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Delivery strategies for treatment of age-related ocular diseases: From a biological understanding to biomaterial solutions

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ABSTRACT

Age-related ocular diseases, such as age-related macular degeneration (AMD), diabetic retinopathy, and glaucoma, result in life-long functional deficits and enormous global health care costs. As the worldwide population ages, vision loss has become a major concern for both economic and human health reasons. Due to recent research into biomaterials and nanotechnology major advances have been gained in the field of ocular delivery. This review provides a summary and discussion of the most recent strategies employed for the delivery of both drugs and cells to the eye to treat a variety of age-related diseases. It emphasizes the current challenges and limitations to ocular delivery and how the use of innovative materials can overcome these issues and ultimately provide treatment for age-related degeneration and regeneration of lost tissues. This review also provides critical considerations and an outlook for future studies in the field of ophthalmic delivery.

1. Introduction

Vision loss poses a major problem to the aging population worldwide, with approximately 285 million people who are visually impaired, and 39 million who are completely blind [1]. In the United States alone, there are more than 20 million people who suffer from impaired vision and age-related eye diseases, representing an average of 8.5% of the population over 18 —gradually increasing to 14.9% for those who are 75 and older [2]. Beyond these striking data, vision loss also significantly impacts national economies, with worldwide direct costs of $2.3 trillion in 2010 alone, and often constitutes the highest national direct costs of any disease category followed by cardiovascular diseases and mental disorders [1,3]. With the aging world population, loss of vision poses a challenge for both economic growth and human health.

In the past 20 years, we have simultaneously witnessed a boom in the design of synthetic materials and nanotechnology for biomedical applications, leading to major advances in the field of ocular delivery. Promising drugs and peptides for ocular treatments were identified, yet stymied by biological barriers to administration. Nanocarriers, for example, solve issues of drug solubility and target specificity while at the same time provide a way to overcome some of these barriers to delivery. Additionally, local delivery of stem cells and/or their progeny to the retina provide the potential to reverse disease. These unprecedented regenerative therapies, in turn, require a new generation of supporting biomaterials to enhance cell survival and integration.

The present review aims to provide a summary of the major challenges and promising solutions in the field of ocular delivery for the treatment of age-related ocular diseases. We start with a short introduction to the eye with a focus on the biology of the retina and structures of the posterior of the eye, and summarize the biological mechanisms of disease that lead to age-related degeneration. We then provide an overview of current strategies used to treat age-related ocular disorders, highlighting the progress and limitations in the field. The review is focused on two main strategies: 1) ocular delivery of drugs, peptides and nucleotides that delay aging disorders, and 2) cell delivery to the posterior segment of the eye as regenerative therapies, emphasizing the diversity of cell sources and biomaterial solutions. A final discussion will address general issues such as materials or in vitro/in vivo models, along with critical considerations and perspectives for the field of ophthalmic delivery.

2. Anatomy and diseases of the posterior segment of the eye

2.1. Biology of the eye

The human eye provides acute visual perception using a biochemical process to convert light energy into electrical impulses. To effectively perform this function, light travels through the anterior segment to

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the posterior segment, wherein it reaches the retina, a photosensitive tissue possessing neural connections to the brain that enables processing of visual information (see Fig. 1).

The inner wall of the posterior segment is composed of a well-organized laminar structure of the photosensitive retinal tissue. The neural retina comprises photoreceptors (rods and cones) which convert light energy and transfer electrical impulses to the brain via horizontal cells, bipolar cells, amacrine cells, and ultimately retinal ganglion axons in the optic nerve (see Fig. 2). In this convergent pathway in humans, information from 100 million rods, which provide light sensitivity, and 5 million cones, which provide high temporal and spatial resolution, is transferred to 1 million nerve fibers [4]. In this process, the macula constitutes the cone-dominated central region responsible for high acuity vision.

Photoreceptors have an intimate and critical functional relationship with the retinal pigment epithelium (RPE) in the outermost layer of the retina. The RPE is a stable epithelial cell layer, characterized by hexagonal-shaped cells, tight junctions and sheet-like microvilli covering the entire apical surface. The RPE cells are integral to photoreceptor function, phagocytosing photoreceptor outer segments and converting all-*trans* retinal to 11-*cis* retinal [5–7].

