxazoline), and poly(2-ethyl-2-oxazoline); polyglycerols (polyglycidol); carbohydrate derivatives (dextran, methylated sorbitol, heparin); and polyzwitterionics (polysulfobetaines and polycarboxybetaines) [121] in the form of coatings, grafts, and conjugates that can be physically adsorbed or covalently grafted on or from the surface in a wide range of architectures (Fig. 11) such as polymer brushes [122], self-assembling monolayers (SAM) [123], layer by layer assembly (LBL) [124], and interpenetrating polymer networks (IPNs) [125]. Table 4 provides a summary of the various categories that exist for surface modification of biomaterials intended for ocular device fabrication.

In addition to surface modification, researchers also sought to understand the role of biomaterial surface packing and homogeneity (topography) in controlling the conformation and orientation of adsorbed proteins and their interactions during the process of fouling [26]. Roach and coworkers studied the effect of surface topography and hydrophobicity on the binding characteristics of biomaterials such as bovine serum albumin (BSA) and bovine fibrinogen (BF) to silica nanospheres [127]. The study concluded that BF lost its secondary structure in binding to particles whereas the structure of BSA became disordered. These hydrophilic molecules (BSA and BF) were bound strongly to surface water such that proteins could not adhere and affording an anti-fouling behavior.

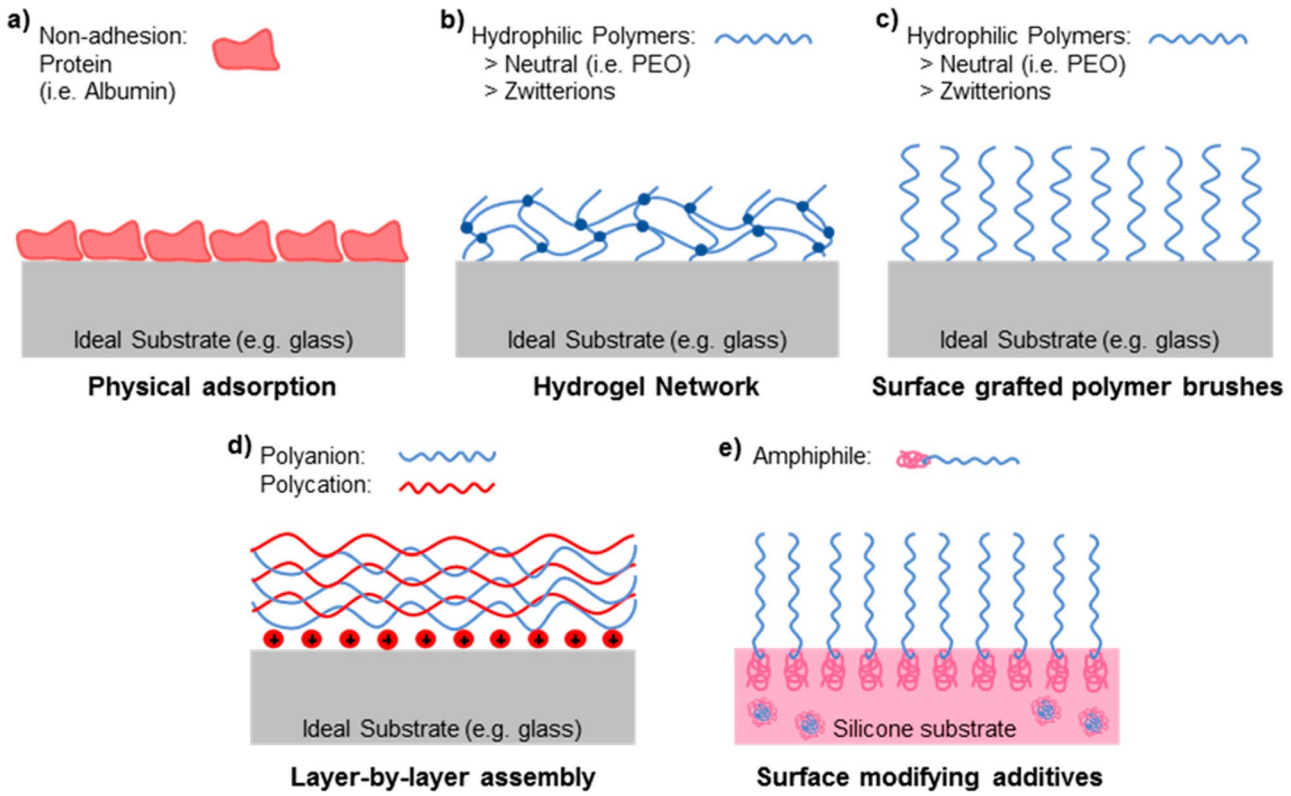

Fig. 11 Possible architectures/configurations for surface modified materials. Reproduced from B. K.D. Ngo and M. A. Grunlan, Protein Resistant Polymeric Biomaterials, *ACS Macro Lett.* Vol. 6, no 9, pp. 992-1000, (2017) with permission from American Chemical Society [126].

Table 4 Categories of surface modifications applied to ocular biomaterials

Category	Biomaterial	Modifier	Archetype	Reference
Surface methods				
Grafting to	Silicone, glass	Poly(glycidyl methacrylate-*co*-sulfobetaine methacrylate)	Self-assembled monolayers (SAMs)	[139]
Grafting	Acrylic IOL	Poly(MPC-MAA)	Covalent grafting with ammonia plasma	[87]
Functionalization	PCL	Helium-oxygen plasma	Electrospun fibers	[140]
Grafting	Silicone hydrogels	UV activated surface		[141]
Grafting from	IOL	PEG	Polymer brushes	[142]
Photochemical and plasma modification	IOL	UV/Ozone or Argon	Concentration of hydroxyl and carboxyl groups	[143]
Surface tethering	PDMS	Sulfadiazine	Film	[144]
Surface coating	PDMS CL	Alginate/chitosan	LBL assembly	[145]
Bulk methods				
Introduction of functional groups	PHEMA	Carboxylic acid, quaternary ammonium	-	[146]
Free radical polymerization	Silicone based diacrylate lens	Polyethylene glycol diacrylate	-	[147]
Crosslinking	Silicone hydrogel lens	Poly(2-methacryloyloxyethyl phosphorylcholine)	IPN	[148]
Crosslinking	MPC	2-(methacryloyloxy)ethyl-N-(2-methacryloyloxy)ethyl phosphorylcholine	Hydrogels	[149]
Copolymerization	HEMA-NVP	Sulfobetaine methacrylate	Hydrogel	[150]

