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## SPECIALTY SECTION

This article was submitted to Ophthalmic Drug Delivery, a section of the journal Frontiers in Drug Delivery

RECEIVED 22 October 2022

ACCEPTED 26 January 2023

PUBLISHED 15 February 2023

## CITATION

Rafiei M, Chung JT and Chau Y (2023), Roles of biomaterials in modulating the innate immune response in ocular therapy. *Front. Drug Deliv.* 3:1077253. doi: 10.3389/fddev.2023.1077253

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# Roles of biomaterials in modulating the innate immune response in ocular therapy

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The eye is a hard-to-treat organ due to its poor regenerative capacity and susceptibility to inflammation; as a result, it has an immune privilege mechanism. In the case of ocular degenerative disorders, chronic and uncontrolled ocular inflammations can overcome this immune response to initiate and exacerbate tissue degeneration, ultimately leading to blindness. Recent landmark discoveries on the key roles of the ocular innate immune system in regulating acute and chronic inflammations as well as tissue fibrosis and homeostasis have shed light on the value of novel treatment interventions in modulating ocular immune responses at the molecular, cellular, and tissue levels. This strategy can be attained by using therapeutics to target resident phagocytes and antigen-presenting cells, namely, microglia and dendritic cells, as well as infiltrating neutrophils and macrophages. Biomaterials are foreign materials to the host and interact with innate immune cells. To leverage such intrinsic immunomodulatory properties, biomaterials such as implants, injectable depots, and nano/micro particles can be used alone as a treatment or with different payloads as carriers in immune-related ocular disorders. This article discusses how physicochemical properties such as biodegradability, size, shape, and charge affect biomaterials' interaction with the eye's innate immune system, therefore influencing outcomes towards pro- or anti-inflammatory responses. Knowledge about the eye's immunological response is required for designing tolerogenic biomaterials including intraocular lenses, cellular scaffolds, therapeutic molecule depots, or carriers of gene therapies. The discussion presented in this review will shed light on the potential use of biomaterials to direct immune responses toward favorable treatment outcomes.

## KEYWORDS

biomaterials, eye, immune-related disorders, innate immune system, immunomodulation

## 1 Introduction

Since eye tissue, which serves as our window to the outside world, lacks the ability to regenerate, immune-related inflammation poses a serious risk to the eye by potentially damaging its tissue, leading to vision loss. As a result, ocular tissue employs an immune privilege strategy to actively prevent any inflammation by providing an immunosuppressive environment (Niederhorn, 2019; Murakami et al., 2020). The term "immune privilege" comes from Medawar and others' definition in the 1940s (Medawar, 1948; Taylor, 2016), where the ocular anti-inflammatory mechanism of having a private microenvironment for improving the anti-inflammatory response and tolerating the ocular immune cell's function and balancing it was discussed. Eye tissue, in homeostatic conditions, has an

immunoregulatory function (Dick et al., 2003). This inherent ocular immune tolerance, however, is compromised by several degenerative disorders including uveitis, diabetic retinopathy (DR), dry eye disease (DED), age-related macular degeneration (AMD), and choroidal neovascularization (CNV) (Perez and Caspi, 2015; Murakami et al., 2020; Gilger and Hirsch, 2022).

The body's immune system response battles danger agents in two ways: the innate immune response and the adaptive immune response (Dempsey et al., 2003). In this way, the innate immune system acts as a first defender during the first days of the inflammation process or injury. If the innate immune cells are activated and do not regulate by proper signaling pathways after treatment, chronic inflammation and even visual impairment may occur (Murakami et al., 2020).

Different innate immune cells, including neutrophils, microglia/macrophages, and dendritic cells in the eye, play essential roles in the aforementioned types of diseases. The infiltration and activity of innate immune cells change depending on the type of ocular disorder, its location, and the milieu supplied by the cells (reviewed in detail by (Murakami et al. (2020))), in the form of inflammatory induction or suppression. When eyes are infected or injured, different proinflammatory cytokines and chemokines (such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin 8 (IL8), IL6, IL12, C-X-C motif chemokine ligand 10 (CXCL10), and C-C motif chemokine ligand 2 (CCL2), etc.) are produced by innate immune cells (Das et al., 2022). For uveitis, literature reports have shown that macrophages are essential innate immune cells in the development and resolution of experimental autoimmune uveitis. Macrophages can impact both proinflammatory side (by TNF- $\alpha$  activation) and immunosuppressive side [by RANTES (CCL5) production that is responsible for recruiting CD8<sup>+</sup> T (killer T) cells] (Mérida et al., 2015; Yang et al., 2016; Murakami et al., 2020; Kubota et al., 2022). In a study on ocular infiltration of macrophages in experimental autoimmune uveitis (EAU), it was found that 1 week (day 16) after the beginning of macrophage infiltration in the eye (day 9), the inflammation reached a maximum amount (Sonoda et al., 2003). Monocytes from the peripheral blood infiltrate and differentiate into macrophages in degenerative retinal diseases with a reduced blood-retinal barrier function (Ginhoux et al., 2013). In the aging retina and choroid, inflammatory macrophages from monocytes, dendritic cells, and tissue-resident macrophages such as microglia are important immune cells. These immune cells are involved in the pathogenesis of AMD, and researchers observed infiltration of macrophages and lymphocytes around the CNV area, as well as an elevated amount of CCL2, IL-8, and vascular endothelial growth factor (VEGF) in circulation blood monocytes (Lopez et al., 1991; Lechner et al., 2017; Chen et al., 2019; Das et al., 2022). A recent review by Das et al. provides more information on the effects of aging on the function of immune cells during ocular disorders (Das et al., 2022). In DR, activated neutrophils and macrophages can cause retinal vascular injury. Moreover, the number of immune cells in the choroid of DR patients was elevated (Schroder et al., 1991; Luttj et al., 1997).

The biocompatibility of a material is defined by William's dictionary as "the ability of a material to perform with an appropriate host response in a specific application" (Donaruma, 1988; Williams, 1999). Biomaterials can act alone as a treatment or can be combined with other modalities to provide therapeutic

intervention. The roles of biomaterials in immunomodulation in ocular therapy can be classified as follows. The first approach is to use biomaterials to construct carriers of therapeutic agents while the biomaterial itself is intended to passively and inertly affect the immune response (Garzón et al., 2022). The second approach is similar but more intriguing. Also for constructing carriers, the biomaterial is designed to interact with the immune system, to promote the immunogenic or immunotolerant effect, depending on the application, and to augment the effect of the cargo (Im, 2020; Gao et al., 2022). For these two approaches, the immunomodulatory cargoes include steroids, proteins, and nucleic acids. In a third approach, biomaterials are used to make ophthalmic devices such as ocular lenses and ocular inserts (Kwon et al., 2020). The functions and longevities of these devices in part depend on their interaction with the immune system. The last approach is to use biomaterials to support cell therapy. There are several reviews on the design criteria of immunomodulatory biomaterials in tissue engineering (Zolnik et al., 2010; Andorko and Jewell, 2017; Li H. et al., 2022; Mitarotonda et al., 2022). One possible therapeutic intervention is to direct the response of immune cells by using immunomodulatory biomaterials alone or in combination with engineered cells. An overview of these approaches is summarized in Figure 1. The biomaterials can be designed to participate in the immunogenic or immunosuppressive pathways based on their physicochemical properties such as form, size, shape, charge, hydrophilicity/hydrophobicity, degradability, and mechanical strength. In this review, we will focus on the interaction of biomaterials with the eye's innate immune system, and consider how they can influence, positively or negatively, the treatment of inflammatory ocular diseases.

## 2 The innate immune system in the eye

Eye tissue has been recognized as an immune-privileged organ for 150 years. The first long-term survival of mouse skin implanted into a dog eye's anterior chamber was described by a Dutch ophthalmologist (van Dooremaal, 1873). Zirm carried out the first successful human corneal transplant a few years later, in 1905 (Zirm, 1906; Niederkorn, 2019). At the time of these observations, neither the human immune system nor the fundamentals of implant rejection had been studied. By inserting rabbit skin into an allogenic rabbit's anterior chamber, Medawar further demonstrated in 1948 the distinct immunologic characteristics of the eye (Medawar, 1948). Immune privilege is an action in the homeostatic condition of the eye that modulates the induction and progression of inflammation to prevent any excessive inflammation that could degenerate tissue (Murakami et al., 2020). Ocular immune privilege consists of an immunosuppressive microenvironment with different components including transforming growth factor- $\beta$  (TGF- $\beta$ ) (Taylor and Ng, 2018), retinoic acid (Zhou et al., 2011), programmed cell death-ligand 1 (PD-L1) (Sugita et al., 2009), galectins (Toscano et al., 2006), and cluster of differentiation-200 receptor (CD200R), etc. (Dick et al., 2003; Murakami et al., 2020). The innate immune cells are dependent on these ocular microenvironment signals to destroy or regenerate tissue during inflammation (Murakami et al., 2020). After infection, injury, or even using implants in the eye, neutrophils, macrophages/microglia cells, and dendritic cells attack the site of inflammation and start secreting proinflammatory cytokine and chemokines. In this way,

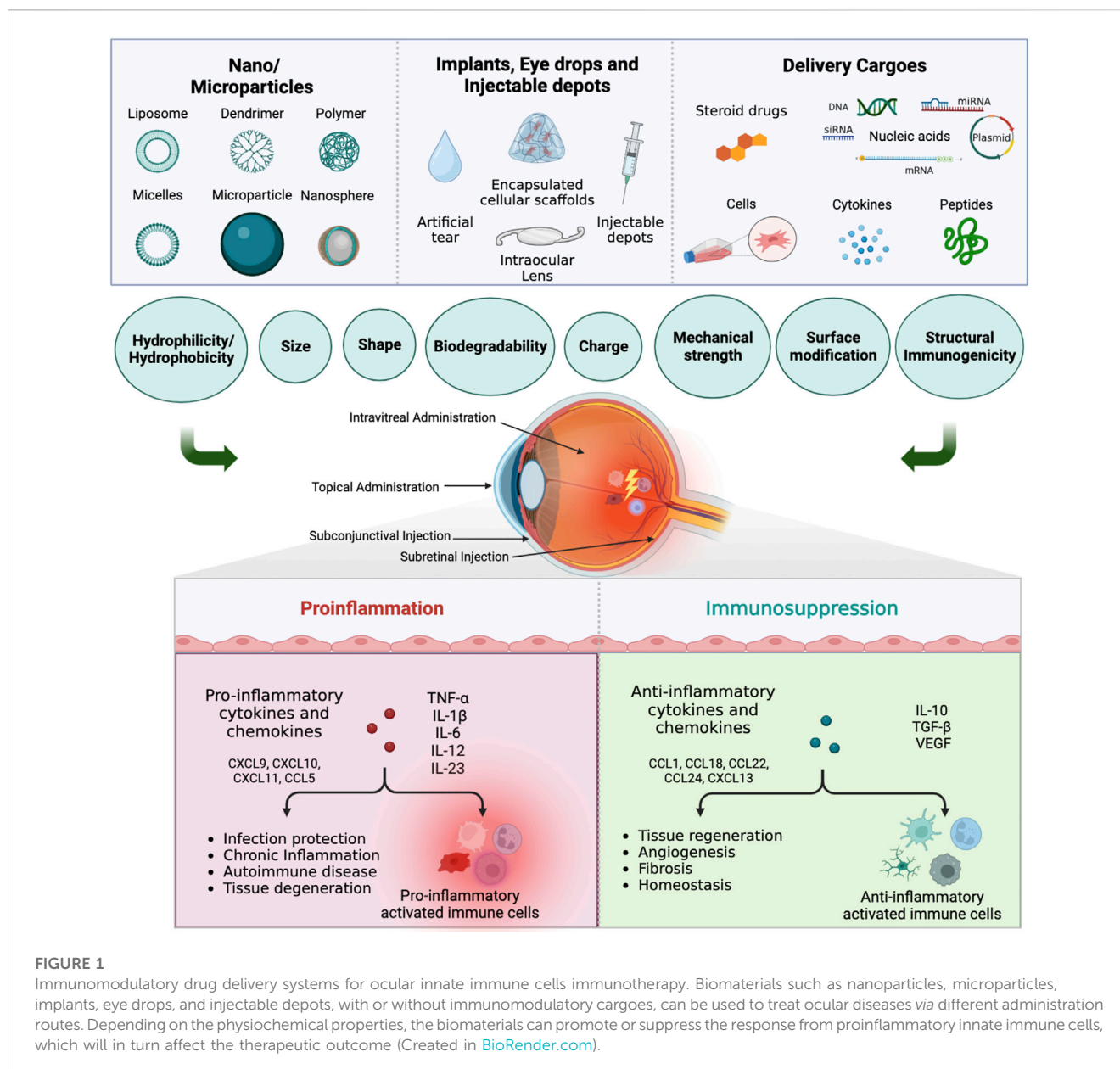


FIGURE 1

Immunomodulatory drug delivery systems for ocular innate immune cells immunotherapy. Biomaterials such as nanoparticles, microparticles, implants, eye drops, and injectable depots, with or without immunomodulatory cargoes, can be used to treat ocular diseases via different administration routes. Depending on the physicochemical properties, the biomaterials can promote or suppress the response from proinflammatory innate immune cells, which will in turn affect the therapeutic outcome (Created in [BioRender.com](https://www.biorender.com)).