The circulation of blood in the posterior segment of the eye relies largely on the choroid vessels – with the exception of the central retinal artery. Besides nourishing the outer retina and supplying the anterior chamber with blood, the choroid is known to regulate eye temperature and maintain the ocular pressure. Changes in vascularization are associated with age-related macular degeneration (AMD) and diabetic retinopathy, resulting in loss of RPE and photoreceptors [8]. The proper functioning and survival of the choroid, RPE and photoreceptors relies on the complex biological interdependency between these structures.

2.2. Associated age-related disorders

Normal aging of the posterior segment of the eye is characterized by continuous loss of photoreceptors, Bruch's membrane thickening, choroidal thinning, scleral stiffening, vitreous degradation and intraocular debris accumulation. Although stemming from normal aging conditions, age-related eye disorders should be distinguished from aging as they are the result of exacerbated degradation mechanisms, leading to severe retina and RPE atrophies, often along with abnormal choroidal neovascularization [9]. Among these disorders, diabetic retinopathy, AMD and glaucoma are the three leading age-related causes of vision loss from the posterior segment of the eye, and together represent 14% of the causes of blindness in the world [10].

In terms of mechanism, diabetic retinopathy originates from hyperglycemia that weakens blood vessels such that they leak or are blocked which then triggers abnormal production of vascular endothelial growth factor (VEGF), resulting in unwanted blood vessel proliferation into the retina, amplifying tissue damage [11]. It is the most common of the vascular eye diseases, along with hypertensive retinopathy and ocular ischemic syndrome, which altogether account for approximately 5% of the 39 million cases of blindness throughout the world [12].

AMD is the leading cause of age-related visual impairments and occurs in dry and wet forms [10]. Dry AMD accounts for 90% of AMD cases [13], and although debated, is believed to stem from an accumulation of cellular debris (drusen) between the choroid and RPE in the macula, causing localized RPE atrophy, epithelium disruption and eventually loss of central vision. Wet AMD progresses from dry AMD and, because of ischemic conditions, triggers abnormal VEGF production followed by abnormal neovascularization in the macula and macular degeneration [14].

Glaucoma, which is the second most common cause of blindness after cataracts, results from an age-related increase of intraocular pressure (IOP). Intraocular hypertension usually occurs due to obstruction of the trabecular beam and reduction of aqueous humor outflow in the anterior chamber, damaging the retinal inner layer and the optic nerve at the back of the eye. The reduction of flexibility and permeability of aging scleral collagen fibers also increase intraocular pressure and similar tissue damage [15].

Other age-related disorders, which affect the posterior segment of the eye, such as myopic or vitreous degeneration, are being studied with drug and cell delivery to either slow the progression of the disease or reverse degeneration, respectively. These diseases will not be reviewed here in order to focus on the most prevalent conditions.