Current attempts to improve the bio-inertness of ocular biomaterials are gradually moving beyond surface modification. Alternative modification method involves bulk processes in which same properties are achieved both externally on the surface and internally in the bulk of the material. For instance, for biomaterials such as polyurethanes that are made up of hard and soft segments (i.e., the degree of crystallinity determines their surface properties by microphase separation), the bulk properties are more significant to ensure anti-fouling behavior. Nanu and coworkers recognized the importance of the bulk properties of biomaterials and their influence on bio-inertness. They attempted to modify the properties of an aromatic methacrylate copolymer using the bulk incorporation of heparin [69] instead of regular surface coating with heparin. Ruiz and colleagues also studied the effect of this approach on hyaluronic acid incorporation into polyurethane and its influence on stability and biocompatibility. Their study found that even though there were no statistically significant difference in protein adsorption (fouling) between the surface and bulk modified polyurethane, the difference became significant when the samples were subjected to dynamic fluid flow in favor of bulk modified samples [128]. This may be particularly important for ocular devices that are used for aqueous humor drainage in glaucoma.

The design of immunological responsive anti-fouling biomaterials for ocular devices

Contemporary biomaterial design has geared towards the development of smart materials that respond intelligently to stimuli that either turn on or turn off specific application. Protein adhesion and the resultant fouling of implanted devices is an integral part of the body's immune response to the device targeted at tissue repair or regeneration or foreign body response to encapsulate the device. The idea of designing immunologically responsive materials is hinged on manipulating the immune response to an implanted device as a strategy for improving drug delivery of biomaterials. Successful methods will initially identify the immunological targets that can serve as a stimulus for drug release. Some potential targets may include temperature change, pH change, reactive oxygen species release, and release of cytokines, interleukins, and other markers of inflammation. A critical look at the biomarkers of ocular immune response shows the release of different

proteins, lipids, ions, and cells, through the three stages of response that comprises the acute innate inflammatory response that lasts from 0 to 4 h, subacute induced innate inflammatory response that lasts from 4 h to 4 days and the chronic adaptive immune response that lasts from 4 days till resolution or healing occurs [129]. Determining the role played by these proteins in the inflammatory process may underscore their potential use as stimuli for immunologic responsive smart biomaterial. It is known, for instance, that the abnormalities with glucose metabolism in diabetic patients result in systemic inflammation that ultimately remodels their physiology through upregulation of immune responses, excessive generation of reactive oxygen species leading ultimately to diabetic retinopathy [130]. One enzyme that has been implicated in the pathogenesis of ocular diseases with inflammatory undertone is the matrix metalloproteinases (MMPs) and their regulators, tissue inhibitors of metalloproteinases (TIMPs) [131]. MMPs are a family of neutral zinc dependent proteolytic enzymes secreted by the ocular surface alongside the inflammatory cells that proliferate in the tissues [132] and are regulated by TIMPs. Their major substrate is the extracellular cell matrix (ECM) components, secreted cytokines, and ocular surface molecules [131]. The balance between MMPs and TIMPs is strictly maintained for normal physiology. Dysregulation or imbalance in the ratio of MMPs: TIMPs can induce cellular changes in the ECM that can lead to the liberation of inflammatory mediators and oxidative stress biomarkers [133] and hence many ocular diseases. Proposed treatment modalities target strict control or inhibition of MMPs in diseases including cancer metastasis, diabetic foot ulcer, and periodontal diseases [134].

Purcell and coworkers developed an in situ forming MMP-responsive hydrogel based on polysaccharides. The aim was to overcome the dose-limiting side effects of systemically injected recombinant TIMPs (rTIMPs) and develop a biomaterial that releases the rTIMPs in response to the presence of MMP [135]. The hyaluronan-based gel remains stable when incubated in the absence of collagenase-type MMP but degraded proportionally in the presence of the enzyme. Though their study was targeted at cardiovascular tissues, the same principle can be harnessed to develop hydrogels that can only release their medicament at the presence of excess MMP activity in ocular tissues in diseases such as glaucoma. The closest to an immunologic responsive biomaterial was designed by du Toit and colleagues. They designed an intelligent intraocular implant that could release an anti-inflammatory agent in response to hydroxyl radical as biochemical implicated in inflammatory processes. The developed implant released an increased quantity of both an antibiotic, ciprofloxacin, and an anti-inflammatory agent, indomethacin.

It is obvious that not much has been done in this area with respect to ocular biomaterials although a huge majority of debilitating and chronic ocular illnesses are tied up to immunological undertones. Inflammation and oxidative stress are major markers of immune response. It is possible to utilize the immune response to implanted biomaterial to the advantage of drug delivery by designing materials that interact with the inflammatory markers that were designed by the body to attack the material.

Future perspectives and conclusions

Zwitterionic polymers are emerging as biomaterials of the future and are being repositioned as anti-fouling polymers with superior bio-inertness [10]. This is attributed to their striking similarity to membrane phospholipids such as glycine betaine and phosphorylcholine that renders them non-toxic while promoting tissue integration [136]. Past research efforts have concentrated on developing surface coatings for ocular biomaterials, but emerging clinical outcomes have shown that in certain dynamic environments, the effect of surface coatings wears off and their stability is dependent on the coating process and application. The density and packing of polymer brushes as well as their configuration determines their anti-fouling properties and efficiency in resisting protein adsorption. An important question is why these zwitterionic biomaterials (that have proven efficient as anti-fouling surface coatings) have not been explored as bulk polymeric biomaterials. A literature search revealed that due to their hydrophilicity, such polymers do not possess physicomechanical robustness [51]. Jansen and coworkers developed hydrogels from comonomers of PEG and phosphorylcholine with the intention of leveraging on their synergistic action. Surprisingly, hydrogels with the higher monomer content elicited the highest FBR. They showed that inhibition of the FBR was closely related to the mechanical modulus of the hydrogel [137]. Goda and coworkers hypothesized that mechanical deficits of zwitterionic polymers could be as a result of the structural dissimilarities between the monomers and the crosslinkers. They were the first to synthesize a zwitterionic crosslinker, 2-(methacryloyloxy) ethyl-N-(2-methacryloyloxy)ethyl] phosphorylcholine that differed from the monomer in having an extra methacrylate group and was used for the crosslinking of 2-methacryloyloxyethylphosphorylcholline [51]. Later on, Carr and colleagues synthesized a zwitterionic crosslinker for carboxybetaine methacrylate [138]. The new crosslinkers (instead of the commonly used N,N′-methylene bis(acrylamide)) yielded hydrogels that were mechanically robust while maintaining protein resistance. Therefore, current