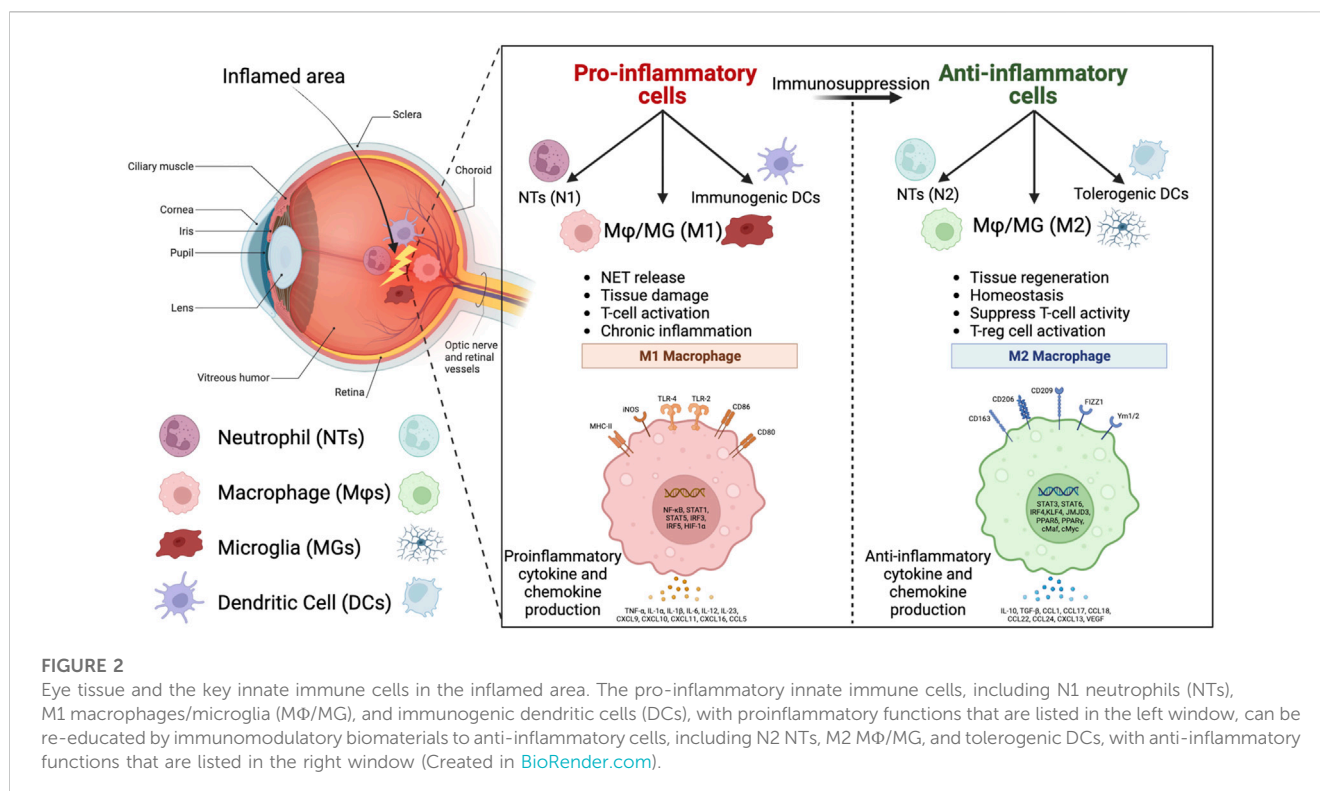
proinflammatory-activated macrophages, broadly classified as “M1 macrophages”, secrete proinflammatory cytokines including IL1- $\beta$ , IL12, inducible nitric oxide synthase (iNOS), and TNF- $\alpha$ . The M1 macrophages kill the pathogens or prepare a fibrotic capsule around the foreign implant, recruit leukocytes to the site, and activate the adaptive immune system. This process spans from the first days to weeks, depending on the damage and implanted biomaterial. Afterward, the macrophage cells’ phenotypes change to the characteristics of “M2 macrophages”, which regenerate and heal the area by angiogenesis and by secreting anti-inflammatory cytokines such as IL10 and TGF- $\beta$  (Anderson, 2003; Mosser and Edwards, 2008; Andorko and Jewell, 2017). As a result, the phenotypic diversity of macrophages with distinct markers and functions can be targeted using biomaterials with specific physicochemical properties to achieve the desired inflammatory function. The M1 markers can be used to upregulate the inflammatory functions and the M2 markers can be used to downregulate the inflammatory function of macrophages

(Figure 2). In the same way as macrophages, neutrophils respond to extracellular stimuli in a context-dependent manner and can polarize from N1 to N2 phenotypes, similar to the M1 and M2 phases of macrophages (Cuartero et al., 2013; García-Culebras et al., 2018). In this review, our focus is on downregulation of the innate immune system inflammatory response in the case of ocular inflammation by using modulatory biomaterials in different forms such as implants, injectable depots, nano/micro systems, and hybrids of these systems (Figure 1).

## 2.1 Key players as innate immune cells in the eye

### 2.1.1 Neutrophils

The main players in acute inflammation and the first line of fighting any danger, including pathogens, inflammation, and injury in the innate immune system, are neutrophils. Neutrophils’ lifespan



has been shown to be very short (less than 24 h) in mice and humans, although recently, a number of studies showed that the lifespan of neutrophils can be increased by inflammatory cytokines and signals that induce the adaptive immune system and aggravate the inflammation for up to 5.4 days (Pillay et al., 2010; Kolaczowska and Kubes, 2013). They are the first immune cells that detect any inflammation that occurs, by sensing the pathogen-associated molecular pattern (PAMP) present in microbes and the danger-associated molecular pattern (DAMP) present in injured tissues. Neutrophils play a critical role in the pro-inflammatory function through phagocytosis and by secreting pro-inflammatory cytokines to induce an innate and adaptive immune response (Ghosh et al., 2019). Neutrophils also release neutrophil extracellular traps (NETs). NETs are composed of nuclear DNA, histones, and other granular proteins. NETs are induced by nitric oxide, cytokines, and other autoantibodies to prevent inflammation progression. However, it has been shown that chronic aggregation of NETs can cause autoimmune, allergic, chronic diseases, tissue damage, and immune rejection to implants (Kolaczowska and Kubes, 2013; Mahajan et al., 2021; Mun et al., 2021; Yildiz and Yildiz, 2022). For example, Mahajan et al. (2021) found that NETs aggregated after ocular surface inflammation, resulting in meibomian gland dysfunction (MGD) due to blockage. Although it has been shown that NETs are useful to prevent inflammation progression in the eye rheum, they are harmful to corneal diseases, uveitis, and diabetic retinopathy and contribute to poor prognosis of these diseases (Estúa-Acosta et al., 2019). Neutrophils perform diversely in inflammation and injury conditions by regulating acute inflammation and repair processes, autoimmune diseases, and chronic inflammatory diseases, based on the type of cytokines and special receptors that exist in the inflamed

environment (Estúa-Acosta et al., 2019; Liew and Kubes, 2019; Tan et al., 2020). The signaling pathways of an inflamed environment can result in different phenotypes of neutrophils: N1, which represents the proinflammatory phase, and N2, which represents the anti-inflammatory phase (Cuartero et al., 2013; García-Culebras et al., 2018).

### 2.1.2 Microglia/macrophages

Macrophages are key players in the innate immune system, fighting any infection and danger in the tissue through phagocytosis and by inducing regeneration and fibrosis afterward. They function in a spectrum between the M1 proinflammatory phase and the M2 anti-inflammatory phase (Tan et al., 2020). The interferon-gamma (IFN- $\gamma$ ), TNF- $\alpha$ , IL-1  $\beta$ , IL12, IL6, and lipopolysaccharides (LPS) signals can activate the M1 macrophage phase and iNOS M1 activated cell expresses surface markers, cluster of Differentiation 36 (CD36), CD86, CD80, C-C chemokine receptor type 7 (CCR7), and major histocompatibility complex class II (MHCII) (Figure 2). On the other hand, the M2 macrophage phase is activated by signaling factors such as IL-4, IL13, TGF- $\beta$ , and IL10, and the M2 activated cell expresses surface markers of CD206, CCL204, and CD163. Throughout the eye, they can be found in the anterior and posterior parts (cornea, iris, ciliary body, choroid, sclera, and vitreous), and play a critical role in controlling inflammation and injury in the first days (Chinnery et al., 1947; Ghasemi et al., 2012). For instance, vitreal macrophages (also known as hyalocytes) are located between the inner limiting membrane of the retina and the vitreous membrane that contains condensed vitreal collagen (Chinnery et al., 1947).

Retina tissue in the eye possesses resident immune cells known as glial cells, which are categorized into three main groups:

astrocytes, microglia, and Müller glia. Microglia cells are myeloid-derived populations in the retina that manage the immune response and environmental cues by interacting with retinal cells and maintaining the retinal cell's homeostatic function and neuronal homeostasis (Tan et al., 2020; Guo et al., 2022; Wang and Cepko, 2022). They play a critical role in interacting with retinal cells and recruiting neutrophils and macrophages for further functions during eye injuries and inflammation (Minghetti et al., 2008; Tan et al., 2020). The resting state of microglia cells is achieved by intraretinal signaling and cytokines secretion such as TGF- $\beta$  and IL-10 and this state has a low expression of membrane receptors (Langmann, 2007). They are sensitive and can be activated through toll-like receptor (TLR) signaling with a variety of triggers, including LPS, calcium level fluctuations, proinflammatory cytokines (IFN- $\gamma$ , TNF- $\alpha$ , etc.), thrombin, aggregates, peptides derived from ocular infections, autoimmune processes, ischemia, neuronal damage, and neurodegeneration-associated signals. Microglia cells are the first players in reacting to injury or inflammation at retina or ocular sites (Langmann, 2007; Minghetti et al., 2008). In the first 24 h of microglia activation, cell proliferation, morphology transition to amoeboid shape, migration, phagocytosis, upregulation of immunoglobulin G (IgG), CD1 receptors, and secretion of different proinflammatory signals such as cytokines (IL1- $\beta$ , IL6, TNF- $\alpha$ ), chemokines (CCL3 (MIP-1  $\alpha$ ), CCL4 (MIP-1  $\beta$ ), CCL2), and other signals (NO, ROS) occurs (Fan et al., 2022). Neutrophils and macrophages are recruited according to the proinflammatory signal's level. The P2 purinergic receptor (P2Y12) is a phagocytic receptor expressed on microglia that responds to tissue damage by sensing ADP/ATP (Adenosine Di/Tri-Phosphate). This receptor has been shown to be necessary for the clearance of apoptotic cells, and inhibiting it increases the clearance time (Blume et al., 2020). A microglia is characterized by three distinct phases: the resting phase with ramified shapes, the activated pro-inflammatory phase or M1 phase with amoeboid, and the anti-inflammatory phase (M2) with ramified shapes. Activation of microglia to the M1 phase occurs when infection, inflammation, or a local ocular injury takes place in the eye tissue. The activated microglia rapidly migrate to the site of inflammation or injury and secrete proinflammatory signals including TNF- $\alpha$ , cyclooxygenase-2 (COX-2), and iNOS to recruit peripheral immune cells (monocytes). Afterward, microglia and recruited macrophages fight the foreign harmful agent using phagocytic functions. Following microglia and macrophage phagocytosis and removal of debris via M1 activation, the M1 activation phase transitions to the M2 anti-inflammatory phase by passing the phenotype from M1 to M2. Arginase 1 (ARG 1), CD206, and IL-10 are among the regenerating and angiogenesis factors that this M2 phenotype secretes, helping to return the inflamed area to homeostasis (Tan et al., 2020). However, chronic activation of microglia is one of the major players in the development of neurodegenerative diseases, including glaucoma, wet AMD, and DR, by the barrier breakdown mechanism (Reichenbach and Bringmann, 2020). The markers for the different phases of microglia are identical to those for monocyte-derived macrophages (TNF- $\alpha$ , COX-2, and iNOS), in addition to specific surface markers for differentiating from monocyte-derived macrophages, such as P2Y12 for the resting and M2 phases of microglia and ionized calcium-binding adapter molecule 1 (Iba-1) protein marker for the phagocytotic and activated microglia (Ito

et al., 1998). Some reports claim that the expression of the Iba-1 surface marker is associated with the microglia's phagocytosis phase (Ohsawa et al., 2000; Morillas et al., 2021). Between microglia and retinal cells, a variety of ligand-receptors exist that inhibit microglia activation and restore their resting phase and homeostasis state. For instance, TGF- $\beta$  signaling is used to downregulate the MHC-II, CD80, and CD86 receptors, which are expressed on the surface of M1 microglia; glycoprotein CD200 (known as mAb OX2) is detected by CD200R (a myeloid-specific receptor on microglia); CD200-CD200R complex inhibits microglia activation; and chemokine fractalkine (CX3CL1) and CX3CR1 receptors produce a complex that inhibits the phagocytotic phase of microglia (Langmann, 2007; Minghetti et al., 2008).

Microglia activation is linked to several inflammatory and degenerative ocular disorders, including retinitis pigmentosa (RP), AMD, glaucoma, DR, and uveitis in the eye. This is due to their status as resident immune cells in the retina, which makes them very sensitive to changes in cell phenotype, ligand-receptor interactions, and environmental signals. For instance, it has been shown that in experimental AMD, aging CX3CR1 deficiency causes microglia to migrate and accumulate in the subretinal space because it lacks the CX3CR1-CX3CL1 complex, which physiologically maintains microglia homeostasis (Penfold et al., 2001; Minghetti et al., 2008). Arroba et al. studied the polarization dynamics of microglia in DR in *in vitro* and *in vivo* in mice and found that the microglia are initially in the M2 phase, but at more advanced stages of DR development, their phase shifts to M1 and chronic pro-inflammatory (Arroba et al., 1862). Since the progression of RP, AMD, glaucoma, DR, and uveitis has been related to the activation of microglia, these cell types are of great interest as a target for treating these diseases. There are two effective ways to accomplish this goal: either preventing their pro-inflammatory response or reprogramming them *via* gene therapy to downregulate the inflammatory response and immune cell recruitment (Arroba et al., 1862; Minghetti et al., 2008; Guo et al., 2022; Wang and Cepko, 2022).

The dynamics of microglia activation and repolarization to homeostasis, with Iba-1 (for M1 phase) and P2Y12 (for M2 phase) as markers, was monitored in an ocular hypertension (OHT)-induced glaucoma mouse model by Ramírez et al. (2020). The authors showed that at first (day 0), the damaged tissue released ATP signals and P2Y12 was upregulated. After a few hours, the P2Y12 expression was downregulated, and this decreasing signal was the most sensitive alarm for the transition from the resting to the M1 phase of microglia with Iba-1+. After 24 h, the Iba-1+ cells showed P2Y12 expression elevation. On the 3rd and 5th days, downregulation of P2Y12 expression was observed. Based on their collected data, the authors stated that the inflammation peaked and was strongest on the 3rd and 5th days after induction. Then, P2Y12 expression increased slowly from day 8 to reach the naïve eye amount on the 15th day for this animal model. The same group conducted a different time point investigation on the levels of proinflammatory cytokines (IFN- $\gamma$ , TNF- $\alpha$ , IL-1  $\beta$ , IL6, IL12, IL17, and IL18) and anti-inflammatory cytokines (IL4, IL10, IL13, and TGF- $\beta$ ) produced following OHT induction in the glaucoma, and found that IL6 expression peaked after 1, 3, and 5 days of induction. Interestingly, the authors discovered that IL4 and IL10 are important modulatory cytokines

that allow activated microglia to repolarize to the M2 phase before further inflammation progression and tissue damage (Fernández-Albarral et al., 2021).