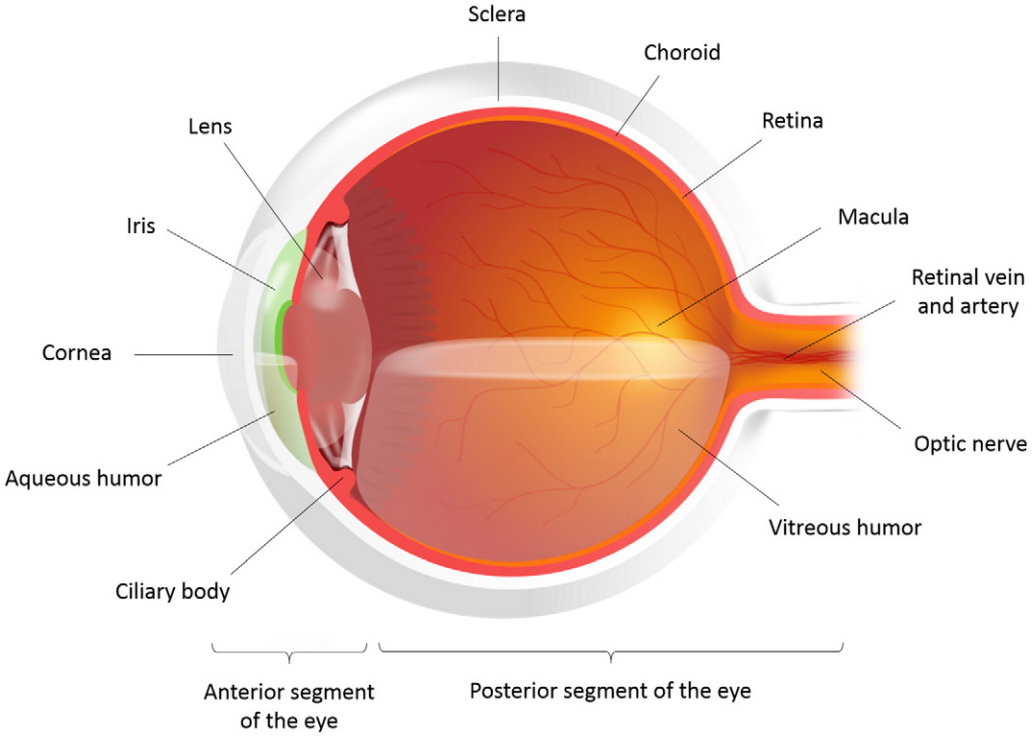

Fig. 1. Anatomy of the eye.

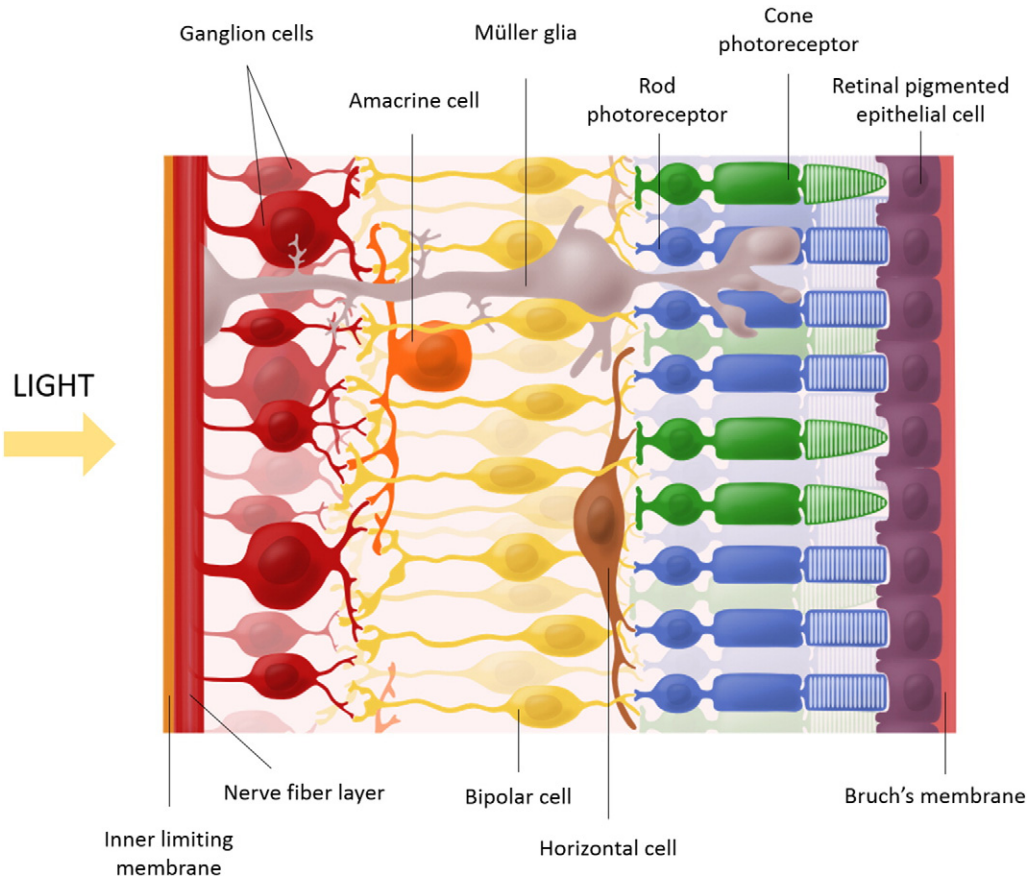

Fig. 2. Cellular architecture of the retina.