research should be geared towards bulk grafting methods utilizing zwitterionic polymers that have shown promise in laboratory settings. With persistent research in this direction the status quo could be disrupted for implantable ocular devices to yield biomaterials with contradicting properties of desirable tissue integration and anti-fouling behavior.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Neves HP. "1 - Materials for implantable systems," in Implantable Sensor Systems for Medical Applications. Inmann A, Hodgins D, Eds. Woodhead Publishing. 2013. pp. 3–38.
2. Du Toit LC, Govender T, Carmichael T, Kumar P, Choonara YE, Pillay V. Design of an Anti-inflammatory composite nanosystem and evaluation of its potential for ocular drug delivery. J Pharm Sci. 2013;102(8):2780–805. https://doi.org/10.1002/jps.23650.
3. Subrizi A, del Amo EM, Korzhikov-Vlakh V, Tennikova T, Ruponen M, Urtti A. Design principles of ocular drug delivery systems: importance of drug payload, release rate, and material properties. Drug Discov Today. 2019. https://doi.org/10.1016/j.drudis.2019.02.001.
4. Choonara YE, Pillay V, Danckwerts MP, Carmichael TR, du Toit LC. A review of implantable intravitreal drug delivery technologies for the treatment of posterior segment eye diseases. J Pharm Sci. 2010;99(5):2219–39. https://doi.org/10.1002/jps.21987.
5. Choonara YE, Pillay V, Carmichael T, Danckwerts MP. An in vitro study of the design and development of a novel doughnut-shaped minitablet for intraocular implantation. Int J Pharm. 2006;310(1–2):15–24. https://doi.org/10.1016/j.ijpharm.2005.10.019.
6. Humar M, Kwok SJJ, Choi M, Yetisen AK, Cho S, Yun S-H. Toward biomaterial-based implantable photonic devices. Nanophotonics. 2016;6(2):414–34. https://doi.org/10.1515/nanoph-2016-0003.
7. Cullen CL. Glaucoma Drainage Devices. In: Tombran-Tink J, Barnstable CJ, Rizzo JF, editors. Visual prosthesis and ophthalmic devices: new hope in sight. Totowa, NJ: Humana Press; 2007. p. 173–90.
8. Lim K et al. Glaucoma drainage devices; past, present, and future. Br J Ophthalmol. 1998;82(9):1083–1089 Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1722728/. Accessed 04 Mar 2019.
9. du Toit LC, Pillay V, Choonara YE, Govender T, Carmichael T. Ocular drug delivery – a look towards nanobioadhesives. Expert Opin Drug Deliv. 2011;8(1):71–94. https://doi.org/10.1517/17425247.2011.542142.
10. Vassileva E. The Challenge of Non Fouling Surfaces: Polymers could be the Answer. p. 2.
11. Bixler Gregory D, Bhushan B. Biofouling: lessons from nature. Philos Trans R Soc Math Phys Eng Sci. 1967;2012(370):2381–417. https://doi.org/10.1098/rsta.2011.0502.
12. Onuki Y, Bhardwaj U, Papadimitrakopoulos F, Burgess DJ. A Review of the biocompatibility of implantable devices: current challenges to overcome foreign body response. J Diabetes Sci Technol. 2008;2(6):1003–15. https://doi.org/10.1177/193229680800200610.
13. Chen S, Li L, Zhao C, Zheng J. Surface hydration: principles and applications toward low-fouling/nonfouling biomaterials. Polymer. 2010;51(23):5283–93. https://doi.org/10.1016/j.polymer.2010.08.022.
14. Zhang TD, Zhang X, Deng X. Applications of protein-resistant polymer and hydrogel coatings on biosensors and biomaterials. 2018. https://doi.org/10.33582/2637-4927/1006.
15. Chirila T, Harkin D. Biomaterials and regenerative medicine in ophthalmology. Woodhead Publishing. 2016.
16. Bawa P, Pillay V, Choonara YE, du Toit LC. Stimuli-responsive polymers and their applications in drug delivery. Biomed Mater Bristol Engl. 2009;4(2):022001. https://doi.org/10.1088/1748-6041/4/2/022001.
17. du Toit LC, Carmichael T, Govender T, Kumar P, Choonara YE, Pillay V. In vitro, in vivo, and in silico evaluation of the bioresponsive behavior of an intelligent intraocular implant. Pharm Res. 2014;31(3):607–34. https://doi.org/10.1007/s11095-013-1184-3.
18. Isaacson A, Swioklo S, Connon CJ. 3D bioprinting of a corneal stroma equivalent. Exp Eye Res. 2018;173:188–93. https://doi.org/10.1016/j.exer.2018.05.010.
19. Xie J, Lee S, Chen X. Nanoparticle-based theranostic agents. Adv Drug Deliv Rev. 2010;62(11):1064–79. https://doi.org/10.1016/j.addr.2010.07.009.
20. Pop-Georgievski O, Rodriguez-Emmenegger C, de los Santos Pereira A, Proks V, Brynda E, Rypáček F. Biomimetic non-fouling surfaces: extending the concepts. J Mater Chem B. 2013;1(22):2859–2867 https://doi.org/10.1039/C3TB20346H.
21. Rønbeck M, Kugelberg M. Posterior capsule opacification with 3 intraocular lenses: 12-year prospective study. J Cataract Refract Surg. 2014;40(1):70–6. https://doi.org/10.1016/j.jcrs.2013.07.039.
22. Jiang S, Cao Z. Ultralow-fouling, functionalizable, and hydrolyzable zwitterionic materials and their derivatives for biological applications. Adv Mater. 2010;22(9):920–32. https://doi.org/10.1002/adma.200901407.
23. McKeown PP, et al. Magnetically actuated left ventricular assist device (lvad): acute animal test results. In: Akutsu T, Koyanagi H, editors., et al., Heart Replacement: Artificial Heart 4. Tokyo: Springer Japan; 1993. p. 295–9.
24. Ayyala RS, et al. Comparison of different biomaterials for glaucoma drainage devices. Arch Ophthalmol. 1999;117(2):233–6. https://doi.org/10.1001/archopht.117.2.233.
25. Gullapalli VK, Khodair MA, Wang H, Sugino IK, Madreperla S, Zarbin MA. Chapter 125 - transplantation frontiers. In: Ryan SJ, Sadda SR, Hinton DR, Schachat AP, Sadda SR, Wilkinson CP, Wiedemann P, Schachat AP, editors. Retina (Fifth Edition). London: W.B. Saunders; 2013. p. 2058–77.
26. Hoffman AS. Non-fouling surface technologies. J Biomater Sci Polym Ed. 1999;10(10):1011–4. https://doi.org/10.1163/156856299X00658.
27. Ferrari M, Cirisano F, Morán MC. Mammalian Cell Behavior on Hydrophobic Substrates: Influence of Surface Properties. Colloids Interfaces. 2019;3(2):48. https://doi.org/10.3390/colloids3020048.
28. Franz S, Rammelt S, Scharnweber D, Simon JC. Immune responses to implants – a review of the implications for the design of immunomodulatory biomaterials. Biomaterials.