### 2.1.3 Dendritic cells

Dendritic cells (DCs), similar to macrophages, are phagocytic and are able to present antigens to immune effector cells. The distinctive feature of DCs is their migration to lymph nodes to activate naïve lymphocytes, thereby bridging innate and adaptive immunity. Most DCs are found in the corneal and conjunctival epithelium, thereby serving as the first line of defense on the ocular surface. In the posterior ocular section, DCs can be mostly found in the retina and choroidal space (McMenamin et al., 2019). Once activated, most ocular DCs migrate to cervical lymph nodes to trigger downstream immune responses. There are several subtypes of DCs that can be found in the eye, such as conventional DCs (cDCs), Langerhans cells (LCs), plasmacytoid DCs (pDCs); they all play key roles in maintaining immune tolerance and resolving post-inflammation challenges.

In mice, cDCs can be classified into types 1 and 2. cDC1 can be identified as CD4<sup>+</sup>CD8 $\alpha$ +CD11b-CD11c+ and cDC2 as CD4<sup>+</sup>CD8 $\alpha$ -CD11b+CD11c+. cDCs recognize both extracellular and intracellular pathogens; of which cDC1 can efficiently cross-present exogenous antigens on MHC-I molecules to CD8<sup>+</sup> T cells, whereas cDC2 activates CD4<sup>+</sup> T cells, and trigger T<sub>H</sub>2 and T<sub>H</sub>17 immune responses. On the other hand, pDCs are distinguished from cDCs by the expression of CD45RA, lymphocyte antigen 6 complex (Ly6C), sialic acid binding immunoglobulin-like lectin H (Siglec-H), and CD317. These cells are important in anti-viral immunity and systemic autoimmunity, because they can sense intracellular self and non-self nucleic acids *via* TLRs pathways and produce type I and III interferons (Musumeci et al., 2019). In addition, LCs are another subtype of DC, which are considered to be potent APC. Under physiological conditions, their population frequency is 5%. However, during a disease/inflammation-challenged state, their population is replenished by infiltrating monocytes and 10%–20% of LCs migrate to the lymph nodes (Merad et al., 2008). LCs play a crucial role in maintaining immune resolution post-infection and tolerance. In the disease context of allergic contact dermatitis, it was observed that LCs can effectively induce anergy and apoptosis of CD8<sup>+</sup> T cells while activating ICOS<sup>+</sup> CD4<sup>+</sup> FoxP3<sup>+</sup> Treg cells (Kaplan et al., 2005).

Resident DCs are considered “immature” during the resting state. During the pathogen infection/inflammation state, DCs undergo maturation, expressing higher level of MHC-molecules, the co-stimulatory molecules CD86, CD83, CD40, and producing pro-inflammatory cytokines such as IL-12, IL-6, and TNF- $\alpha$ . Indeed, the activation of CD86<sup>+</sup> DC participated in the onset and progression of dry eye disease (Maruoka et al., 2018). In addition, DCs were also found to promote the progression of anterior uveitis (Lin et al., 2019).

Under physiological conditions, ocular cells can actively participate in the suppression of DC immunogenic activation to maintain an anti-inflammatory state in the ocular environment. For instance, retinal pigment epithelial cells can produce IL-1Ra to suppress DC activation. Corneal stromal cells can produce TGF- $\beta$ 1 to inhibit DC activity while promoting corneal wound

healing (Hamrah et al., 2003; Lu et al., 2012; Sugita et al., 2013; Morante-Palacios et al., 2021). In fact, DCs can also be activated into tolerogenic phenotypes. These DCs can produce anti-inflammatory cytokines such as IL-10, TGF- $\beta$ , and indoleamine 2, 3-dioxygenase (IDO) to suppress T-cell activity and function in maintaining ocular tolerance. Tolerogenic DCs can be generated *in vitro* with the co-culture of stromal cells or by treatment with immunosuppressive agents such as IL-10, TGF- $\beta$ , vitamin D receptor agonists, and vasoactive intestinal peptide (VIP) (Dempsey et al., 2003; Hu and Wan, 2011; Haneklaus et al., 2012; Perez and Caspi, 2015; Puri et al., 2022). Although tolerogenic DCs demonstrated therapeutic strengths in autoimmune diseases, the exploration of their potential in the ocular field is still under investigation.

## 3 Application of biomaterials in immunomodulation of the innate immune system

Biomaterials are widely used as carriers or scaffolds for ocular therapeutic entities, such as small molecular drugs, biomacromolecules such as proteins or nucleic acids and living cells. The carriers however have been known to actively interact with the immune system. The resulting host reaction as a result of the implanted materials is coined “foreign body response” (FBR). Biomaterial-induced FBR can lead to cargo clearance and elimination, countering therapeutic intentions. However, if properly gauged by appropriate material selection and design, the immune reaction can be utilized for pro-healing responses. Therefore, the design of biomaterials generally adopts strategies to 1) mitigate or 2) leverage FBR depending on the therapeutic goals in the eye. Indeed, this can be achieved with the high responsivity and plasticity of the above-mentioned innate immune cells in response to the exogenous biomaterials’ cues. With the appropriate selection of biomaterials and platform characteristics, these cells can be strategically manipulated and programmed toward a pro- or anti-immunomodulatory response to facilitate the overall therapeutic outcome.

Understanding the dynamics of FBR, that is, the biomaterials-innate immune cell interplay, is critical for this goal. The activation mechanism of innate immune cells by biomaterials is mainly governed by pattern-recognition receptors (PRRs). PRRs are present on the plasma membrane surface or in the cytoplasm and can sense a broad range of damage and pathogenic cues. PRRs consist of TLRs, nod-like receptors (NLRs), and inflammasomes. TLRs exist on the surface or in the endosomal compartment of antigen-presenting cells (APCs) including microglia, macrophages, and dendritic cells, and recognize a broad range of microbial molecules such as proteins, nucleic acids, and LPS, *etc.* NLRs are intracellular receptors with inflammasome subunits. Inflammasomes are the complex of these proteins, act as receptors of the innate immune system, and are responsible for the inflammatory response by cysteine-aspartic acid protease-1 (caspase-1) induction to produce the proinflammatory cytokines IL-1  $\beta$  and IL-18. NLR1, NLR3, NLR4, and absent in melanoma 2 (AIM2) are different inflammasomes that play a key role in ocular inflammatory

disorders such as glaucoma, DED, AMD, and DR in recent years (Yerramothu et al., 2018). It has been demonstrated in studies that dopamine, DMSO, microRNA-223 (miR223), and other inflammasome suppressors can lower the severity of inflammatory ocular illnesses. However, the mechanism by which inflammasomes function in the human body is unknown, necessitating more study to identify novel therapeutic approaches that focus on the inflammasome cascade (Bauernfeind et al., 2012; Haneklaus et al., 2012; Ahn et al., 2014; Yerramothu et al., 2018).

The activation of PRRs begins with the detection of foreign patterns including DAMP and PAMP and the secretion of signaling pathways to combat harmful agents (Andorko and Jewell, 2017). PAMPs and DAMPs can take in diverse forms; for instance, polysaccharides, peptides, glycopeptides, lipopeptides, LPSs, and nucleic acids, etc., which are derived from microbes or damaged host cells fragments during invasion and tissue injuries. The eye's innate immune system is extremely sensitive in detecting these molecular entities. Once the cells are activated, they secrete proinflammatory cytokines to initiate FBR. Similarly, the surfaces of biomaterials and delivery platforms also exhibit physicochemical features that resemble PAMPs. Therefore, FBR is inevitable with the introduction of ocular implants, injectable depots, and nano/micro particles. On the other hand, several TLRs are expressed by different ocular tissues, such as the cornea, conjunctiva, retinal pigment epithelial cells, and the uvea, to protect and isolate the eyeball from any specific PAMP (Wakefield et al., 2010). The uvea, for instance, is particularly susceptible to LPS-mediated TLR4, and acute anterior uveitis has been observed, based on TLR4 cell response to LPS (Yu and Hazlett, 2006). The ocular innate immune system, however, is also perceptive to anything that poses a threat to the host tissue through endogenous DAMPs. These molecules are released from the injured tissue or dead cells' intracellular or extracellular regions including ATP, high mobility group protein B1 (HMGB1), and other molecules derived from injured tissue (Mahaling et al., 2022). According to the review by Mahaling et al. (2022), these DAMPs are linked to inflammations brought on by age, increased ocular pressure, oxidative stress, ischemia, stress, and environmental factors, etc., in retinal illnesses.

A vast diversity of biomaterials has been explored and commercialized in ophthalmic drug delivery systems, mostly aiming to circumvent FBR. Conversely, with a deeper dive into the ocular immune response and biomaterial interplay and dissections, we can better understand the active role of biomaterials, and derive potential therapeutic approaches in ocular regenerative medicine and immune interventions. This can be achieved by targeting the FBR cascade, in terms of the distribution and timing of the key immune cellular and molecular players, using biomaterials and delivery devices. Moreover, learning from the natural defense mechanism against pathogens, the biomaterial polymer structure's repeating units, size, hydrophobicity, and patterning can be fine-tuned to mitigate or engage innate immune cell activation (Kakizawa et al., 2017). In the next section, we discuss several biomaterial systems, such as implants and injectable depots, nano/micro particles, and hybrid systems, as well as their physicochemical requirements for directing ocular innate immune cells to the desired anti- or pro-inflammatory phenotypes.

## 3.1 Implants and injectable depots

FBR is inevitable with the introduction of ocular implants and injectable depots. In ocular therapy, biomaterials can be used to implant cells, create therapeutic implants, and create injectable depots. During the initial stage of FBR, the acute inflammatory response generates pro-inflammatory cytokines to promote inflammatory cell infiltration, extracellular matrix (ECM), vascular remodeling, and perfusion. This can lead to an increase in ocular pressure, oxidative stress, ischemia, stress, and retinal illnesses, all of which are detrimental to the ocular structure and function. The chronic inflammation process often leads to deposition of the collagenous matrix surrounding the implants, causing rejection. Particularly for the intraocular lens (IOL), intravitreal drug depots, retinal prostheses, other long-term ocular implants, and fibrotic encapsulation not only result in device wastage but also vision compromise (Anderson et al., 2008; Veiseh and Vegas, 2019). Therefore, the timing and dynamics of FBR are important targets for biomaterial development.

An anti-FBR approach is rather common in ocular applications, especially for extended, controlled delivery platforms and prostheses. Biomaterials and delivery platforms are often used in an "immune stealth" or anti-inflammatory context to inhibit immune recognition and suppress the deposition of proteins and cells; thereby extending the half-life and bioavailability of therapeutic entities. Polyethylene glycol (PEG) is one of the most popular stealth materials in suppressing non-specific protein deposition on hydrophilic polymer coated devices. In some applications, it is useful for the biomaterial to mimic the ECM of the tissue, in terms of biochemical and biomechanical properties, to suppress the immune activation. The major compositions of ocular ECM are hyaluronic acid and collagens. For this ECM-mimicking purpose, the use of ECM-derived components and analogs, such as hyaluronic acid, fibrin, and collagen, as well as decellularized tissue, has been extensively explored (Rowley et al., 2019). These materials are commonly used in the development of intravitreal implants and corneal grafts. Moreover, ECM-derived peptides, including arginyl-glycyl-aspartic acid (RGD), matrix metalloproteinase (MMP)-sensitive peptides, or leukocyte-associated immunoglobulin-like receptor-1 (LAIR-1) ligand, are also incorporated on synthetic materials to improve the biocompatibility of the implants (Rowley et al., 2019). The design parameters of biomaterials for the anti-FBR approach is further discussed in the following section.

### 3.1.1 Hydrogels and polymeric depots

Hydrogels are widely used as delivery devices and supporting scaffolds in the ocular field. Hydrogels are 3D crosslinked hydrophilic polymers. They can hold small hydrophilic molecular drugs, and bioactive molecules such as proteins and nucleic acids. They can protect labile cargoes from tissue clearance and enzymatic degradation. Controllable hydrogel architecture design and degradability can help provide spatial and temporally controlled release of cargoes. More importantly, hydrogels also possess mechanical and optical characteristics that are compatible with those of the eyes.

For anterior ocular treatments, hydrogels are commonly used in the preparation of artificial tears, corneal regeneration, and IOL fabrication to provide structural support. Non-ethereal, implantation sites such as

the ocular surface and epithelial and stromal regions are populated with innate immune cells. They are sensitive to environmental anomalies triggered by the implants, eye drops, and injectables, subsequently inducing a cascade inflammatory response. Indeed, corneal haze and posterior capsular opacification (PCO) are common post-surgical complications in artificial corneal and IOL transplants, respectively.

On the other hand, for the ocular posterior, hydrogels can be used as vitreous substitutes to regulate intraocular pressure and structures. Delivery depots can protect laden drugs and therapeutic cells while providing controlled release of the therapeutic molecules directly to the diseased sites, circumventing the blood-retinal barrier. With appropriate biomaterial selection, FBR can be suppressed. For instance, a single intravitreal injection of *in-situ* crosslinkable hyaluronate (HA)/dextran hydrogel, which was designed to provide sustained release of anti-VEGF for 6-months, showed no inflammation of the ocular structures (Yu et al., 2015; Yu et al., 2019). In addition, the prolonged presence of thermosensitive methoxy-poly (ethylene glycol)-block-poly (lactic-co-glycolic acid) (mPEG-PLGA-BOX) hydrogel in the vitreal region, providing extended release of anti-VEGF for 42 days, also avoided inflammation in the posterior ocular region (Hu et al., 2019). However, another study that adopted PolyActive™, degradable PEG-polybutylene terephthalate-based (PEG-PBT-based) microparticles, to deliver anti-VEGF, observed inflammation at both acute initial and later stages of the treatment, suggesting that degradation products from the microparticles could trigger immunogenic responses in the eye (Adamson et al., 2016). The co-delivery of immunosuppressive signals also inhibited FBR against the long-term device. For instance, the commercial intravitreal injectable Ozurdex® is a degradable poly (lactide-co-glycolide) (PLGA) matrix for extended release of dexamethasone to circumvent FBR and actively suppress inflammatory events of uveitis.

Therefore, it is crucial to maintain ocular immune tolerance, that is, anti-inflammatory and anti-FBR responses, in order to improve the lifetime and optimal performance of the delivery device (Allyn et al., 2022). The general design strategies of implants and injectables often aim to 1) reduce non-specific protein and cellular adhesion or design anti-fouling properties to circumvent FBR, 2) introduce a delivery system with tissue-matching properties, and 3) mask receptors associated with pro-inflammatory pathway activation for suppressing innate immune activations. In the first approach, biomaterials and delivery platforms are often used in an “immune stealth” or anti-inflammatory context to inhibit immune recognition and to suppress the deposition of proteins and cells, thereby extending the half-life and bioavailability of therapeutic entities. PEG is amongst the most popular stealth material in suppressing non-specific protein deposition on hydrophilic polymer-coated devices.