3. Drug delivery to the posterior segment of the eye

The eye is considered an immune privileged organ due to the blood-retinal barrier (BRB) and the absence of a lymphatic system [16]. Penetration into the retina by systemically-administered drugs is limited by the BRB, necessitating local delivery. The eye has a number of properties that make it well suited to local delivery strategies, including its relative accessibility for delivery, its size which can reduce the amount of drug required, and its inner barriers, which limit drug clearance [17]. However, unlike the anterior segment, topical delivery to the posterior segment is limited by pre-corneal drainage, the lipoidal nature of the corneal epithelium, and systemic circulation absorption, which leads to low drug bioavailability – typically less than 5% [18–20]. Therefore, subconjunctival (between the conjunctiva and the sclera) or intravitreal (into the vitreous humor) injections are the most common routes of administration for drug delivery to the posterior segment of the eye [21]. Routes of administration, barriers, and transporters have been extensively reviewed elsewhere [22–24] and will not be further discussed here. Many well-established and non-invasive diagnostic techniques, such as light-induced pupillary size measurements, fundus photography (also called fundography), electroretinography (ERG) and optical coherence tomography, allow visual function to be assessed [25].

3.1. Diabetic retinopathy and AMD

Both diabetic retinopathy and wet AMD stem from abnormal neovasculature, mainly due to VEGF overexpression. Different categories of drugs have been studied as potential anti-VEGF candidates for intravitreal injections, which aim to decrease either vascular permeability or neovascularization [26]. Corticosteroids, neurotrophic factors and anti-angiogenic antibodies should be highlighted as most promising treatments for angiogenesis inhibition.

3.1.1. Angiogenesis inhibitors

Intraocular injections of corticosteroids (such as dexamethasone and fluocinolone acetonide) have been shown to inhibit both VEGF and VEGF gene expression, resulting in better outcomes and improved vision in patients with diabetic macular edema (DME) than the traditional laser photocoagulation technique. Unfortunately, corticosteroid use has been limited by adverse side effects, such as elevated intraocular pressure and glaucoma and cataract related adverse effects [27].

Various proteins and peptides, especially cytokines, have been shown to provide protective neurotrophic activity or inhibit endothelial cell proliferation in various rodent models of retinal neovascularization [28–31]. For example, ciliary neurotrophic factor (CNTF) has been shown to be protective against retinal degeneration disorders in various animal models, including those in mice, rats, cats and dogs [32]; however, the short half-life of CNTF and the resulting concerns of repeated intraocular injections have limited its translation to the clinic.

Recent innovations in anti-angiogenic antibodies and nucleotides have generated new opportunities for ocular treatments of age-related diseases. Two monoclonal antibodies, bevacizumab (Avastin™) and ranibizumab (Lucentis™), have shown reduced macular edema and improved vision, with significantly better results than macular laser therapy. Pegaptanib (Mucagen™), a PEGylated RNA aptamer designed to treat neovascular ophthalmic diseases, was the first aptamer therapeutic approved for use in humans [33]. Although potentially safer than the two antibodies due to a more selective inhibition, it was ultimately shown to be less effective [34]. Interestingly, ranibizumab remains the only FDA approved VEGF inhibitor for the treatment of both wet AMD and DME, despite similar results with off-label use of bevacizumab [27,35,36].

Aside from the previously mentioned angiogenic inhibitors, a variety of alternative mechanisms of action and gene transfer therapies are currently under investigation, such as targeting vascular endothelial

receptor tyrosine kinase [37], overexpressed integrins [38], hypoxia-induced activator [39] or metalloproteinases [40], among others [41]. Notwithstanding the potential of these strategies, only preliminary studies have been conducted and the possible adverse effects on normal choroidal vessels and retinal neurons remain to be evaluated [27,42].