2011;32(28):6692–709. https://doi.org/10.1016/j.biomaterials.2011.05.078.
29. Kohn J, Khan IJ, Iovine C, Velagaleti P, Anglade E, Gilger B. Ocular biocompatibility, toxicity, and distribution from erodible polycarbonate polymer episcleral implants (LX212) in rabbits. Invest Ophthalmol Vis Sci. 2010;51(13):5326–5326. Available: https://iovs.arvojournals.org/article.aspx?articleid=2373928. Accessed 22 Mar 2019.
30. Puleo DA, Bizios R. Biological interactions on materials surfaces: understanding and controlling protein, cell, and tissue responses. Springer Science & Business Media. 2009.
31. Mariani E, Lisignoli G, Borzì RM, Pulsatelli L. Biomaterials: foreign bodies or tuners for the immune response? Int J Mol Sci. 2019;20(3):636. https://doi.org/10.3390/ijms20030636.
32. Masli S, Vega JL. Ocular immune privilege sites. Methods Mol Biol Clifton NJ. 2011;677:449–58. https://doi.org/10.1007/978-1-60761-869-0_28.
33. Keino H, Horie S, Sugita S. Immune Privilege and Eye-Derived T-Regulatory Cells. J Immunol Res 2018. https://www.hindawi.com/journals/jir/2018/1679197/. Accessed 18 Feb 2020.
34. Davis JL, Gilger BC, Robinson MR. Novel approaches to ocular drug delivery. Curr Opin Mol Ther. 2004;6(2):195–205.
35. "US Patent Application for compositions, systems, and methods for scar tissue modification Patent Application (Application #20190117746 issued April 25, 2019) - Justia Patents Search." https://patents.justia.com/patent/20190117746. Accessed 27 Apr 2020.
36. "- Optician." https://www.opticianonline.net/cet-archive/5915. Accessed 27 Apr 2020.
37. Mann A, Tighe B. Contact lens interactions with the tear film. Exp Eye Res. 2013;117:88–98. https://doi.org/10.1016/j.exer.2013.07.013.
38. Willcox MD. Tear film, contact lenses and tear biomarkers. Clin Exp Optom. 2019;102(4):350–63. https://doi.org/10.1111/cxo.12918.
39. Fonn D. Targeting contact lens induced dryness and discomfort: what properties will make lenses more comfortable. Optom Vis Sci. 2007;84(4):279–85. https://doi.org/10.1097/OPX.0b013e31804636af.
40. Kaji H, Nagai N, Nishizawa M, Abe T. Drug delivery devices for retinal diseases. Adv Drug Deliv Rev. 2018;128:148–57. https://doi.org/10.1016/j.addr.2017.07.002.
41. Jacob JT. Biocompatibility in the development of silicone-hydrogel lenses. Eye Contact Lens. 2013;39(1):13–9. https://doi.org/10.1097/ICL.0b013e31827dbb00.
42. Hui A. Contact lenses for ophthalmic drug delivery. Clin Exp Optom. 2017;100(5):494–512. https://doi.org/10.1111/cxo.12592.
43. Choi SW, Kim J. Therapeutic contact lenses with polymeric vehicles for ocular drug delivery: a review. Materials. 2018;11(7):1125. https://doi.org/10.3390/ma11071125.
44. Nasr FH, Khoee S, Dehghan MM, Chaleshtori SS, Shafiee A. Preparation and evaluation of contact lenses embedded with polycaprolactone-based nanoparticles for ocular drug delivery. Biomacromol. 2016;17(2):485–95. https://doi.org/10.1021/acs.biomac.5b01387.
45. Lu C, Yoganathan RB, Kociolek M, Allen C. Hydrogel containing silica shell cross-linked micelles for ocular drug delivery. J Pharm Sci. 2013;102(2):627–37. https://doi.org/10.1002/jps.23390.
46. Mandal A, Bisht R, Rupenthal ID, Mitra AK. Polymeric micelles for ocular drug delivery: from structural frameworks to recent preclinical studies. J Controlled Release. 2017;248:96–116. https://doi.org/10.1016/j.jconrel.2017.01.012.
47. Danion A, Arsenault I, Vermette P. Antibacterial activity of contact lenses bearing surfaceimmobilized layers of intact liposomes loaded with levofloxacin. J Pharm Sci. 2007;96(9):2350–63. https://doi.org/10.1002/jps.20871.