### 3.1.2 Encapsulated cell implants

#### 3.1.2.1 Immunomodulatory cells

For decades, it has been demonstrated that mesenchymal stem cells (MSCs) are potential immunomodulators of the innate and adaptive immune systems (by inhibiting Th1 and Th17 and inducing the Treg and M2 macrophage phases) for various ocular inflammatory disorders such as corneal angiogenesis, neovascularization, autoimmune uveitis, and autoimmune DED (Lee et al., 2015; Song et al., 2018; Oh and Lee, 2021; Li Y. et al., 2022).

For targeted delivery to the eye, MSCs can be injected naked or encapsulated in a polymeric scaffold such as hydrogels to promote ocular tissue regeneration or suppress degeneration. The hydrogels can serve as a supporting matrix to separate the cells' cargo from the host tissue. In addition, they will support cell growth and functions, while the meshwork can facilitate sufficient exchange of materials between implanted cells and their host tissues, ensuring that laden cells are functioning properly. The choice of biomaterial is critical in the second strategy, to achieve immunomodulatory and biocompatibility goals using different administration routes such as topical or contact lenses or injectable scaffolds.

#### 3.1.2.2 Implants for encapsulating engineered cells

Based on previous works on several anti-inflammatory applications using MSCs and bandage contact lenses, the amniotic membrane (AM) is the most employed scaffold in the topical administration of MSCs in ocular surface therapy (Abu-Ain and Webber, 2010). AM exhibited remarkable anti-inflammatory and immunomodulatory effects (Parolini et al., 2009; Orozco Morales et al., 2019; Beeken et al., 2021). However, due to donor variability and the danger of disease transmission, this procedure lacks standard safety regulations. Synthetic and natural hydrogels can be employed as substitutes for AMs in this application. For instance, fibrin gel was used in a study as the carrier of rabbit MSCs and was transplanted on the surface of damaged rabbit cornea; it can be differentiated to corneal epithelial cells and inhibited inflammation in the area (Gu et al., 2009). Another scaffold that has been used is polylactic acid (PLA) nanofibers for seeding bone marrow-derived MSCs (BM-MSCs), adipose tissue-derived MSCs (Ad-MSCs), or limbal epithelial stem cells (LSCs) for the treatment of corneal optical properties after alkali burns that precede the inflammatory response (Cejka et al., 2016). BM-MSCs nanofibers and LSCs nanofibers are capable of suppressing corneal inflammation and neovascularization by suppressing MMP9, iNOS, and VEGF in the cornea. Polyamide 6/12 nanofiber scaffold (Zajicova et al., 2010) is another example of using hydrogels with MSCs in ocular surface inflammations; it significantly reduced the local inflammatory response in various ocular surface injuries.

Counterintuitively, the inflammatory response triggered by biomaterials can be leveraged to accelerate tissue regeneration, involving MSC and LSC. Polysaccharide has been shown to accelerate the tissue repair process by stimulating the inflammatory phase, with increased activation of macrophages, infiltrating cells, and fibroblasts (Matica et al., 2019). In this way, the acute inflammatory phase can be soon taken over by the proliferative phase to facilitate rapid re-epithelization and wound closure. The timing and dynamics of the inflammatory response are important targets for biomaterial development. Particularly, at the early stage of inflammation, intervention using biomaterials can promote pro-healing responses, predominantly for the delivery of therapeutic entities for ocular tissue regeneration.

Besides the use of MSC-encapsulated implants as an immunomodulatory treatment, there is another intriguing cellular therapeutic strategy that has been tested in clinical trials for eye disorders. In this strategy, cells are genetically transfected before encapsulation, and by then loading cells inside the polymeric implant, the engineered cells are capable of producing the



targeted protein for a prolonged time (Zhang et al., 2011; Wong et al., 2017; Belhaj et al., 2020). The polymeric implant is permeable, allowing the therapeutic drug to diffuse while protecting cells from the host's immunological responses. As a result, the selection of biomaterial as a protective carrier is critical to avoid inducing an unwanted immune response, or, even one step better, inducing an anti-inflammatory response. Neurotech is a pioneer in this technology, having developed the NT-501 device to provide sustained delivery of ciliary neurotrophic factor (CNTF; a growth factor shown to decrease photoreceptor degeneration in RP animal models) to treat retinal degenerative diseases such as RP, AMD, and glaucoma (Zhang et al., 2011; Kauper et al., 2012a; Kauper et al., 2012b; Chew et al., 2015).

Early clinical trials employed polymeric matrix-based systems, such as NT-501 (Renexus®), which is composed of a semi-permeable, non-biodegradable polysulfone scaffold, with polyethylene terephthalate as an internal matrix, to support CNTF-producing ARPE-19 cells. However, this cell-encapsulating device measured 1 mm in diameter and 6 mm in length, and requires surgical insertion in the vitreal region. NT-501 is currently under stage 2 clinical trials for glaucoma, and no device-related adverse events have been reported so far (Zhang et al., 2011; Wong et al., 2017). This method may be used for long-term delivery of different proteins and polypeptides such as VEGF-antagonist, inhibitory domain of factor H (complement receptor 2 and factor H (CR2-fH)) as a complement inhibitor of CNV, or anti-inflammatory cytokine target to suppress inflammation in inflammatory diseases (Adamson et al., 2016; Belhaj et al., 2020).

To improve patient compliance and ease of use, several hydrogel alternatives have been proposed, using a less-invasive injection procedure in encapsulated cell therapy. Immune-compatible materials, such as alginate and collagen-based hydrogels have been developed to deliver cells. Studies demonstrated minimal host-cells attachment on the hydrogel surface, the presence of living cell colonies, and the generation of active biomolecules over an extended number of days of implantation (Wikström et al., 2008; Wong et al., 2017; Belhaj et al., 2020). For instance, in one animal study, ARPE-19 cells were transfected to express the gene of choice and encapsulated in alginate polymer using a microencapsulation method coupled with electrospray to generate an encapsulated cell alginate capsule. The size of the capsule was controlled by the alginate concentration and the voltage of the electrospray. The results showed that a size of 150  $\mu$ l was more suitable for intravitreal injection, and that this method can be used for long-term delivery (around 6 weeks) of complement inhibitors for AMD treatment. The authors' technique was reported to be appropriate for animal models as it lacks the stability of alginate, which prevents it from being destroyed during injection (Wikström et al., 2008; Belhaj et al., 2020). In future, it may be worthwhile to study the immunomodulatory effect of biomaterials as implants for improving the functionalities of these encapsulated cell implants.

### 3.1.3 Implants and injectable depots design parameters

#### 3.1.3.1 Mechanical strength

Ocular tissues exhibit different mechanical strengths, with the cornea at 3.8 MPa, IOL at 2.5–6 MPa, and vitreous 20–50 Pa. Tissue stiffness is subject to differences in species, age, and disease states

(Nickerson et al., 2004; Formisano et al., 2021). Corneas and IOLs undergo substantial mechanical loading and stretch as part of their normal functions in maintaining ocular pressure and visual acuity. Resident innate immune cells have been exposed and habituated to these mechanical stimuli during physiological conditions (Liu and Li, 2021; Du et al., 2022). However, during diseased conditions, such as during glaucoma, the change in intraocular pressure and mechanical environment may induce pro-inflammatory activation of resident immune cells and may exacerbate disease progression. In fact, mechanical sensors, transient receptor potential vanilloid (TRPV), pannexin-1, and P2X7 can be found on retinal ganglion cells (RGCs) and glial (Müller) cells in posterior ocular structures (Križaj et al., 2014). The activation of mechanosensors may result in the release of pro-inflammatory mediators, such as IL-1 $\beta$ , which can in turn promote the activation of nuclear factor kappa B (NF- $\kappa$ B) in microglia. On the other hand, the corneal epithelium, which comprises the major ocular anterior surface, is able to sense shear stress. Abnormalities in mechanical properties can trigger the activation of resident innate immune cells (Liu and Li, 2021). Pathological conditions may result in dry eye disease.

Therefore, hydrogel stiffness should match tissue stiffness depending on the implantation site, to help maintain ocular structures and immune responses. The mechanical strength of hydrogels can be tuned by changing the polymer concentration, molecular weight of polymers, and crosslinking densities, as well as by incorporating nanomaterials and composites. For instance, in dry eye symptom relief, our group reported a HA-based soft hydrogel, which matched the mechanical properties of the tear film and provided surface lubrication for an extended period of time, without frequent corneal instillation. Moreover, when combined with cyclosporine, an immunosuppressant, the treatment regime significantly improved the symptoms of dry eye diseases in canine clinical studies, in comparison to cyclosporine treatment alone (Yu et al., 2021). It was reported that hard methacrylate-gelatin (GelMA) hydrogel, with a measured strength of 29 kPa, can induce M1 differentiation of macrophages *in vitro* and severe FBR responses *in vivo*, in contrast to softer alternatives with strengths of 2 and 10 kPa (Zhuang et al., 2020). A similar trend was observed in the THP-1 macrophage line culture on collagen-coated polyacrylamide gels, with higher M1 polarization on hard gels (323 kPa) than softer gels (11 kPa and 88 kPa). It was also demonstrated that the hydrogel stiffness modulated macrophage migration behavior, with a higher spreading area and slower movement on the stiffer gel. Moreover, it was reported that macrophages exhibit lower phagocytic ability on a stiffer gel (Sridharan et al., 2019; Li and Bratlie, 2021).

Soft hydrogels are generally preferred in ocular applications and are favored in the structural design of the ocular surface and intravitreal implants, with minimal adverse immune responses. However, tissue engineering for corneas and IOLs requires hydrogel scaffolds with much higher mechanical strengths to withstand ocular structural changes and functions. To accommodate these mechanical needs, other design modifications, such as surface hydrophobicity and topography are pursued to suppress immune activation.

#### 3.1.3.2 Surface chemistry: Charge and hydrophobicity

In the case of cornea and IOL implantations, hydrophobic materials are generally preferred in order to resist swelling, lens

epithelial cell engagement, and migration from the peripheral to the visual region (Zhao et al., 2017). Nonetheless, PCO and corneal haze are common among patients after surgery, both of which are characterized by the FBR of prostheses, resulting in secondary visual impairment (Pintwala et al., 2014; Tamura et al., 2017). Indeed, it is generally accepted that a hydrophobic surface can promote non-specific protein deposition and initiation of FBR. Hunter et al. (1981) were the first researchers who worked on the adjuvant efficiency of the polymer backbone structure. It has been shown that different inflammatory and immune responses are stimulated based on the physicochemical properties (hydrophile-lipophile balance) of the biomaterial and that the hydrophobic part of the molecule can stimulate the innate immune cells and cause inherent immunogenicity by PAMP or DAMP (Seong and Matzinger, 2004; Andorko and Jewell, 2017). The process is characterized by the fusion of macrophages to form giant body cells to facilitate the clearance of foreign materials. The cells also secrete immunomodulatory cytokines such as TNF- $\alpha$ , IL-1, and TGF- $\beta$  which can further promote nearby fibroblasts to secrete fibrinogen that surrounds the prostheses to isolate them from the host tissue environment.

Common strategies to bypass FBR include modifying the surface charge and hydrophobicity of implants. Hydrophilic PEG and anionic and zwitterionic polymers are often selected as coating materials for such purposes. There are several ways to modify the implant surface, and these generally involve physical or chemical methods, as discussed in a previous review (Song et al., 2020). The physical methods include electrospinning/spraying, spin coating, dip coating, and layer-by-layer (LbL) polymer assembly; chemical methods generally involve radical polymerization, 3-aminopropyltriethoxysilane (APTES) and glutaraldehyde, carbodiimide coupling, or “click” chemistry. Indeed, studies on surface modification of the commercial artificial corneas Keraklear, Korea Seoul-type, and T-style keratoprosthesis demonstrated that coatings of hydrophobic poly (methyl methacrylate) (PMMA) or poly (2-hydroxyethyl methacrylate) (PHEMA) with PEG, a hydrophilic polymer, can effectively resist immune cell engagement and suppress the secretion of pro-inflammatory cytokines (Kim et al., 2002; Xiang et al., 2015; Farid et al., 2020). As well as PEG, implant surface coatings with zwitterionic polymer brushes, such as phosphorylcholine and sulfobetaine, have also been utilized, and results demonstrated superior capabilities in suppressing FBR (Han et al., 2017; Wang et al., 2021). Other natural hydrophilic polymers, such as anionic HA, have been employed together with lysozyme in PMMA surface coating; they exhibited anti-bacterial properties and reduced the adhesion of cells and bacteria in *in vitro* culture (Wang et al., 2014). Moreover, a silicone-based hydrogel with a surface LbL assembly of alginate and chitosan was developed to achieve sustained release of the immunosuppressant diclofenac to suppress post-surgical complications related to IOLs (Silva et al., 2016). The hydrogel surface charge can also influence the treatment outcomes of several posterior ocular diseases. In the case of glaucoma, the suprachoroidal injection of HA hydrogel produced a shorter retention time and showed minor inflammation and fibrosis at the injection site. However, the application of the zwitterionic hydrogel polycarboxybetaine significantly suppressed inflammation and prolonged the reduction of intraocular

pressure (IOP) via suprachoroidal space expansion (Hao et al., 2022).

### 3.1.3.3 Surface topography and porosity

On top of the choice of hydrophilic or hydrophobic material chemistry, the surface roughness or topography of a hydrogel can also affect the wetting state, protein adsorption, and cell interactions. There is increasing evidence that hydrogel surface topography can modulate cell behaviors such as adhesion, migration, proliferation, and differentiation. During fabrication, hydrogel surface patterning can be achieved, up to micron and sub-micron resolutions, with the appropriate choice of materials and pattern design to counter the swelling behavior while preserving the pattern fidelity. The fabrication methods often include casting, nanoimprinting, 3D printing, electrospinning, multiphoton patterning, lithographic patterning, and swelling-induced patterning (Cui et al., 2021).

Surface patterning of hydrogels can influence the wettability of materials. In the case of micropillar array design, the spacing and height interfere with the water contact angle and protein adsorption, as well as cell-material interactions. A high throughput screening approach using a diverse library of 2,176 micropatterns was recently developed to study the relationship between monocyte-derived macrophages and topography. The study revealed that diameters of 5–10  $\mu\text{m}$  favored macrophage attachment, and smaller, denser micropillars pattern can instruct M2 phenotype polarization (Vassey et al., 2020). Another study also reported that micropillars with 2  $\mu\text{m}$  spacing and 4.5  $\mu\text{m}$  in height are able to resist silicone hydrogel wettability as well as protein and cell adhesion (Papenburg et al., 2010). On the other hand, PVA with 2  $\mu\text{m}$  gratings and a concave lens topography of 1.8  $\mu\text{m}$  can promote endothelial cell adhesion on PVA hydrogel, compared with wider (10  $\mu\text{m}$ ) gratings, pillars, and convex lens textures (McWhorter et al., 2013). In general, surface texture design often aims to mimic niche tissue topographical features to better direct cell behaviors for optimal delivery device performance and therapeutic efficacy. IOLs with surface micropatterning are able to resist PCO. The presence of micron-sized isotropic elements arranged in a symmetric and regular pattern can resist cell adhesion and migration. It was suggested that the texture interfered with the formation of focal adhesion within cells, which hampers cell adhesion and spreading. Indeed, the study demonstrated that ridge(R)/grooves(G) patterns with sizes comparable to cells, e.g., R5G10 with a gradient spacing, can also significantly suppress fibroblast cell adhesion and promote directional cell migration on the culture surface (Kwon et al., 2017).