Although rates of adverse ocular effects are generally low, anti-angiogenic treatments require repeated intravitreal injections over prolonged periods of time (months to years), which leads to complications such as ocular inflammation, endophthalmitis (1% of the patients), subconjunctival hemorrhage, increased intraocular pressure and retinal detachment [27,36]. Topical administration via eye drops avoids these complications, yet suffers from low bioavailability, which has restricted this route mainly to the treatment of anterior segment and corneal diseases. These observations underline the need for innovative delivery strategies, which has become a biomedical engineering challenge.

3.1.2. Delivery strategies

The ideal ocular delivery system for age-related diseases should meet the following criteria: (i) sustained and controlled drug release, with a rate in accordance with the optimal therapy duration (usually months to years); (ii) limited number of surgical interventions (and ideally none); (iii) high specificity to the targeted tissue; (iv) limited side effects; and ideally (v) fast clinical translation. While viral vectors for ocular gene therapy are promising [43–45], they will not be discussed herein. Instead, we will focus on implants, nanocarriers and innovative delivery strategies.

3.1.2.1. Implants. To avoid frequent intravitreal injections, the first serious attempts of anti-angiogenic controlled delivery focused on the development of intravitreal rod-shaped implants containing corticosteroids for prolonged drug release [46]. The recently FDA-approved Iluvien™ offers 36-month delivery of fluocinolone acetonide from an injectable silicone adhesive tube, with the drug diffusing through a poly(vinyl alcohol) (PVA) membrane [47]. The choice to use a non-degradable material is questionable as it requires surgical removal [48]. This problem has been overcome in Ozurdex™, a similar material which delivers dexamethasone from a degradable matrix of poly(lactic-co-glycolic acid) (PLGA) [49]. Implants reduce the risk of vision loss and improve the speed of visual recovery while avoiding side effects associated with multiple injections. However, the use of implants can increase intraocular pressure and cataract progression due to both traction exerted on the vitreous [50] and the side effects of corticosteroid therapy. As an example, the recent results of a 3-year randomized phase II/III clinical trial on another implant containing fluocinolone acetonide, namely Retisert™, showed reduced recurrence rate of non-infectious posterior uveitis, but also an overall elevated IOP incidence of 68–71% (vs 19–24% for non-implanted eyes). Moreover, nearly all (94%) of the patients with a phakic implanted eye – eye with intraocular lens implant – resorted to cataract surgery (vs 30% for phakic non-implanted fellow eyes) [51–53].

Another remarkable implant-based strategy consists of transplanting a capsule that contains genetically-engineered mammalian cells able to sustainably produce therapeutic proteins [54]. The NT-501 implant contains human RPE cells transfected to release CNTF and encapsulated in a poly(ethylene terephthalate) scaffold (see Fig. 3) [55]. Encouraging results, such as long-term photoreceptor protection, were obtained using several animal models (rats, rabbits and dogs) [56,57] and have led to advanced clinical trials [58]. Despite this, no significant improvement over controls has been observed in retinitis pigmentosa patients (an inherited, degenerative eye disease), necessitating further examination to definitively assess implant efficacy [59]. While encapsulated cell therapy has been investigated for over 2 decades, and this approach shows some promise, it also underscores the complex interactions of the disease and cell therapy, even when the cells are physically isolated from the system to deliver bioactive proteins. Nevertheless, this approach may inspire future innovations in drug delivery.

3.1.2.2. Ocular nanotherapies. Drug encapsulation in nanoparticles has been widely investigated for ocular delivery, as described in numerous review articles. For example, Kompella et al. [61] extensively reviewed the field of ocular nanotherapies, Bochot et al. [62] presented a complete review of state of the art liposomes for intravitreal drug delivery, and Kang-Mieler et al. [63] summarized the delivery systems currently in clinical trials. Here, we highlight the most recent developments in nanomedicine concerning age-related ocular diseases, discussing the emerging use of transscleral administration and peptide-targeted therapies.