48. Katzer T, Chaves P, Bernardi A, Pohlmann AR, Guterres SS, Beck RCR. Castor oil and mineral oil nanoemulsion: development and compatibility with a soft contact lens. Pharm Dev Technol. 2014;19(2):232–7. https://doi.org/10.3109/10837450.2013.769569.
49. Lattimore MR, Harding TH, Williams ST. Hydrogel Contact lens water content is dependent on tearfilm pH. Mil Med. 2018;183 Suppl_1:224–30. https://doi.org/10.1093/milmed/usx233.
50. Lorenz KO, Kakkassery J, Boree D, Pinto D. Atomic force microscopy and scanning electron microscopy analysis of daily disposable limbal ring contact lenses. Clin Exp Optom. 2014;97(5):411–7. https://doi.org/10.1111/cxo.12148.
51. Goda T, Matsuno R, Konno T, Takai M, Ishihara K. Protein adsorption resistance and oxygen permeability of chemically crosslinked phospholipid polymer hydrogel for ophthalmologic biomaterials. J Biomed Mater Res B Appl Biomater. 2009a;89B(1):184–90. https://doi.org/10.1002/jbm.b.31204.
52. Maulvi FA, et al. Design and optimization of a novel implantation technology in contact lenses for the treatment of dry eye syndrome: In vitro and in vivo evaluation. Acta Biomater. 2017;53:211–21. https://doi.org/10.1016/j.actbio.2017.01.063.
53. Yuan X, et al. Ocular drug delivery nanowafer with enhanced therapeutic efficacy. ACS Nano. 2015;9(2):1749–58. https://doi.org/10.1021/nn506599f.
54. Ciolino JB, et al. In vivo performance of a drug-eluting contact lens to treat glaucoma for a month. Biomaterials. 2014;35(1):432–9. https://doi.org/10.1016/j.biomaterials.2013.09.032.
55. Maulvi FA, Soni TG, Shah DO. A review on therapeutic contact lenses for ocular drug delivery. Drug Deliv. 2016;23(8):3017–26. https://doi.org/10.3109/10717544.2016.1138342.
56. "Contact Lens Spectrum - CONTACT LENSES 2017," *Contact Lens Spectrum*. https://www.clspectrum.com/issues/2018/january-2018/contact-lenses-2017. Accessed 23 Mar 2019.
57. Peng CC, Burke MT, Carbia BE, Plummer C, Chauhan A. Extended drug delivery by contact lenses for glaucoma therapy. J Control Release Off J Control Release Soc. 2012;162(1):152–8. https://doi.org/10.1016/j.jconrel.2012.06.017.
58. Peng C-C, Ben-Shlomo A, Mackay EO, Plummer CE, Chauhan A. Drug delivery by contact lens in spontaneously glaucomatous dogs. Curr Eye Res. 2012;37(3):204–11. https://doi.org/10.3109/02713683.2011.630154.
59. Ross AE, et al. Topical sustained drug delivery to the retina with a drug-eluting contact lens. Biomaterials. 2019;217:119285. https://doi.org/10.1016/j.biomaterials.2019.119285.
60. "TECHNOLOGY," *OcuMedic*. https://ocumedic.net/technology/. Accessed 23 Mar 2019.
61. "Sensimed Triggerfish – Sensimed S.A." https://www.sensimed.ch/sensimed-triggerfish/. Accessed 23 Mar 2019.
62. Lee JH, Pidaparti RM, Atkinson GM, Moorthy RS. Design of an implantable device for ocular drug delivery. J Drug Deliv. 2012. https://www.hindawi.com/journals/jdd/2012/527516/. Accessed 06 Nov 2018.
63. Badugu R, Reece EA, Lakowicz JR. Glucose-sensitive silicone hydrogel contact lens toward tear glucose monitoring. J Biomed Opt. 2018;23(5):1–9. https://doi.org/10.1117/1.JBO.23.5.057005.
64. Omali N, Subbaraman L, Coles-Brennan C, Fadli Z, Jones L. Biological and clinical implications of lysozyme deposition on soft contact lenses. Optom Vis Sci. 2015;92(7):750–7. https://doi.org/10.1097/OPX.0000000000000615.
65. Peng C-C, Fajardo NP, Razunguzwa T, Radke CJ. In vitro spoilation of silicone-hydrogel soft contact lenses in a model-blink cell. Optom Vis Sci Off Publ Am Acad Optom. 2015;92(7):768–80. https://doi.org/10.1097/OPX.0000000000000625.
66. Krysztofiak K, Szyczewski A. Study of dehydration and water states in new and worn soft contact lens materials. Opt Appl. 2014;44(2):237–50. https://doi.org/10.5277/oa140206.