Conversely, anisotropic geometries, such as gratings, can promote cell differentiation. It was observed that macrophages in the pro-healing M2 state exhibit extended or oblong morphology, in comparison to M1. Several studies demonstrated that by controlling macrophage morphology using micropatterning methods, macrophages can be polarized into the M2 state without the addition of cytokines. The cells cultured on confined micropatterned fibronectin lines 20  $\mu\text{m}$  in width were able to produce higher levels of IL-4 and IL-13 and resisted the effect of M1-inducing LPS stimulus (McWhorter et al., 2013). In addition, a honeycomb-like surface pattern 90 nm in size can also promote M2 differentiation, with highest expressions observed for CD206, IL-4, IL-10, and growth factors, which support tissue regeneration. It

was suggested that the honeycomb-like texture can promote filopodia formation, which is associated with RhoA/ROCK signaling pathways, and can induce M2 polarization (Zhu et al., 2021). Moreover, a study reported that fibrous meshes of gelatin hydrogel nanofibers mimicking ECM promoted macrophage adhesion and differentiation into M2 phenotypes, with upregulation of CD206 expression and downregulation of IL-1 $\beta$  and IL-8 in *in vitro* culture (Taskin et al., 2021).

The porosity of hydrogel implants can also be tuned to modulate immune cell behaviors. Under physiological conditions, cells reside in porous ECM which provides optimal mechanical cues and spaces for biochemical cue exchange and cell-cell communications. In pathological challenges, ECM polymer backbones can support immune cell infiltration to wound sites. The design of microporous hydrogels aims to promote immune cell infiltration for local antigen delivery or immunomodulation. This can be achieved by introducing degradable porogens during hydrogel fabrication. A study reported an alginate-based porous hydrogel system incorporating rapidly degradable alginate beads into a non-degrading bulk alginate hydrogel. The authors further adjusted the porosity of the hydrogel by adjusting the percentage of porogens. The study revealed that a system with 50% porogen significantly promoted DC infiltration and maintained the immature phenotype, compared with 25% and 70% porosity (Verbeke et al., 2015).

The size of pores can also be adjusted to protect cargoes from immune cell-mediated clearance while preserving materials exchange between the carrier and host tissue environments. For instance, nanopores can be introduced to cell-laden hydrogels to ensure that the cargo survives and functions. Indeed, an alginate hydrogel with a pore size of 600 nm was developed to encapsulate mesenchymal stem cells and was able to resist pro-inflammatory immune cell infiltration (Moshaverinia et al., 2015). Such hydrogel design could promote stem cell survival and the maintenance of phenotypes to support tissue regeneration.

#### 3.1.3.4 Degradability

Biodegradable hydrogels have received increasing attention for the design of drug delivery systems for spatiotemporally controlled release, protection from physiological degradation and clearance, and improved patient compliance. Hydrogel drug depots can be injected into the vitreal space to provide extended release and to improve the bioavailability of therapeutics for posterior ocular disease treatment. Drug depots are often designed to match the optical and mechanical properties of tissue sites to preserve visual functions. Moreover, degradable drug depots are more favored in intravitreal injections to circumvent the invasive surgical retrieval of non-degradable implants from the eye.

Generally, depending on the hydrogel design, the depots can undergo different types of biodegradation mechanisms, namely, solubilization, chemical hydrolysis, and enzymatic degradation. More importantly, the drug release kinetics can be controlled by the hydrogel degradation rate. There are several strategies that have been developed to regulate hydrogel degradation kinetics, which involve physical and chemical factors. For instance, physical interventions include changing the polymer concentration, the molecular weights of hydrogel precursors, hydrogel size,

architecture, and microstructure. On the other hand, chemical methods include introducing functional groups to modify polymer charge or hydrophobicity, the nature of crosslinkers, and crosslinking density (Kong et al., 2004; Jain et al., 2017; Lau et al., 2021).

Nonetheless, the long-term presence of hydrogel depots in the intravitreal space is often associated with FBR, and the design of degradable depot formulations can induce chronic inflammation, thereby hampering the immune compatibility of the delivery device. In fact, an undesirable immune response has been observed in vitreous substitutes that consisted of HA and PEG. In the case of PEG, despite being known for its excellent anti-fouling properties in bypassing FBR, its *in vivo* degradation has been shown to induce the generation of anti-PEG antibodies and local inflammatory responses (Reid et al., 2015; Chen et al., 2021). Moreover, for HA hydrogels, the choice of molecular weights during preparation is crucial in regulating its immunomodulating properties. Generally, higher HA molecular weights (>500 kDa) are preferred, as they can induce anti-inflammatory responses by promoting macrophage M2 polarization and tolerogenic dendritic cell induction. Our group observed that a higher HA molecular weight of 670 kDa could avoid inflammatory responses when the polymers were used to coat lipid-based nanoparticles to improve intravitreal retention in rabbit eyes. Nonetheless, with the use of small HA molecular weights such as 36 kDa and 120 kDa, inflammation is observed in posterior ocular structures (Xiaonan, 2020). The underlying mechanism is due to HA interactions with PAMP/DAMP receptors on innate immune cells, in which the high molecular weight biopolymer exerts competitive engagement of TLR2 and/or TLR4 receptors of the immune cells, resulting in signaling inhibition of pro-inflammatory pathways governed by Myeloid differentiation primary response 88 (MyD88) and NF- $\kappa$ B. The smaller molecular weight alternatives, on the other, hand can act as TLR agonists (Østerholt et al., 2011; Rayahin et al., 2015; Gebe et al., 2017). A recent study used zwitterionic hydrogel composed of polycarboxybetaine and demonstrated its superior anti-fouling ability against proteins and cells. The material was then used as a vitreous substitute in a rabbit model, with no visible adverse effect (He et al., 2021) (Figure 3).

## 3.2 Nano/micro particles

For years, nano/micro particles have been used as common drug delivery systems in the eye and could be a potential drug delivery carrier for ophthalmic applications. Nanoparticles (NPs) are considered to have a size under 1000 nm and microparticles (MPs) between 1 micron and 1 mm. MPs can be used as microcapsules (a core drug with a polymeric layer surrounding it) or microspheres (drugs dispersed throughout the polymer matrix), based on their structure (Herrero-Vanrell et al., 2014). Microcapsules are also referred to as ocular implants and these have already been covered in the section on implants (Zimmer and Kreuter, 1995; Adamson et al., 2016).

MPs are usually used in ocular applications for prolonged delivery (at least 1 week) of proteins, peptides, and biomolecules. PLGA is the most commonly used polymer in this area (Cohen et al., 1991; Carrasquillo et al., 2003; Gavini et al., 2004; Mandal et al.,

2018). For instance, Gavini et al. (2004) developed vancomycin-encapsulated PLGA microspheres for topical ocular delivery, and showed a high concentration of peptide drug in the rabbit aqueous humor just after 3 h of topical administration. Albumin, gelatin, PLA, polyanhydrides (Ron et al., 1993), and cyclodextrins (Davis and Brewster, 2004) are other biodegradable polymers that are used as microspheres. For the sustained release of pilocarpine, which is used to lower intraocular pressure, Rathod et al. developed pilocarpine-loaded egg albumin microspheres as an eye drop (Rathod and Deshpande, 2008). Another work on the transscleral delivery of PLGA microspheres encapsulated with pegaptanib sodium (an RNA aptamer (EYE001) that inhibits VEGF) showed sustained delivery of EYE001 over 20 days on the surface of the sclera to treat choroidal and retinal diseases such as wet AMD (Carrasquillo et al., 2003). The administration route and the type of polymer significantly alter the inflammatory response of innate immune cells in microsphere ocular delivery systems. For instance, it has been demonstrated that intravitreal injection of PLA and PLGA microparticles may increase inflammatory responses due to their propensity to aggregate, making them more suitable for use as depots for the simultaneous delivery of several biomolecules loaded into nanoparticles (Herrero-Vanrell et al., 2014).

It has been demonstrated in the literature that NPs are favored over MPs in circumstances of prolonged drug delivery and targeted delivery to deeper ocular layers (Zimmer and Kreuter, 1995; Andrés-Guerrero et al., 2015; Huang and Chau, 2019a). The use of NPs in the treatment of ocular disorders is a promising new tactic that may pave the way for more successful ocular therapy and penetration for targeting posterior parts of the eye. They may target the cornea, retina, and choroid, and exhibit several advantages for use in the treatment of eye disorders. These systems are capable of transporting various cargoes. For instance, the use of NPs may make it easier and more effective to distribute hydrophobic anti-inflammatory drugs such as corticosteroids and unstable nucleic acids such as mRNA. Furthermore, since they can pass through intricate ocular barriers such as ocular-retinal barriers and blood-retinal barriers of the eye, their delivery route through difficult-to-access areas of the eye is facilitated. Additionally, they sustain the long-term release of immunomodulatory medications for chronic ocular inflammatory conditions (Diebold and Calonge, 2010; Huang and Chau, 2019a; Tang et al., 2022). Various nano/microparticles that have been employed in immunomodulatory ocular applications are listed in Table 1 as a summary. Smart biomaterials, on the other hand, may be created to target specific tissue locations by employing optical, electrical, or mechanical targeting properties. They have several uses in biological imaging, targeting, smart drug delivery systems, and anti-inflammatory eye treatments (Ren et al., 2019; Luo et al., 2020).

### 3.2.1 Nanoparticle design parameters

Immune cells may respond in either a pro- or anti-inflammatory manner depending on the physiochemical characteristics of nanoparticles, including their size, shape, chemical composition, and surface charge (Figure 4). Therefore, by taking these variables into account, nanoparticles can be designed to regulate the immune response. The impact of these parameters is discussed in the following sections.

#### 3.2.1.1 Size

The size of the particle is a key characteristic that drives the innate immune cell response, and as the particle size grows, the innate immune cells' inflammatory and phagocytosis responses are amplified. The main disadvantages of corneal topical applications are drug bioavailability over time and increasing corneal penetration. Studies have indicated that the nanoparticle size should be less than 200 nm to allow easy uptake via endocytosis in the conjunctiva and cornea. Particle size is directly associated with penetration through the barriers of the cornea. A 180 nm gelatin nanoparticle, used as an eye drop in rabbit eye, for instance, could be retained in the cornea for a long time as a result of being taken up by ocular epithelial cells (Tseng et al., 2013; Soiberman et al., 2017; Tsai et al., 2018; Souto et al., 2019).

The literature also mentions the possibility of injecting positively charged particles with a size range of 50–350 nm into the vitreous body. Notably, for particles bigger than 350 nm, the size impact may be a significant component affecting their distribution, but for particles smaller than 350 nm, the charge effect is a significant parameter (Tsai et al., 2018; Mobaraki et al., 2020). A previous review paper by our group, on intravitreal nanoparticles for retinal delivery (Huang and Chau, 2019a), also noted that nanoparticles, after passing the internal limiting membrane (ILM), are directed to inner layers *via* endocytosis. To determine whether a particle with a particular size and charge may pass through the vitreous and ILM barriers or not, it is crucial to consider the size-cut off for nanoparticles passing through those barriers. Peynshaert et al. provide an in-depth discussion on drug delivery barriers in the posterior segment of the eye (Peynshaert et al., 2018; Peynshaert et al., 2019).

On the other hand, for the treatment of posterior ocular diseases, particles and implants larger than 2  $\mu$  m in size remain in the vitreous and are not able to pass through the retinal and other ocular barriers, similar to earlier reports of intravitreal sustained delivery of fluocinolone acetonide (FA) from a micron-size polymeric implant for over 1 month (Glybina et al., 2009; Glybina et al., 2010; Iezzi et al., 2012). Depending on the type of polymer and administration route used, the particles have the potential to be immunogenic, as previously discussed. Injecting ganciclovir-loaded PLGA microspheres intravitreally, for instance, resulted in their tendency to aggregate by building a depot in the eye, as well as a modest localized FBR response (Herrero-Vanrell et al., 2014). Adamson et al. (2016) also covered the limits of intravitreal injection of anti-VEGF-loaded PolyActive™ microparticles for the treatment of wet AMD. Particle migration from the vitreous to the anterior chamber, a delay in the breakdown of the polymer relative to the release of the payload, and early and late stages of ocular inflammatory response were listed as challenges in using these microparticles in clinical settings (Adamson et al., 2016).