For nanotherapy, we require high drug loading, a defined size between 30 and 200 nm, stability of biomolecules in the intraocular space, material biocompatibility and bioresorbability. A variety of systems have been proposed, based on solid lipid nanoparticles [64,65], polymeric nanoparticles [66,67], liposomes [68], micelles [69] and dendrimers [70,71]. When injected in the vitreous, these nanotherapies allows for prolonged drug release [72,73], which reduces the number of injections required. However, although reduced, similar complications

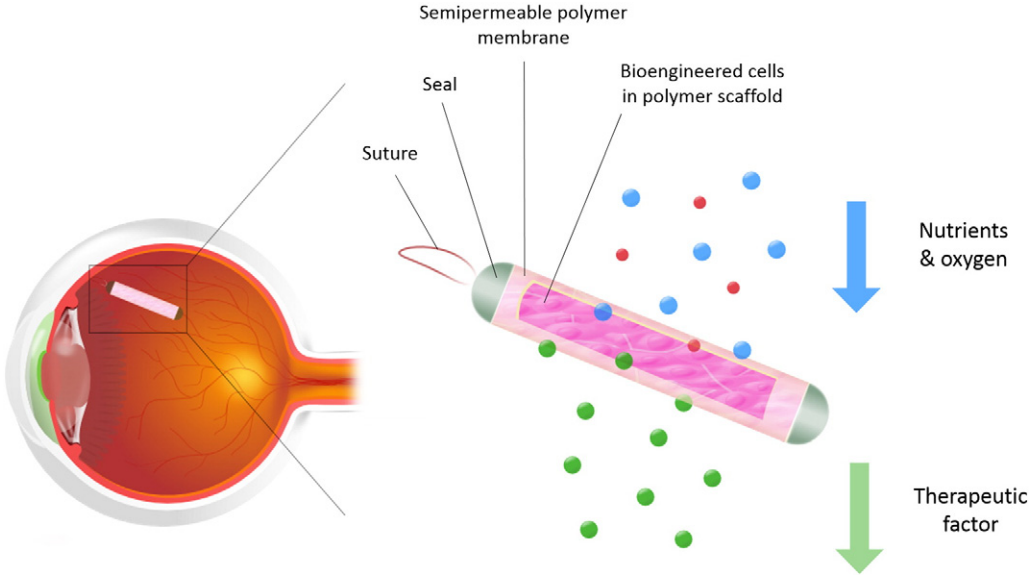

Fig. 3. Encapsulated cell therapy (ECT) for ocular drug delivery. Figure inspired by [60].

to traditional intravitreal drug delivery may be expected, including ocular inflammation and elevated intraocular pressure. Therefore, transscleral delivery for topical applications has recently attracted much attention as it constitutes the only non-invasive route of administration to deliver drugs to the posterior segment of the eye. For example, polymeric micelles of dexamethasone applied topically

Table 1
Ocular delivery strategies for the administration of angiogenesis inhibitors to the posterior segment of the eye.