67. Zhang W, Li G, Lin Y, Wang L, Wu S. Preparation and characterization of protein-resistant hydrogels for soft contact lens applications via radical copolymerization involving a zwitterionic sulfobetaine comonomer. J Biomater Sci Polym Ed. 2017;28(16):1935–49. https://doi.org/10.1080/09205063.2017.1363127.
68. Shimizu T, Goda T, Minoura N, Takai M, Ishihara K. Super-hydrophilic silicone hydrogels with interpenetrating poly(2-methacryloyloxyethyl phosphorylcholine) networks. Biomaterials. 2010;31(12):3274–80. https://doi.org/10.1016/j.biomaterials.2010.01.026.
69. Nanu RV et al. An overview of the influence and design of biomaterial of the intraocular implant of the posterior capsule opacification. Romanian J Ophthalmol. 2018;62(3):188–193. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6256071/. Accessed 21 Mar 2019.
70. Thrimawithana TR, Rupenthal ID, Räsch SS, Lim JC, Morton JD, Bunt CR. Drug delivery to the lens for the management of cataracts. Adv Drug Deliv Rev. 2018;126:185–94. https://doi.org/10.1016/j.addr.2018.03.009.
71. Callahan MA. Technique of congenital cataract surgery with the kelman cavitron phacoemulsifier. Ophthalmology. 1979;86(11):1994–8. https://doi.org/10.1016/S0161-6420(79)35319-2.
72. Hucknall A, Rangarajan S, Chilkoti A. In pursuit of zero: polymer brushes that resist the adsorption of proteins. Adv Mater. 2009;21(23):2441–6. https://doi.org/10.1002/adma.200900383.
73. Xu X, Tang JM, Han YM, Wang W, Chen H, Lin QK. Surface PEGylation of intraocular lens for PCO prevention: an in vivo evaluation. J Biomater Appl. 2016;31(1):68–76. https://doi.org/10.1177/0885328216638547.
74. Kochounian HH, Kovacs SA, Sy J, Grubbs DE, Maxwell WA. Identification of intraocular lens-adsorbed proteins in mammalian in vitro and in vivo systems. Arch Ophthalmol. 1994;112(3):395–401. https://doi.org/10.1001/archopht.1994.01090150125034.
75. Han Y, et al. Drug eluting intraocular lens surface modification for PCO prevention. Colloid Interface Sci Commun. 2018;24:40–4. https://doi.org/10.1016/j.colcom.2018.03.007.
76. Qin Y, Zhu Y, Luo F, Chen C, Chen X, Wu M. Killing two birds with one stone: dual blockade of integrin and FGF signaling through targeting syndecan-4 in postoperative capsular opacification. Cell Death Dis. 2017;8(7):e2920. https://doi.org/10.1038/cddis.2017.315.
77. Chen HC, Lee CY, Sun CC, Huang JY, Lin HY, Yang SF. Risk factors for the occurrence of visual-threatening posterior capsule opacification. J Transl Med. 2019;17(1):209. https://doi.org/10.1186/s12967-019-1956-6.
78. Pérez-Vives C. Biomaterial influence on intraocular lens performance: an overview. J Ophthalmol. 2018. https://www.hindawi.com/journals/joph/2018/2687385/. Accessed 15 Feb 2020.
79. Liu Y-C, Wong T, Mehta J. Intraocular lens as a drug delivery reservoir. Curr Opin Ophthalmol. 2013;24(1):53–9. https://doi.org/10.1097/ICU.0b013e32835a93fc.
80. Kao ECY, McCanna DJ, Jones LW. Utilization of in vitro methods to determine the biocompatibility of intraocular lens materials. Toxicol In Vitro. 2011;25(8):1906–11. https://doi.org/10.1016/j.tiv.2011.06.005.
81. Auffarth GU, Golescu A, Becker KA, Völcker HE. Quantification of posterior capsule opacification with round and sharp edge intraocular lenses. Ophthalmology. 2003;110(4):772–80. https://doi.org/10.1016/S0161-6420(02)01980-2.
82. Findl O, Buehl W, Menapace R, Sacu S, Georgopoulos M, Rainer G. Long-term effect of sharp optic edges of a polymethyl methacrylate intraocular lens on posterior capsule opacification: a randomized trial. Ophthalmology. 2005;112(11):2004–8. https://doi.org/10.1016/j.ophtha.2005.06.021.
83. Werner L, Legeais JM, Nagel MD, Renard G. Neutral red assay of the cytotoxicity of fluorocarbon-coated polymethylmethacrylate intraocular lenses in vitro. J Biomed Mater Res. 1999;48(6):814–9.
84. Li DJ, Cui FZ, Gu HQ. F+ ion implantation induced cell attachment on intraocular lens. Biomaterials. 1999;20(20):1889–96. https://doi.org/10.1016/S0142-9612(99)00084-8.
85. Wang J, Jiang A, Joshi M, Christoforidis J. Drug delivery implants in the treatment of vitreous inflammation. Mediators Inflamm. 2013. https://www.hindawi.com/journals/mi/2013/780634/. Accessed 01 Mar 2019.
86. Haldar RS, Chauhan R, Kapoor K, Niyogi UK. Development of a hydrophobic polymer composition with improved biocompatibility for making foldable intraocular lenses. Opt Mater. 2014;36(7):1165–76. https://doi.org/10.1016/j.optmat.2014.02.022.
87. Tan X, et al. Improvement of uveal and capsular biocompatibility of hydrophobic acrylic intraocular lens by surface grafting with 2-methacryloyloxyethyl phosphorylcholine-methacrylic acid copolymer. Sci Rep. 2017;7:40462. https://doi.org/10.1038/srep40462.
88. Molokhia SA, et al. The capsule drug device: novel approach for drug delivery to the eye. Vision Res. 2010;50(7):680–5. https://doi.org/10.1016/j.visres.2009.10.013.
89. Pan T, Brown JD, Ziaie B. "An Artificial Nano-Drainage Implant (ANDI) for Glaucoma Treatment," in 2006 International Conference of the IEEE Engineering in Medicine and Biology Society. Aug. 2006. pp. 3174–3177. https://doi.org/10.1109/IEMBS.2006.260147.
90. Natarajan JV, Ang M, Darwitan A, Chattopadhyay S, Wong TT, Venkatraman SS. Nanomedicine for glaucoma: liposomes provide sustained release of latanoprost in the eye. Int J Nanomedicine. 2012;7:123–31. https://doi.org/10.2147/IJN.S25468.
91. Editor Senior CK, "Managing & preventing tube shunt problems." https://www.reviewofophthalmology.com/article/managing-preventing-tube-shunt-problems. Accessed 2018 Jul 2018.
92. Li T, et al. Comparative effectiveness of first-line medications for primary open angle glaucoma – a systematic review and network meta-analysis. Ophthalmology. 2016;123(1):129–40. https://doi.org/10.1016/j.ophtha.2015.09.005.
93. "Trabeculectomy - EyeWiki." https://eyewiki.aao.org/Trabeculectomy. Accessed 26 Mar 2019.
94. Ko F, Papadopoulos M, Khaw PT. "Chapter 9 - Primary congenital glaucoma," in *Progress in Brain Research*, vol. 221. Bagetta G, Nucci C, Eds. Elsevier. 2015. pp. 177–89.
95. Mercieca K, Drury B, Bhargava A, Fenerty C. Trabeculectomy bleb needling and antimetabolite administration practices in the UK: a glaucoma specialist national survey. Br J Ophthalmol. 2018;102(9):1244–7. https://doi.org/10.1136/bjophthalmol-2017-310812.
96. Amoozgar B, et al. A novel flexible microfluidic meshwork to reduce fibrosis in glaucoma surgery. PLoS ONE. 2017;12(3):e0172556. https://doi.org/10.1371/journal.pone.0172556.
97. "Enzyme Injection to Reopen Blocked Ocular Drainage Devices in Glaucoma Patients - 15872 - University of Florida Office of Technology Licensing." https://www.technologylicensing.research.ufl.edu/technologies/15872_enzyme-injection-to-reopen-blocked-ocular-drainage-devices-in-glaucoma-patients. Accessed 04 Mar 2019.
98. Ayyala RS, et al. A clinical study of the Ahmed glaucoma valve implant in advanced glaucoma. Ophthalmology. 1998;105(10):1968–76. https://doi.org/10.1016/S0161-6420(98)91049-1.