Regarding the immunogenicity and cellular uptake mechanism of smaller nanoparticles, there are still several unanswered problems. Therefore, a crucial factor in identifying whether the innate immune cell interaction pathway is pro- or anti-inflammatory is particle size. In 1998 (D'Orazio and Niederkorn, 1998) an intriguing experiment was carried out by D'Orazio et al. The authors investigated the ocular APC response to various antigen types, as well as how the type of antigen affected anterior chamber-associated immune deviation (ACAID), which is a defense mechanism for controlling and avoiding immunologically induced damage. Ovalbumin (OVA) antigen was

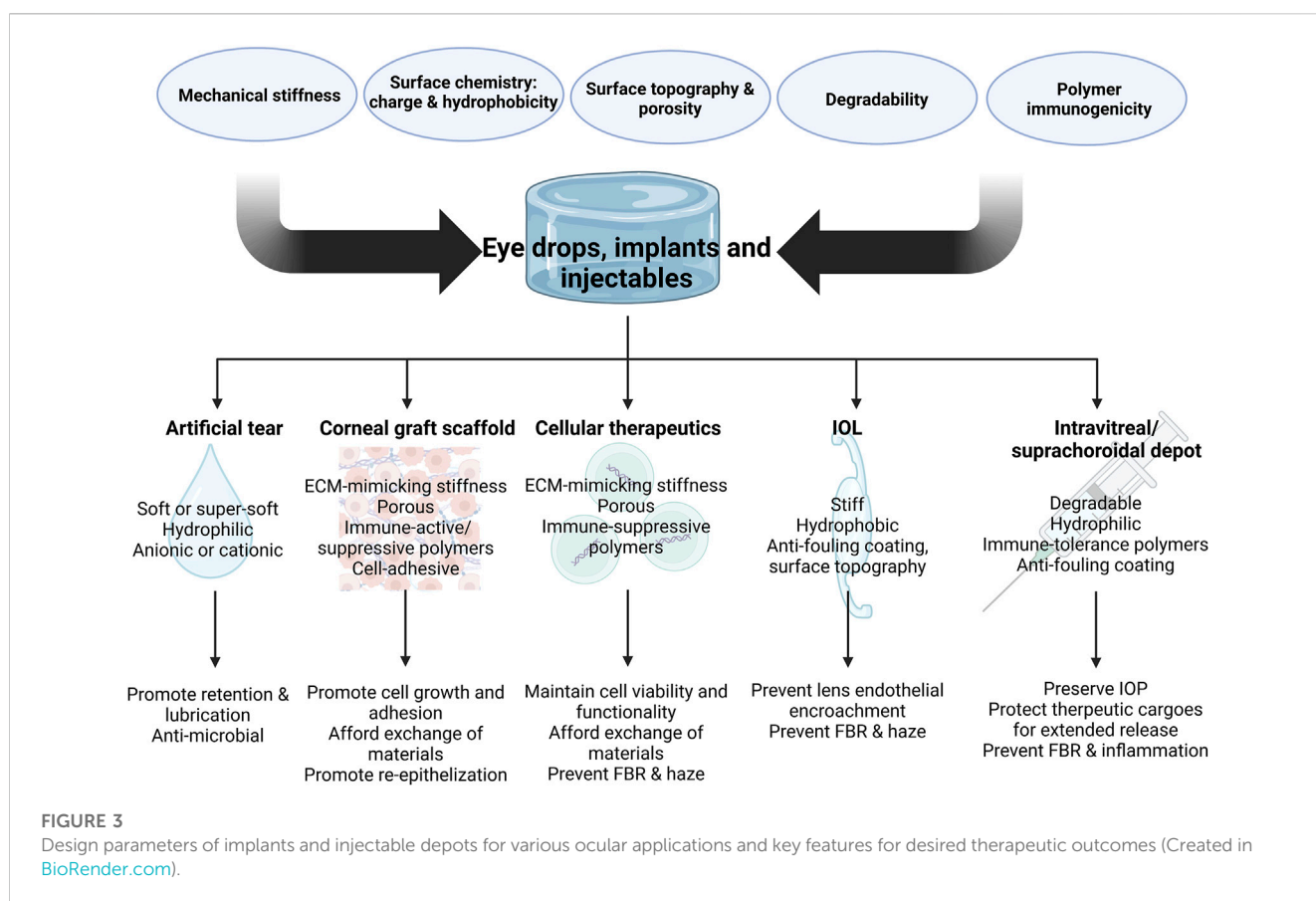
TABLE 1 Summary of different micro/nano particles used in the immunomodulation of ocular disorders.

Material	Physicochemical properties	Anti-inflammatory cargo	Ocular disease	Anti-inflammatory agent	Ref.
Pegaptanib sodium-PLGA microsphere	Size 14–16 $\mu$ m	EYE001	Choroidal and retinal diseases (wet AMD)	EYE001 RNA to inhibit VEGF	Carrasquillo et al. (2003)
Pilocarpine-egg albumin microsphere eye drop	Size 1–12 $\mu$ m	Pilocarpine	IOP in eye	Pilocarpine to reduce IOP	Rathod and Deshpande (2008)
Vancomycin-PLGA microsphere as eye drop	Size ~11 $\mu$ m	Vancomycin	Ocular infections	Vancomycin as peptide antibiotic	Gavini et al. (2004)
Dexamethasone sodium phosphate-Zn-PLGA nanoparticle (DSP-Zn-NP)	Size 210 nm, near neutral surface charge ( $-9$ mV), hydrophobic	Dexamethasone	Uveitis by EAU	Pluronic F127 surface coating and corticosteroid drug	Luo et al. (2019)
Polymeric implant (PVA and silicone)	Size 2 mm, long cylinders, 300 $\mu$ m in diameter	Fluocinolone acetonide (FA)	Retinal degeneration	FA as corticosteroid drug	Glybina et al. (2009), Glybina et al. (2010)
Rapamycin-loaded PCL-micelles	Size 40nm, sphere, surface charge of $-0.89$ mV	Rapamycin	EAU	Rapamycin as immunosuppressant drug	Wu et al. (2016)
HA-coated PLGA nanoparticle	Size 173–200 nm, negative surface charge, hydrophilicity increased by using HA	Lutein	AMD	Lutein as antioxidant drug and HA coating	Chittasupho et al. (2019)
Double-headed polyester nanoparticles using gambogic acid (GA)-coupled PLGA (PLGA-GA <sub>2</sub> -CUR)	Size 250 nm, double-headed nanoparticle, hydrophobic	Curcumin (CUR)	Acute intraocular inflammation by EAU	Curcumin as anti-inflammatory drug	Ganugula et al. (2020)
DuraSite/synthetic polymer of cross-linked PAA (Bromfenac)	Adjusted to a viscosity of 1100–1900 cP, pH 6–6.6, osmolality 260–340 mOsm/kg, suitable for dispensing in the eye	1% azithromycin or 0.6% besifloxacin	Post cataract surgery inflammation and pain	Antibiotic drugs	Bowman et al. (2009), Trattler and Hosseini (2017) NCT01576952
Dexamethasone-PAMAM dendrimer conjugates (DEX/PAMAM)	Size ~145 nm, surface charge ~ $-50$ mV	Dexamethasone	Ocular diseases affecting retina such as AMD, DR, and glaucoma	Dexamethasone as corticosteroid drug	Yavuz et al. (2016)
Hydroxyl-terminated PAMAM dendrimer-drug conjugate nanodevices	Size ~3–10 nm, PMMA with $-OH$ terminal groups, non-cytotoxic	FA	Retinal neuroinflammation in AMD and retinitis pigmentosa	FA as corticosteroid drug	Iezzi et al. (2012)
Pilocarpine-loaded hCe Chitosan/ZM nanoparticle	Size less than 70 nm, positive surface charge of 5–20 mV	Pilocarpine	Glaucoma	Pilocarpine drug to reduce IOP and cerium oxide nanoparticles with anti-inflammatory effects	Luo et al. (2020)
Lipoidal-chitosan-poly ( $\epsilon$ -caprolactone) nano system (DSPC-chit-PCL NS)	Size ~140.7 nm, surface charge of ~ $+55$ mV	Indomethacin	Inflammatory disorder in the posterior part of the eye	Use of DSPC lipid and indomethacin drug	du Toit et al. (2013)
Betamethasone phosphate/PEG-PLA nanoparticle	Size ~120 nm	Betamethasone phosphate	Uveitis by EAU	Betamethasone as steroid drug and use of PEG surface coating	Sakai et al. (2006), Sakai et al. (2011)
Gold nanoparticle (AuNP)	Size ~25 nm	No drug	LPS-induced uveitis model	Inherent anti-inflammatory properties of AuNP by downregulating the TLR4 and NF- $\kappa$ B pathways	Pereira et al. (2012)
VIP-loaded pegylated liposome	Size 300–600 nm	VIP	EAU	VIP as immunosuppressant	Lajavardi et al. (2007)
Cy A-loaded hyaluronic acid-coated PCL/benzalkonium chloride (BKC) nanospheres	Size over 200–300 nm	Cy A	Immune-mediated corneal disease	HA reduced the BKC cytotoxicity and Cy A as inhibitor of IL-2 proinflammatory cytokine	Yenice et al. (2008)

(Continued on following page)

**TABLE 1 (Continued) Summary of different micro/nano particles used in the immunomodulation of ocular disorders.**

Material	Physicochemical properties	Anti-inflammatory cargo	Ocular disease	Anti-inflammatory agent	Ref.
siRNA targeting VEGF nanoball (PEI/HA)	Size 260 nm, surface charge of -41 mV	siRNA anti-VEGF	Ocular neovascularization	siRNA to inhibit the VEGF expression	Ryoo et al. (2017)
K5 plasmid-loaded PLGA/chitosan NP	Size 260 nm, surface charge of 8.4 mV	Expression plasmid of plasminogen Kringle 5 (K5)	Retinal inflammation	K5 plasmid to downregulate the VEGF expression	Park et al. (2009)
IL10 mRNA-loaded SLN/polymeric ligands of dextran and HA/1%PVA as eye drop	Size between 94 and 348 nm, positive surface charge between 26 and 45 mV	IL10 mRNA	Corneal inflammation	IL10 mRNA as anti-inflammatory cytokine expression agent	Gómez-Aguado et al. (2021)



used as a model antigen. It arrived in two forms: soluble and particulate, and it was passively absorbed on the surface of latex (polystyrene) particles with a size of 460 nm. The authors demonstrated that particulate antigens can stimulate APCs, increasing IL12 production and Th1 activation, whereas soluble antigens activate the ACAID pathway, increasing IL10 production and Th2 regulatory cells (D’Orazio et al., 2001).

**3.2.1.2 Chemical structure**

Another factor that may affect whether the response of the innate immune system is pro- or anti-inflammatory, as previously

mentioned, is the intrinsic chemical structure of the nanoparticle. Natural biomaterials such as gelatin (Vandervoort and Ludwig, 2004; Mathurm and Gilhotra, 2011), chitosan (Maró’a et al., 2003; Enríquez de Salamanca et al., 2006; Tsukamoto et al., 2013; Li et al., 2009; Aşık et al., 2013), collagen (Luis et al., 2016; Simpson et al., 2021; Song et al., 2021), albumin (Zimmer et al., 1994; Tiwari et al., 2021), alginate (Shafie and Fayek, 2013; Kostenko et al., 2022), and HA (de La Fuente et al., 2008; Yenice et al., 2008; Rayahin et al., 2015; Gebe et al., 2017; Guter and Breunig, 2017; Casey-Power et al., 2022) are frequently used as anti-inflammatory agents in eye treatment because they do not cause an inflammatory response

from the innate immune system (Sharma et al., 2016). They come in the form of nanoparticles, nano emulsions, nano capsules, liposomes, and lipid nanoparticles. Although these biomaterials have been used in numerous previous studies as carriers to support drug release, enhance ocular penetration, lengthen ocular retention, and improve ocular bioavailability, future research could focus on the materials' interaction with ocular innate immune cells to suppress the inflammatory phase of macrophages, without the use of steroid drugs.

Chitosan, a common nanomaterial in ocular research, has been proven in several studies to exhibit minimal immunogenicity for innate immune cells, as previously stated. Chitosan is bioadhesive, can enhance ocular penetration, and does not cause an inflammatory response, according to several experiments (Maró'a et al., 2003; Enríquez de Salamanca et al., 2006). Furthermore, HA as a nanoparticle or coating of polymeric nanoparticles has shown substantial potential in reprogramming ocular innate immune cells (Yenice et al., 2008; Guter and Breunig, 2017; You et al., 2020). A higher HA molecular weight, as previously noted, may trigger an anti-inflammatory response of innate immune cells (Casey-Power et al., 2022).

On the other hand, PLGA (Casey et al., 2019; Ganugula et al., 2020; Luo et al., 2020), PLA (Sakai et al., 2006; Sakai et al., 2011), poly-caprolactone (PCL) (Yenice et al., 2008; du Toit et al., 2013), polyacrylic acid (PAA) (Trattler and Hosseini, 2017), and poly (amidoamine) (PAMAM) (Iezzi et al., 2012; Yavuz et al., 2016) are the most commonly used synthetic biomaterials as carriers of anti-inflammatory medications in ophthalmic therapy. According to Casey et al. (2019), PLGA and PLA particles have broad-acting mechanisms that inhibit TLR signaling by programming innate immune cells, and they exhibit inherent immunomodulatory properties depending on their physiochemical properties. The authors declared that more research into the inherent immunomodulatory properties of polymer-based particles is necessary since they have the potential to treat a wide range of human disorders *via* abnormal TLR activation (Casey et al., 2019). Similar to natural biomaterials, they come in form of dendrimers, nano capsules, and nano emulsions. Nevertheless, the fact that they degrade *in vivo* raises further questions regarding their immunogenicity, and more research is required to ascertain how different types of materials impact immunity. For instance, in order to prevent the development of experimental autoimmune uveitis (EAU), Wu et al. created PCL-micelles loaded with rapamycin that were 40 nm in size, spherical in form, and with  $-0.89$  mV charge (Wu et al., 2016). Another study aimed to reduce uveitis inflammation by employing PLGA nanoparticles (210 nm) containing dexamethasone (Luo et al., 2019). The cytotoxicity of several materials, including PLGA, PCL, and PEG-PLGA, toward the retinal cell line (ARPE-19) was also tested by Lin et al. The authors found that PEG-PLGA had the lowest cytotoxicity over 6 days, in comparison to the other materials, which exhibited different cytotoxicities (Lin et al., 2016). Another group claimed that surface modification of synthetic polymers reduces their cytotoxicity and subsequent immune responses since HA-coating on PLGA nanoparticles did not exhibit any cytotoxic impact on RPE cells (Chittasupho et al., 2019).

Aside from these two groups, there are other nanomaterials with inherent immunosuppressive functions (anti-inflammatory, anti-

angiogenesis, anti-bacterial, and anti-oxidative stress) that have been shown to influence ocular inflammation, including cerium oxide NPs for AMD treatment (Tisi et al., 2019; Luo et al., 2020), gold NPs for uveitis and AMD (Pereira et al., 2012; Singh et al., 2020), and silver NPs for fungal keratitis (Shi et al., 2021). For instance, Pereira et al. (2012) studied the inflammatory response of gold nanoparticles (AuNP) in endotoxin-induced uveitis and showed that the topical use of AuNP reduces inflammation by downregulating the TLR4 and NF- $\kappa$  B pathways. Another example is cerium oxide nanoparticles (nanoceria), which exhibit inherent immunomodulatory, antioxidant, and anti-inflammatory effects on innate immune cells such as macrophages. These effects can increase the production of anti-inflammatory cytokines while decreasing the release of pro-inflammatory cytokines (Hirst et al., 2009; Schanen et al., 2013; Eitan et al., 2015; Domala et al., 2019; Mitarotonda et al., 2022). Luo et al. (2020) designed antioxidant and anti-inflammatory hollow nanoparticles that deliver anti-glaucoma pilocarpine drugs in a sustained manner for 7 days, as compared to typical eye drops with just 4 h moderate efficacy for glaucoma therapy. The authors chose ceria nanoparticles because of their intrinsic antioxidant, anti-inflammatory, and anti-angiogenesis capabilities. Following that, the authors exploited surface dual crosslinking to simultaneously target ciliary body tissue (through a non-xanthine adenosine receptor antagonist (ZM241385)) and increase corneal epithelium penetration (by chitosan). The authors studied the anti-inflammatory properties of nanoparticles by measuring IL6 and MCP-1 levels and showed that by increasing the chitosan coating amount on the surface of ceria NPs, IL6 and monocyte chemoattractant protein-1 (MCP-1) production slightly increased. The authors showed that materials with dual functions, such as chitosan and ZM, may serve as antioxidants and anti-inflammatory agents, reducing inflammatory cytokines such as IL6 and MCP-1, when applied to the surface of ceria NPs. However, it should be noted that these metallic materials have the potential to form reactive oxygen species (ROS), which can sometimes lead to cytotoxicity in the eye (e.g., ZnO and Fe nanoparticles) (Zhu et al., 2019).