Drug category	Vehicle structure	Material	Route of administration	Benefits	Stage of development	Reference
Corticosteroids and anti-inflammatory drugs						
Dexamethasone	Microparticle	β-cyclodextrine	Transscleral delivery (eye drop)	Reduced retinal thickness improved visual acuity	Phase I	[76,89]
Dexamethasone	Micelle	Chitosan	Transscleral delivery (eye drop)	Improved intraocular absorption	In vivo (rabbit)	[69]
Dexamethasone	Polymeric micelle	PHEA-PEG-C16[a]	Transscleral delivery (eye drop)	Greater drug bioavailability	In vivo (rabbit)	[74]
Dexamethasone	Polymeric micelle	Crosslinked poly(NIPAAM-co-VP)[b]	Transscleral delivery (eye drop)	Reduced inflammation	In vivo (rabbit)	[75]
Dexamethasone	Implant	PLGA[c]	Intravitreal injection	Reduced risk of vision loss improved the speed and incidence of visual improvement	Marketed (Ozurdex)	[90–92]
Fluocinolone acetonide	Implant	Cellulose/PVA[d]	Intravitreal injection	Reduced risk of vision loss improved the speed and incidence of visual improvement	Marketed (Retisert)	[52,93]
Fluocinolone acetonide	Implant	polyimide/PVA[d]	intravitreal injection	Reduced risk of vision loss improved the speed and incidence of visual improvement	Marketed (Iluvien)	[47]
Triamcinolone acetonide	Solid lipid nanoparticle	Precirol ATO5®[e]/Squalene	transscleral delivery (eye drop)	Targeted and prolonged release effect	Ex vivo (rabbit)	[64,65]
Diclofenac	Surface-modified liposome	PVA[d] coating, DSPC[f]/cholesterol	Transscleral delivery (eye drop)	Effective retinal delivery	In vivo (rabbit)	[94]
Tyrosine kinase inhibitors						
Pazopanib	Dipeptide-based nanotube	(Phe–Δphe) peptide	intravitreal injections	Non-cytotoxicity on RPE cells prolonged release effect	In vivo (rat)	[73]
Semaxanib	Peptide-modified liposome	APRPG peptide[g] DPPC[h]/POPC[i]/cholesterol	intravitreal injections	Inhibitory effects enhanced by peptide	Ex vivo (rat)	[81]
Other drugs						
Edaravone	Nanoliposome	egg PC[j]/cholesterol	transscleral delivery (eye drop)	inhibition of light-induced ROS (in vitro) prevented shrinkage of ONL	In vivo (mice)	[77,78]
Doxorubicin	Peptide-conjugated liposome	(YSA) peptide DSPE-PEG[k]/cholesterol	intravitreal injection	least CNV area and fluorescence leakage	In vivo (rat)	[82]
Verteporfin (photosensitizer)	Liposome	egg PG[l]/DMPC[m]/ascorbyl palmitate	Intravenous injection	significantly reduced risk of moderate and severe visual acuity loss	Marketed (Visudyne)	[85]
Peptides/proteins						
CNTF[n]	Encapsulated cell intraocular implant	Poly(ethylene terephthalate)	Intravitreal injection	Therapeutic efficacy (dog model) No significant changes in visual acuity	Phase II	[55,57–59,95]
Kringle 5	Nanoparticle	PLGA[c]	Intravitreal injection	Reduced retinal neovascular area and vascular permeability reduced preretinal neovascular cells	In vivo (rat)	[66,67]
bFGF[o]	Crosslinked nanoparticle	Gelatin	Intravitreal injection	Higher number of photoreceptors	In vivo (rat)	[96]
Antibodies						
Bevacizumab (avastin™)	Crosslinked hydrogel	Glycol chitosan/alginate	–	Controlled degradation rate sustained drug release rate	In vitro	[97]
Bevacizumab (avastin™)	Crosslinked hydrogel	PEG-PCL-PEG[p]	Intravitreal injection	No retinal toxicity in vivo No significant changes in visual acuity	In vivo (rabbit)	[98]
Bevacizumab (avastin™)	Liposome	PLV[q]	Intravitreal injection	Prolonged drug residency	In vivo (rabbit)	[72]
Bevacizumab (avastin™)	Peptide-grafted liposome	annexin 5 on PLV[q]	Transscleral delivery (eye drop)	Peptide significantly enhanced bioavailability	In vivo (rat/rabbit)	[88]
Nucleotides						
Flt23K plasmid gene	Dual-functionalized nanoparticle	RGD[r] and transferrin[s] on PLGA[c]	Intravenous injection	40% restoration of visual loss	In vivo (monkey)	[86,87]
ODN-1	Dendrimer	peptide-based dendrimers	Intravitreal injection	Reduced CNV development	In vivo (rat)	[70,71]
siRNA	Peptide-grafted liposome	RGD[r] on DSPE-PEG[k]	–	Higher siRNA delivery efficiency with RGD down-regulation of VEGF expression	In vitro	[79,80]
siRNA	Liposome	PEG protamine-hyaluronic acid	Intravitreal injection	Reduced CNV area	In vivo (rat)	[68]

Table 1 (*continued*)

Drug category	Vehicle structure	Material	Route of administration	Benefits	Stage of development	Reference
Raf mutant gene	Peptide-grafted cationic Polymerized lipid-based nanoparticle	αvβ3 ligand diacetylene phospholipid	Intravitreal injection	Reduction of CNV size and Leakage	In vivo (rat)	[99]
pDNA	nanoparticle	PLGA[c]	Intravitreal injection	Decreased leakage in CNV membranes decreased thickness in CNV lesions	In vivo (rat)	[100]