99. Acosta AC et al. "Ocular biocompatibility of QuatromerTM (polystyrene–polyisobutylene triblock polymers) for glaucoma implants." Invest Ophthalmol Vis Sci. 2004;45(13):2929 Available: https://iovs.arvojournals.org/article.aspx?articleid=2408470. Accessed 16 Jul 2018.
100. Choritz L, Koynov K, Renieri G, Barton K, Pfeiffer N, Thieme H. Surface topographies of glaucoma drainage devices and their influence on human tenon fibroblast adhesion. Invest Ophthalmol Vis Sci. 2010;51(8):4047–53. https://doi.org/10.1167/iovs.09-4759.
101. Patel S, Pasquale LR. Glaucoma drainage devices: a review of the past, present, and future. Semin Ophthalmol. 2010;25(5–6):265–70. https://doi.org/10.3109/08820538.2010.518840.
102. "Investigational MIGS device could minimize fibrotic response," American Academy of Ophthalmology. Oct. 19, 2017. https://www.aao.org/headline/investigational-migs-device-could-minimize-fibroti. Accessed 04 Mar 2019.
103. Chaudhary A, Salinas L, Guidotti J, Mermoud A, Mansouri K. XEN Gel Implant: a new surgical approach in glaucoma. Expert Rev Med Devices. 2018;15(1):47–59. https://doi.org/10.1080/17434440.2018.1419060.
104. Buffault J, Baudouin C, Labbé A. XEN® Gel Stent for management of chronic open angle glaucoma: a review of the literature. J Fr Ophtalmol. 2019;42(2):e37–46. https://doi.org/10.1016/j.jfo.2018.12.002.
105. Lewis RA. Ab interno approach to the subconjunctival space using a collagen glaucoma stent. J Cataract Refract Surg. 2014;40(8):1301–6. https://doi.org/10.1016/j.jcrs.2014.01.032.
106. Chang PY, Kresch Z, Samson CM, Gentile RC. Spontaneous dissociation of fluocinolone acetonide sustained release implant (Retisert) with dislocation into the anterior chamber. Ocul Immunol Inflamm. 2015;23(6):454–7. https://doi.org/10.3109/09273948.2014.902074.
107. Humayun M, et al. Implantable micropump for drug delivery in patients with diabetic macular edema. Transl Vis Sci Technol. 2014;3(6):5. https://doi.org/10.1167/tvst.3.6.5.
108. Lloyd AW. Ophthalmology: biomaterials. In: Buschow KHJ, Cahn RW, Flemings MC, Ilschner B, Kramer EJ, Mahajan S, Veyssière P, editors. Encyclopedia of materials: science and technology. Oxford: Elsevier; 2001. p. 6411–5.
109. Williams RL, Levis HJ, Lace R, Doherty KG, Kennedy SM, Kearns VR. Biomaterials in ophthalmology. In: Narayan R, editor. Encyclopedia of biomedical engineering. Oxford: Elsevier; 2019. p. 289–300.
110. Thompson JT, Chambers WA. Good ideas gone bad: the MIRAgel saga. Ophthalmology. 2016;123(1):5–6. https://doi.org/10.1016/j.ophtha.2015.09.038.
111. Song J, Woo I, Eom Y, Kim H. Five misconceptions related to punctal plugs in dry eye management. Cornea. 2018;37 https://doi.org/10.1097/ICO.0000000000001734.
112. "Punctal Plugs for Dry Eyes," *All About Vision*. https://www.allaboutvision.com/conditions/punctal-plugs.htm. Accessed 27 Mar 2019.
113. Kim BM, Osmanovic SS, Edward DP. Pyogenic granulomas after silicone punctal plugs: a clinical and histopathologic study. Am J Ophthalmol. 2005;139(4):678–84. https://doi.org/10.1016/j.ajo.2004.11.059.
114. March 31 and 2008, "QLT begins phase 2 trial of punctal plug drug delivery system for treating glaucoma, ocular hypertension." https://www.healio.com/ophthalmology/glaucoma/news/online/%7ba3de4c13-da9a-4508-948e-7333145a0f8e%7d/qlt-begins-phase-2-trial-of-punctal-plug-drug-delivery-system-for-treating-glaucoma-ocular-hypertension. Accessed 27 Mar 2019.
115. "Ocular Therapeutix Announces DEXTENZA® (dexamethasone ophthalmic insert) Recommended for Unique J-Code by CMS," BioSpace. https://www.biospace.com/article/ocular-therapeutix-announces-dextenza-dexamethasone-ophthalmic-insert-recommended-for-unique-j-code-by-cms/. Accessed 27 Apr 2020.
116. Palchesko RN, Carrasquilla SD, Feinberg AW. Natural biomaterials for corneal tissue engineering, repair, and regeneration. Adv Healthc Mater. 2018;e1701434. https://doi.org/10.1002/adhm.201701434.
117. Akpek EK, Alkharashi M, Hwang FS, Ng SM, Lindsley K. Artificial corneas versus donor corneas for repeat corneal transplants. Cochrane Database Syst Rev. 2014;11:CD009561. https://doi.org/10.1002/14651858.CD009561.pub2.
118. Baino F, Potestio I. Orbital implants: state-of-the-art review with emphasis on biomaterials and recent advances. Mater Sci Eng C. 2016;69:1410–28. https://doi.org/10.1016/j.msec.2016.08.003.
119. Pillay V, Choonara YE, Kumar P. Frontiers in biomaterials: unfolding the biopolymer landscape. Bentham Science Publishers. 2016.
120. Vermette P. Biomedical applications of polyurethanes. Landes Bioscience. 2001.
121. Tsay RY, Imae T. "Development of nonfouling biomaterials," in Encyclopedia of Biocolloid and Biointerface Science 2V Set. Wiley, Ltd. 2016. pp. 145–160.
122. Feng W, Zhu S, Ishihara K, Brash JL. Adsorption of fibrinogen and lysozyme on silicon grafted with poly(2-methacryloyloxyethyl phosphorylcholine) via surface-initiated atom transfer radical polymerization. Langmuir ACS J Surf Colloids. 2005;21(13):5980–7. https://doi.org/10.1021/la050277i.
123. Senaratne W, Andruzzi L, Ober CK. Self-assembled monolayers and polymer brushes in biotechnology: current applications and future perspectives. Biomacromol. 2005;6(5):2427–48. https://doi.org/10.1021/bm050180a.
124. Kujawa P, Schmauch G, Viitala T, Badia A, Winnik FM. Construction of viscoelastic biocompatible films via the layer-by-layer assembly of hyaluronan and phosphorylcholine-modified chitosan. Biomacromol. 2007;8(10):3169–76. https://doi.org/10.1021/bm7006339.
125. Gong M, et al. Investigation on the interpenetrating polymer networks (ipns) of polyvinyl alcohol and poly(N-vinyl pyrrolidone) hydrogel and its in vitro bioassessment. J Appl Polym Sci. 2012;125(4):2799–806. https://doi.org/10.1002/app.36247.
126. Ngo BKD, Grunlan MA. Protein resistant polymeric biomaterials. ACS Macro Lett. 2017;6(9):992–1000. https://doi.org/10.1021/acsmacrolett.7b00448.
127. Roach P, Farrar D, Perry CC. Surface tailoring for controlled protein adsorption: effect of topography at the nanometer scale and chemistry. J Am Chem Soc. 2006;128(12):3939–45. https://doi.org/10.1021/ja056278e.
128. Ruiz A, Rathnam KR, Masters KS. Effect of hyaluronic acid incorporation method on the stability and biological properties of polyurethane–hyaluronic acid biomaterials. J Mater Sci Mater Med. 2014;25(2):487–98. https://doi.org/10.1007/s10856-013-5092-1.
129. Vishwakarma A, et al. Engineering immunomodulatory biomaterials to tune the inflammatory response. Trends Biotechnol. 2016;34(6):470–82. https://doi.org/10.1016/j.tibtech.2016.03.009.
130. Homme RP et al. Remodeling of retinal architecture in diabetic retinopathy: disruption of ocular physiology and visual functions by inflammatory gene products and pyroptosis. Front Physiol. 2018;9. https://doi.org/10.3389/fphys.2018.01268.
131. Sivak JM, Fini ME. MMPs in the eye: emerging roles for matrix metalloproteinases in ocular physiology. Prog Retin Eye Res. 2002;21(1):1–14. https://doi.org/10.1016/s1350-9462(01)00015-5.
132. Zaleska-Żmijewska A, Strzemecka E, Wawrzyniak ZM, Szaflik JP. Extracellular MMP-9-based assessment of ocular surface