### 3.2.1.3 Shape

The shape of the material and the way it affects how nanomaterials interact with innate immune cells is another crucial factor. There is no assurance that the innate immune system will not react negatively to the nanoparticles. Nanoparticle size and shape have the potential to stimulate macrophages to phagocytose and to consume and frustrate them, causing them to secrete an increasing amount of pro-inflammatory cytokines, eventually causing chronic inflammation, or even to stimulate DCs to mature and activate T cells (Bartneck et al., 2010; Niikura et al., 2013; Andorko and Jewell, 2017). According to Bartneck et al., macrophage absorption of gold nanorods is higher than that of nanospheres *via* the macropinocytosis process; nanorods elicited a stronger inflammatory response *in vivo* even after surface modification with polyethylene oxide (PEO) (Bartneck et al., 2010; Andorko and Jewell, 2017). Another intriguing work by Niikura et al. (2013) reported that the size and shape of gold nanoparticles (AuNPs) *in vitro* and *in vivo* may be used to tailor the responses of innate immune cells such as macrophages and DCs. Cells exposed to rod-shaped nanoparticles released cytokines *via*

pro-inflammatory inflammasome pathways, such as IL-1  $\beta$  and IL18. Cells treated with cubical and spherical nanoparticles produced TNF- $\alpha$ , IL6, and IL12 through various cytokine pathways (Niikura et al., 2013). The stiffness and aspect ratio of the nanoparticle increase as the shape of the particle changes from spherical to rod-shaped, cubical, hexagonal, or any other shape, and, as a result, macrophages triggering and the inflammatory response also increase based on the potential membrane damage by stiff particles in phagocytic cells (Woźniak et al., 2017; Li et al., 2021). In addition, it has been demonstrated in ocular studies that nanoparticles with a larger aspect ratio, such as those in the shape of fibers, carbon nanotubes, or 2D nanomaterial sharp sheets, are cytotoxic to eye tissue (Zhu et al., 2019).

### 3.2.1.4 Surface charge

Another crucial factor is surface charge, which is particularly important for nanoparticles due to concerns regarding delivery, corona protein aggregation, and stability. Researchers have discovered that nanoparticles with a charge lower than  $-30$  mV may have an anti-inflammatory impact on the immune system. A higher amount of negatively charged particles causes a lower immunogenic response and they may be immunosuppressive (Andorko and Jewell, 2017; Li H. et al., 2022; Wen et al., 2016; Getts et al., 2014). Despite the fact that positively charged particles may be more easily taken up by cells than negatively charged particles, they will indeed be more cytotoxic and trigger an inflammatory response in the cells (Zhu et al., 2019). Similarly, our group noted that surface charge plays an important role in the biodistribution of nanoparticles, while simultaneously triggering an immunogenic response (Huang and Chau, 2019a).

Yavuz et al. used  $-50$  mV negatively charged dexamethasone-PAMAM dendrimer conjugates for various ocular diseases affecting retinae such as AMD, DR, and glaucoma. The authors demonstrated that these dendrimers can effectively permeate to the back of the eye and release anti-inflammatory drugs in a sustained manner; however, the clearance time was quick. The authors suggested that the use of cationic dendrimers to determine the impact of surface charge on clearance time be taken into account (Yavuz et al., 2016). Additional information on the immunological characteristics of various engineered nanomaterials is discussed in the review of Dobrovolskaia (Dobrovolskaia and McNeil, 2007). Generation 3.5 PAMAM conjugated to glucosamine-negative dendrimers is one example that can inhibit human macrophages and DCs' proinflammatory response and is immunosuppressive (Shaunak et al., 2004).

Lipid-based nanomaterials are another category of nanoparticles that have been widely used for ocular treatment, based on their controllable surface charge, especially as non-viral gene delivery systems. Due to their tendency to disassemble and aggregate, these materials are less stable in the eye compared to polymeric nanoparticles (Huang and Chau, 2019a). Lipid-based nanoparticles (LNPs) encapsulated with the model drug small interfering RNA (siRNA) were studied by our group to determine the impact of charge on intraocular distribution. We discovered that LNPs with neutral or negative charges exhibit problems with rapid clearance, whereas LNPs with a positive charge of  $35$  mV can

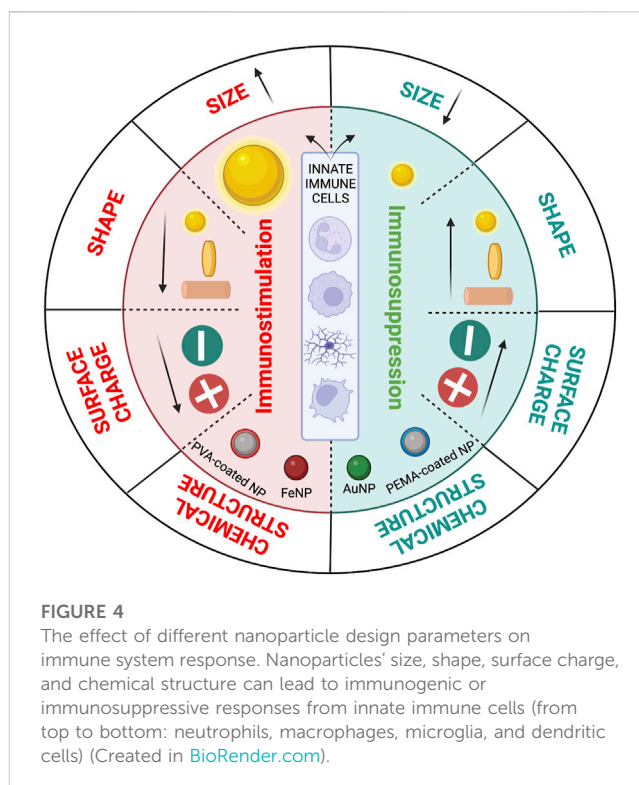


FIGURE 4

The effect of different nanoparticle design parameters on immune system response. Nanoparticles' size, shape, surface charge, and chemical structure can lead to immunogenic or immunosuppressive responses from innate immune cells (from top to bottom: neutrophils, macrophages, microglia, and dendritic cells) (Created in BioRender.com).

diffuse through the retina and deliver the siRNA (Huang and Chau, 2019a; Huang and Chau, 2019b; Huang and Chau, 2021). In a different study conducted by our group, we found that siRNA-encapsulated LNPs with a positive surface charge of  $+33$  mV did not cause activation of microglia cells or an inflammatory response (Xiaonan, 2020).

The particle clearance time and immunogenic reactions should be taken into account in ocular studies. The circulation and retention period of nanoparticles inside the eye can be prolonged by adopting a stealth technique that coats the nanoparticles with a hydrophilic substance called PEG. One example of this use is the systemic administration of PEG-stealth-PLA nanoparticles encapsulated with betamethasone for targeting the inflamed uvea and retina in a rat with EAU. The authors demonstrated that these stealth NPs reduced inflammation by the first day after administration, and their effects remained for 2 weeks. This period was significantly greater than their earlier experiment, which employed betamethasone/PLA NPs alone, which presented quick systemic phagocytosis clearance (Sakai et al., 2006; Sakai et al., 2011).

In order to inhibit the TLR-mediated innate immune pathway, Casey et al. (2019) used cargo-free nanoparticles of PLA and PLGA with different coatings of poly (ethylene-alt-maleic anhydride) (PEMA) and poly (vinyl alcohol) (PVA), different molecular weights, and different charges. The authors demonstrated that the PEMA coating caused a larger immunosuppression effect compared with the PVA coating (Figure 4). The downregulation of pro-inflammatory cytokines and the suppression of TLR-mediated inflammation were accomplished by altering the physicochemical characteristics of the nanomaterials, such as the charge, molecular weight, and polymer composition.



### 3.2.2 Immunomodulatory cargoes for nanoparticle

Using nanoparticles is the most common method for treating challenging ocular disorders related to the posterior part of the eye. By penetrating beyond ocular barriers, they can reach and distribute in the posterior segment. Based on the importance of chronic inflammatory diseases affecting the posterior region of the eye (e.g., glaucoma, AMD, and DR), the most common immunomodulatory cargoes used in nanoparticles are discussed in the following section. In light of this information, more efficient treatment strategies for chronic inflammatory eye disorders may be suggested, taking into account these potential cargoes and understanding the criteria for designing immunomodulatory nanoparticles.

#### 3.2.2.1 Steroids

The most common immunosuppressive agents are steroids. They have been used in a large number of commercial anti-inflammatory ocular drugs such as Bromfenac and INVELTYS™, both of which contain cross-linked PAA or chitosan polymer; they are widely used for treating post-ocular surgery inflammation, reducing post-surgery pain, and DED (Bowman et al., 2009; Schopf et al., 2015; Trattler and Hosseini, 2017; Kim et al., 2018; Gupta and Venkateswaran, 2021). Steroidal immunosuppressants have several drawbacks; they require high administration dosages, frequent injections in chronic ocular inflammatory diseases that lead to defects in the innate immune system, and other long-term side effects such as cataracts and IOP in the eye. By using immunomodulatory biomaterials as carriers instead of traditional inert carriers and alternative immunosuppressive drugs instead of steroids, such as anti-inflammatory cytokines, anti-inflammatory peptides, and nucleic acids, it is possible to overcome these problems in the eye.

#### 3.2.2.2 Biomolecules (proteins and peptides)

Another type of cargo used in ocular immunomodulatory treatment includes biomolecules such as proteins and peptides. However, there are drawbacks to employing these cargoes, for example, cytokine's short half-life and biomolecules' poor ocular bioavailability. Different immunosuppressive biomolecules such as TGF- $\beta$ ,  $\alpha$ -melanocyte-stimulating hormone, and VIP are produced in the eye to retain its homeostasis and immune-privilege mechanism (Lajavardi et al., 2007). Each of these biomolecules, in an inflammatory state, may act as a possible immunosuppressant payload, restoring homeostasis. Several studies have used VIP as an immunosuppressant for the treatment of ocular inflammatory diseases (Lajavardi et al., 2007; Taylor, 2007). In uveitis, VIP-encapsulated liposome nanoparticles regulate macrophages and dendritic cells immune responses (Camelo et al., 2009). By combining VIP with liposome nanoparticles, the slow release of VIP effectively reduced the degree of uveitis and pro-inflammatory cytokines and prevented retinal damage (Camelo et al., 2009). Another immunomodulatory peptide from fungi, cyclosporine A (Cy A), is being investigated as an immunosuppressant for inflammatory ocular conditions because it suppresses the proinflammatory cytokine IL2 (Nussenblatt and Palestine, 1986; Serda et al., 1990; Gupta and Sahu, 2001; Rumelt et al., 2002; Lallemand et al., 2003; Yenice et al., 2008). A study by Yenice et al. (2008) investigated the bioavailability of Cy A in the cornea

with regard to HA-coated PCL nanoparticles. In this respect, regulatory cytokines, and their prolonged release in the site of inflammation, may treat ocular inflammatory diseases by polarizing innate immune cells in an anti-inflammatory manner. IL4, IL13, and IL10 are the most frequently mentioned anti-inflammatory cytokines that are used as immunomodulatory payloads for the innate immune response and M2 polarization (Reeves et al., 2015; Schirmer et al., 2016; Cha et al., 2017; Riabov et al., 2017; He et al., 2019; Li et al., 2021).

As previously mentioned, TNF- $\alpha$  is a pro-inflammatory cytokine that is produced in large amounts in inflammatory conditions; thus, blocking its receptor may be a promising way to suppress inflammation. For instance, Woo Ji et al. developed a TNF- $\alpha$  blocker HL036 peptide for the topical treatment of dry eye, and showed that it could effectively eliminate TNF- $\alpha$  on the ocular surface and suppress inflammation by lowering the IFN- $\gamma$ , IL6, and IL21 proinflammatory cytokines (Ji et al., 2013).

A recent study was conducted on the dynamics of microglia polarization and their regulation by an anti-inflammatory mixture of cytokines IL4/IL13 or the antitumor agent bicyclic nojirimycin derivative (1R)-1-dodecylsulfanyl-5N,6O-oxomethylidenenojirimycin (R-DS-ONJ) in a mouse DR model. The authors reported that using M2 cytokines or R-DS-ONJ as a modulating agent in the environment of activated microglia cells reduced retinal degeneration and inflammatory progression both *in vitro* and *in vivo* (Arroba et al., 2022). Further research can be conducted in this area to determine if inflammatory microglia targeting can be used as a therapeutic method to postpone or stop the impairment of visual function in DR.

#### 3.2.2.3 Nucleic acids

Gene therapy for ocular inflammation may be an excellent option, even in clinical trials, and may use DNA, RNA, aptamers, and oligonucleotides. The stability of nucleic acid and the efficiency of its targeted delivery to minimize off-target effects are two challenges in this approach (Guzman-Aranguel et al., 2013; Raghunath and Perumal, 2015).

Viral and non-viral vectors are the two main types of nucleic acid delivery methods. Although viral vectors have been widely used as nucleic acid delivery methods, their immunogenicity, which may result in inflammation by inducing an immune response, is a major concern when employing them in clinical studies (Bordet and Behar-Cohen, 2019). These viruses include adenoviruses (AVs), adeno-associated viruses (AAVs), and lentiviruses. AAVs have been used in several studies on ocular gene therapy and chronic ocular disorders, although it has been demonstrated that they produce a mild immune response (Timmers et al., 2020). The first FDA-approved ocular gene therapy product, Luxturna®, also used an AAV2 vector and targeted diseases caused by the mutation of RPE65 genes such as retinitis pigmentosa (Russell et al., 2017). In this way, the type of vector, route of administration, and viral dosage cause different immune responses. For instance, the intravitreal route showed a higher immune response in comparison to other routes, and subretinal injection showed a lower immune response (Wasnik and Thool, 2022). An interesting study on the immunomodulation of uveitis by gene therapy is the use of a mutant serotype 8 adeno-associated virus (AAV8) (Y733F)-chicken  $\beta$ -actin (CBA)-MIF vector to express the macrophage

migration inhibitory factor (MIF), which is an important cytokine for regulating macrophage function and T cell activation (Yang et al., 2016). It has been shown that MIF is critical for modulating ocular inflammation in EAU, linked to the Notch signaling pathway; this may be a promising therapeutic approach for uveitis.