inflammation in patients with primary open-angle glaucoma. J Ophthalmol 2019. https://www.hindawi.com/journals/joph/2019/1240537/. Accessed 06 May 2020.
133. Singh M, Tyagi SC. Metalloproteinases as mediators of inflammation and the eyes: molecular genetic underpinnings governing ocular pathophysiology. Int J Ophthalmol. 2017;10(8):1308–18. https://doi.org/10.18240/ijo.2017.08.20.
134. Weinreb RN, Robinson MR, Dibas M, Stamer WD. Matrix metalloproteinases and glaucoma treatment. J Ocul Pharmacol Ther. 2020. https://doi.org/10.1089/jop.2019.0146.
135. Purcell BP et al. Injectable and bioresponsive hydrogels for on-demand matrix metalloproteinase inhibition. Nat Mater. 2014;13(6) https://doi.org/10.1038/nmat3922.
136. Zhang L, et al. Zwitterionic hydrogels implanted in mice resist the foreign-body reaction. Nat Biotechnol. 2013;31(6):553–6. https://doi.org/10.1038/nbt.2580.
137. Jansen LE, et al. Zwitterionic PEG-PC hydrogels modulate the foreign body response in a modulus-dependent manner. Biomacromol. 2018;19(7):2880–8. https://doi.org/10.1021/acs.biomac.8b00444.
138. Carr LR, Xue H, Jiang S. Functionalizable and nonfouling zwitterionic carboxybetaine hydrogels with a carboxybetaine dimethacrylate crosslinker. Biomaterials. 2011;32(4):961–8. https://doi.org/10.1016/j.biomaterials.2010.09.067.
139. Chou YN, Wen TC, Chang Y. Zwitterionic surface grafting of epoxylated sulfobetaine copolymers for the development of stealth biomaterial interfaces. Acta Biomater. 2016;40:78–91. https://doi.org/10.1016/j.actbio.2016.03.046.
140. Sharma S, Gupta D, Mohanty S, Jassal M, Agrawal AK, Tandon R. Surface-modified electrospun poly (ε-caprolactone) scaffold with improved optical transparency and bioactivity for damaged ocular surface reconstruction. Invest Ophthalmol Vis Sci. 2014;55(2):899–907. https://doi.org/10.1167/iovs.13-12727.
141. Wang JJ, Liu F. Photoinduced graft polymerization of 2-methacryloyloxyethyl phosphorylcholine on silicone hydrogels for reducing protein adsorption. J Mater Sci Mater Med. 2011;22(12):2651–7. https://doi.org/10.1007/s10856-011-4452-y.
142. Lin Q, Tang J, Han Y, Xu X, Hao X, Chen H. Hydrophilic modification of intraocular lens via surface initiated reversible addition-fragmentation chain transfer polymerization for reduced posterior capsular opacification. Colloids Surf B Biointerfaces. 2017;151:271–9. https://doi.org/10.1016/j.colsurfb.2016.12.028.
143. Matsushima H, Iwamoto H, Mukai K, Obara Y. Active oxygen processing for acrylic intraocular lenses to prevent posterior capsule opacification. J Cataract Refract Surg. 2006;32(6):1035–40. https://doi.org/10.1016/j.jcrs.2006.02.042.
144. Amoozgar B, Morarescu D, Sheardown H. Sulfadiazine modified PDMS as a model material with the potential for the mitigation of posterior capsule opacification (PCO). Colloids Surf B Biointerfaces. 2013;111:15–23. https://doi.org/10.1016/j.colsurfb.2013.05.002.
145. Silva D, Pinto LF, Bozukova D, Santos LF, Serro AP, Saramago B. Chitosan/alginate based multilayers to control drug release from ophthalmic lens. Colloids Surf B Biointerfaces. 2016;147:81–9. https://doi.org/10.1016/j.colsurfb.2016.07.047.
146. Ashtiani MK, Zandi M, Shokrollahi P, Ehsani M, Baharvand H. Surface modification of poly (2-hydroxyethyl methacrylate) hydrogel for contact lens application. Polym Adv Technol. 2018;29(4):1227–33. https://doi.org/10.1002/pat.4233.
147. Askari F, Zandi M, Shokrolahi P, Tabatabaei MH, Hajirasoliha E. Reduction in protein absorption on ophthalmic lenses by PEGDA bulk modification of silicone acrylate-based formulation. Prog Biomater. 2019;8(3):169–83. https://doi.org/10.1007/s40204-019-00119-x.
148. Shimizu T, Goda T, Minoura N, Takai M, Ishihara K. Super-hydrophilic silicone hydrogels with interpenetrating poly(2-methacryloyloxyethyl phosphorylcholine) networks. Biomaterials. 2010;31(12):3274–80. https://doi.org/10.1016/j.biomaterials.2010.01.026.
149. Goda T, Matsuno R, Konno T, Takai M, Ishihara K. Protein adsorption resistance and oxygen permeability of chemically crosslinked phospholipid polymer hydrogel for ophthalmologic biomaterials. J Biomed Mater Res B Appl Biomater. 2009;89(1):184–90. https://doi.org/10.1002/jbm.b.31204.
150. Zhang W, Li G, Lin Y, Wang L, Wu S. Preparation and characterization of protein-resistant hydrogels for soft contact lens applications via radical copolymerization involving a zwitterionic sulfobetaine comonomer. J Biomater Sci Polym Ed. 2017;28(16):1935–49. https://doi.org/10.1080/09205063.2017.1363127.