Recently, Gilger and Hirsch (2022) reviewed the potential of using the human leukocyte antigen G (HLA-G) gene in AAV vectors for ocular inflammatory treatments. HLA-G is an important anti-inflammatory agent that can suppress the inflammatory function of innate immune cells such as neutrophils, dendritic cells, macrophages, and natural killer cells. The authors stated that, based on the anti-vascular performance of the HLA-G, it could be a great target for the treatment of different ocular diseases including corneal inflammation, corneal graft rejection, DED, uveitis, AMD, and DR (Gilger and Hirsch, 2022).

Nevertheless, based on concerns regarding the immunogenicity of viral vectors (Bordet and Behar-Cohen, 2019), non-viral vectors (with low immunogenic risk) are alternatives for gene therapy, especially in immunomodulatory approaches. LNPs, nano polymers, and self-assembly peptides with nucleic acid are the most common non-viral delivery systems in this area. There are several studies and clinical trials on ocular gene therapy for immunomodulatory approaches using siRNA, miRNA, mRNA, DNA, and plasmid DNA (Ghoraba et al., 2022).

The use of siRNA in different ocular inflammatory diseases was reported for silencing different innate immune cell-mediated inflammatory genes (Guzman-Aranguez et al., 2013). For instance, SYLO40012 (bamosiran) is a commercial siRNA topical drug used to suppress the  $\beta$ -Adrenergic Receptor 2 as well as to lower intraocular pressure in glaucoma (Pintor, 2012; Bordet and Behar-Cohen, 2019; Ghoraba et al., 2022). For treating neovascularization-related disorders such as retinopathy and AMD, an important key regulatory agent is VEGF. Inhibition of VEGF was achieved by using recombinant AAV-mediated soluble VEGF receptor 1 (sFlt-1) expression (Bainbridge et al., 2002; Rota et al., 2004; Shen et al., 2006) or siRNA-targeting VEGF (Reich et al., 2003; Jiang et al., 2009; Ashikari et al., 2010). It was shown that neovascularization was reduced in the retina and choroidal, respectively. Interestingly, Ryoo et al. (2017) developed a novel siRNA-based anti-VEGF nanoball that was composed of siRNA-targeting VEGF as the core hydrogel with a coating of branched PEI and HA, achieved by applying an electrical force, for the treatment of choroidal neovascularization in AMD. The authors demonstrated excellent therapeutic results over 2 weeks as a result of intravitreal injection and targeting efficiency in the sub-retinal space via CD44 receptor endocytosis. AAV-mediated gene delivery of pigment epithelium derived factor (PEDF) reduced neovascularization in the choroid (Mori et al., 2002). The potential role of RTP801 in retinopathy was also studied, and the results indicated that by inhibition of its expression, the development of retinopathy was significantly reduced (Brafman et al., 2004).

miRNA is also used for regulating inflammatory-mediated genes in different diseases in the eye (Raghunath and Perumal, 2015). For instance, in AMD treatment, it has been shown that the upregulation of miR-9, miR-125b, miR-146a, and miR-155, alone or in combination, regulates the innate immune system and

inflammation signals via the NF- $\kappa$ B or other pathogen pathways (Li et al., 2011; Lukiw et al., 2012; Kutty et al., 2013; Raghunath and Perumal, 2015; Pogue and Lukiw, 2018). In an interesting work by Zou et al., the impact of miRNA on uveitis treatment was studied. The authors demonstrated that transfecting the DCs using miR-155 inhibits the expression of pro-inflammatory cytokines such as IL6 and IL-1  $\beta$ , and increases the production of the anti-inflammatory IL10 cytokine (Zhou et al., 2012). Park et al. (2009) showed that using the expression plasmid of plasminogen Kringle 5 (K5) encapsulated in PLGA/chitosan nanoparticles has the potential to treat retinal inflammation in DR by downregulating retinal VEGF expression and the anti-inflammatory effect (Diebold and Calonge, 2010). Our group's review study and research on effective siRNA delivery systems for ocular therapy provides more information regarding nucleic acid ocular delivery cargoes (Huang and Chau, 2019a; Huang and Chau, 2019b; Huang and Chau, 2021).

Messenger RNA (mRNA) is another type of nucleic acid that has been widely used in gene therapy. It allows faster protein translation as it does not require trafficking of the cargo to the cell nucleus in comparison to DNA. A primary anti-inflammatory cytokine is IL10, and delivery of the IL10 gene to the disorders causing ocular inflammation may be an effective therapy. To treat ocular inflammation, one method employed is to distribute IL10 mRNA using solid lipid nanoparticles (SLN) and various polymeric ligands such as dextran or HA for long-term stability (Gómez-Aguado et al., 2021). In this study, the authors used mRNA and plasmid DNA (pDNA) for *de novo* production of IL10 and showed that the mRNA systems induced a higher expression of IL10 in corneal epithelial cells than pDNA systems, and that they suppress corneal inflammation.

### 3.3 Hybrid systems of biomaterial carriers and different cargoes

New drug delivery systems that combine several drug delivery techniques such as hydrogel and nano systems, have shown intriguing results in recent years, leading to the development of more intelligent and controlled drug delivery systems. In ophthalmic drug delivery systems, it is important to reduce side effects and increase treatment efficiency and bioavailability by minimal injection or surgery in the eye (Sharma et al., 2016). One example of these hybrid scaffolds is provided by du Toit et al. (2013). The hybrid system employed was an indomethacin anti-inflammatory non-steroidal drug encapsulated in a lipoidal-chitosan-PCL nano system with a size of 140.7 nm and a positive surface charge for targeting the inflammatory disorder in the posterior part of the eye. The authors demonstrated that, in comparison to the chitosan-PCL nano system alone, the composite lipoidal nano system suppressed the inflammation by decreasing the amount of NF- $\kappa$ B and by enhancing the inflammatory cellular uptake of the drug. Gomes do Santos et al. also developed a hybrid system comprising antisense TGF- $\beta$  2 phosphorothioate oligonucleotides/PEI nanoparticle that was encapsulated in PLGA microspheres, namely, "Trojan" microspheres. The authors stated that this "Trojan" system could

prevent post-surgery fibrosis for 42 days (Gomes dos Santos et al., 2006). The DNA/PLGA hybrid hydrogel (HDNA), which is used to sustain the release of water-insoluble anti-inflammatory drugs such as dexamethasone, is another example of these systems. In animal models of allergic conjunctivitis, once-daily topical treatment using this porous hybrid structure outperformed multiple treatments using commercial dexamethasone drops (Ren et al., 2019).

## 4 Conclusion

In ocular inflammatory illnesses, innate immune cells play a key role in removing the inflammatory pathogen or infection and subsequent regeneration of the inflamed region by homeostatic action and fibrosis development. Since the eye is extremely sensitive to inflammation and injury, it is critical to maintain its homeostasis and to avoid any chronic or harmful inflammation that can lead to ocular disorders such as DED, uveitis, glaucoma, AMD, as well as any other chronic inflammation that can result in eye tissue degeneration and blindness. Further research regarding the eye's immunological response is required for designing tolerogenic biomaterials that act as intraocular lenses, cellular scaffolds, therapeutic molecule depots, or carriers of gene therapies. The discussion presented in this article sheds light on the potential use of biomaterials to direct immune responses toward favorable treatment outcomes.

Biomaterials can be utilized as manipulating agents for interacting with ocular innate immune cells and directing pro- or anti-inflammatory responses by using them either cargo-less or cargo-loaded. In this review, we discussed several physiochemical features of biomaterials such as mechanical strength, size, shape, charge, wettability, and biodegradability, as well as how each of these factors might program the fate of the innate immune cells' phase by inhibiting or inducing special receptors and signaling pathways. These physiochemical parameters also affect the biodistribution and the interaction between the target cells and the cargoes. While previous efforts have focused on the intended action of the carrier, the influence of these parameters on the immune response has been neglected. They are often "discovered" as a surprise or treated as an unexpected side effect.

However, one of the most difficult issues to address is determining how to identify the influence of each physiochemical feature on the underlying biomaterial-related immune response and what cross-talks exist between them. More study and deeper understanding are required to determine the precise cell-biomaterial interaction mechanism by combining these

physiochemical features and determining the effect of combining them on innate immune system programming. In the future, machine learning and artificial intelligence (AI) will be useful to forecast the ocular innate immune system's reaction to a given biomaterial with defined features. A combination of gene therapies and immunomodulatory biomaterials carriers could be also a promising method for programming targeted overacting pro-inflammatory innate immune cells in a downregulating manner to retain their anti-inflammatory action, without side-effects on other immune cells' fighting action.

Overall, there is significant therapeutic potential in ocular inflammatory diseases by focusing on triggering the anti-inflammatory phase of ocular-activated innate immune cells and providing homeostasis and tissue regeneration signals to the eye via immunomodulatory biomaterials that can sustain the release of novel therapeutic agents such as nucleic acids, biomolecules, or MSCs for an extended period of time with only one administration.

## Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

## Acknowledgments

The authors acknowledge the use of BioRender to generate Figures 1–4.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Glossary

<b>NTs</b> Neutrophils	<b>AAVs</b> Adeno-associated viruses
<b>MG</b> Microglia	<b>mRNA</b> Messenger RNA
<b>Mφs</b> Macrophages	<b>miRNA</b> Micro RNA
<b>DCs</b> Dendritic Cells	<b>siRNA</b> small interfering RNA
<b>cDC</b> conventional DC	<b>pDNA</b> Plasmid DNA
<b>pDC</b> plasmacytoid DC	<b>NPs</b> Nanoparticles
<b>MSCs</b> Mesenchymal stem cells	<b>MPs</b> Microparticles
<b>BM-MSCs</b> Bone marrow-derived MSCs	<b>LNPs</b> Lipid-based nanoparticles
<b>LCs</b> Langerhans cells	<b>SLN</b> Solid lipid nanoparticles
<b>AM-MSCs</b> Adipose tissue-derived MSCs	<b>AuNPs</b> Gold nanoparticle
<b>LSCs</b> Limbal epithelial stem cells	<b>AI</b> Artificial intelligence
<b>APCs</b> Antigen-presenting cells	<b>AM</b> Amniotic membrane
<b>ECM</b> Extracellular matrix	<b>AIM2</b> Absent in melanoma 2
<b>AMD</b> Age-related macular degeneration	<b>TNF-α</b> Tumor necrosis factor-alpha
<b>DED</b> Dry eye disease	<b>IFN-γ</b> Interferon gamma
<b>DR</b> Diabetic retinopathy	<b>TGF-β</b> Transforming growth factor-β
<b>EAU</b> Experimental autoimmune uveitis	<b>iNOS</b> inducible nitric oxide synthase
<b>OHT</b> Ocular hypertension	<b>IL-</b> Interleukin-
<b>IOP</b> Intraocular pressure	<b>P2Y12</b> P2 purinergic receptor
<b>RP</b> Retinitis pigmentosa	<b>Caspase-1</b> Cysteine-aspartic acid protease-1
<b>RGCs</b> Retinal ganglion cells	<b>Iba-1</b> Ionized calcium-binding adapter molecule 1
<b>MGD</b> Meibomian gland dysfunction	<b>APTES</b> Aminopropyltriethoxysilane
<b>DAMP</b> Danger-associated molecular pattern	<b>ARG</b> Arginase
<b>PAMP</b> Pathogen-associated molecular pattern	<b>ILM</b> Internal limiting membrane
<b>NETs</b> Neutrophil extracellular traps	<b>MCP-1</b> Monocyte chemoattractant protein-1
<b>ACAID</b> Anterior chamber-associated immune deviation	<b>IgG</b> Immunoglobulin G
<b>ADP/ATP</b> Adenosine di/tri-phosphate	<b>CCL-</b> C-C motif chemokine ligand
<b>NF-κB</b> Nuclear factor kappa B	<b>CCR-</b> C-C chemokine receptor
<b>IOL</b> Intraocular lens	<b>CD-</b> Cluster of differentiation
<b>FA</b> Fluocinolone acetonide	<b>CD200R</b> Cluster of differentiation-200 receptor
<b>FBR</b> Foreign body response	<b>MHCII</b> Major histocompatibility complex class II
<b>HLA-G</b> Human leukocyte antigen G	<b>CNTF</b> Ciliary neurotrophic factor
<b>HMGB1</b> High mobility group protein B1	<b>CNV</b> Choroidal neovascularization
<b>LPS</b> Lipopolysaccharides	<b>COX-</b> Cyclooxygenase
<b>IDO</b> Indoleamine 2, 3-dioxygenase	<b>CR2-fH</b> Complement receptor 2 and factor H
<b>PEDF</b> Pigment epithelium derived factor	<b>CXCL-</b> C-X-C motif chemokine ligand
<b>PRR</b> Pattern-recognition receptors	<b>Cy A</b> Cyclosporine A
<b>LAIR-1</b> Leukocyte-associated immunoglobulin-like receptor-1	<b>PD-L1</b> Programmed cell death-ligand 1
<b>RANTES</b> Regulated upon activation, normal T cell expressed and secreted	<b>NLR</b> Nod-like receptors
<b>Ly6C</b> Lymphocyte antigen 6 complex	<b>VEGF</b> Vascular endothelial growth factor
<b>OVA</b> Ovalbumin	<b>TLR-</b> Toll-like receptor
<b>HA</b> Hyaluronate	<b>ROS</b> Reactive oxygen species
<b>GelMA</b> Methacrylate-gelatin	<b>TRPV</b> Transient receptor potential vanilloid
<b>AVs</b> Adenoviruses	<b>K 5</b> Kringle 5
	<b>VIP</b> Vasoactive intestinal peptide
	<b>LBL</b> Layer-by-layer

**Siglec-H** Sialic acid binding immunoglobulin-like lectin H

**MIF** Migration inhibitory factor

**MMP** Matrix metalloproteinase

**MyD88** Myeloid differentiation primary response 88

**PCO** Posterior capsular opacification

**RGD** Arginyl-glycyl-aspartic acid

**PAA** Polyacrylic acid

**PAMAM** Poly (amidoamine)

**mPEG-PLGA-BOX** Methoxy-poly (ethylene glycol)-block-poly (lactic-co-glycolic acid)

**PBT** Polybutylene terephthalate

**PCL** Poly-caprolactone

**PEG** Polyethylene glycol

**PEI** Polyethylenimine

**PEMA** Poly (ethylene-alt-maleic anhydride)

**PEO** Polyethylene oxide

**PHEMA** Poly (2-hydroxyethyl methacrylate)

**PLA** Polylactic acid

**PLGA** Poly(lactide-co-glycolide)

**PMMA** Poly (methyl methacrylate)

**PVA** Poly (vinyl alcohol)