[a] Poly(hydroxyethyl-aspartamide)-g-Polyethylene glycol-g-hexadecylamine.
[b] Poly(N-isopropylacrylamide-co-vinyl pyrrolidone).
[c] Poly(lactic-co-glycolic acid).
[d] Poly(vinyl alcohol).
[e] Glyceryl palmitostearate.
[f] 1,2-Distearoyl-sn-glycero-3-phosphocholine.
[g] Ala-Pro-Arg-Pro-Gly (APRPG) peptide.
[h] Dipalmitoylphosphatidylcholine.
[i] 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine.
[j] L-α-phosphatidylcholine.
[k] PEGylated 1,2-distearoyl-sn-glycero-3-phosphoethanolamine.
[l] Egg phosphatidylglycerol.
[m] Dimyristoyl phosphatidylcholine.
[n] Ciliary neurotrophic factor.
[o] Basic fibroblast growth factor.
[p] poly(ethylene glycol)-poly(ε-caprolactone)-poly(ethylene glycol).
[q] phospholipid vesicles containing: egg phosphatidylcholine (PC), porcine brain phosphatidylserine (PS), cholesterol and α-Tocopherol.
[r] Arg-Gly-Asp (RGD) peptide.
[s] Transferrin was only used for one of the studies.

provide a promising alternative to intravitreal injections. Using materials such as poly(hydroxyethyl-aspartamide) (PHEA) or crosslinked poly(N-isopropylacrylamide-co-vinyl pyrrolidone) (poly(NIPAAM-co-VP)), this new approach showed greater drug bioavailability and significantly reduced inflammation in animal models [74,75]. Furthermore, a pilot study of eye drops containing dexamethasone-cyclodextrin microparticles for the treatment of diabetic macular edema has demonstrated some clinical success (see Table 1) [76]. Thus, despite a lingering skepticism about the appropriateness of topical treatments for the posterior segment, these results suggest that this administration route is promising for retinal disease.

Liposomes, which are the most studied system for any ocular treatment [62,77,78], have recently been advanced by grafting specific binding peptides for active tissue targeting. For example, PEGylated 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE-PEG) has been modified with a series of cell-adhesive peptides to promote binding to receptors expressed in neovascular tissue: the integrin binding RGD tripeptide [79,80], the angiogenic vessel specific APRPG pentapeptide [81], and an ephrin mimetic dodecapeptide (YSAYPDSVPMMS) [82]. In animal models, these studies showed enhanced drug delivery, down-regulated VEGF expression, and/or reduced choroidal neovascularization. Despite the appeal of such advanced strategies and more than 20 years of research on liposomes for ocular delivery [83], no liposomal formulation for intravitreal or topical treatment of retinal disorders has reached the market to date [62]. This highlights the major limitations of the two main routes of administration – side effects after intravitreal injections and low bioavailability after transscleral administration. Conversely, systemic administration of liposomes has been successful in the treatment of other diseases [84]. Interestingly, the only marketed liposomal treatment for age-related retinopathy, namely Visudyne®, uses systemic administration to deliver a photosensitizing agent (Verteporfin) for photodynamic therapy of neovascularized retina [85]. Systemic administration also prevents some blurring effects induced by the presence of particles in the humor, which is a well-known side effect of intravitreal micro/nanotherapies and a source of visual discomfort [62]. An inspiring alternative is intravenous delivery of RGD-functionalized PLGA nanoparticles that are designed to deliver a recombinant Flt23k intracellular receptor, an antagonist of VEGF, and have shown to restore 40% of vision loss in a monkey choroidal neovascularization model [86,87].

Finally, ocular nanotherapies for antibody delivery should be highlighted as an unmet challenge in the field. The benefits of anti-angiogenic therapy have already resulted in the translation of two antibodies to the market for ocular therapies: bevacizumab (Avastin™) and ranibizumab (Lucentis™). However, advanced delivery strategies have been ineffective at increasing their efficacy, suggesting opportunities for further innovation. For example, bevacizumab-loaded, peptide-conjugated liposomes showed enhanced drug delivery and prolonged intravitreal residency in animal models, yet efficacy was not demonstrated [72]. Similarly, bevacizumab delivery from a thermosensitive, biodegradable and biocompatible intravitreal hydrogel revealed no significant improvement over controls [88]. This emphasizes the challenge and the opportunity: local, sustained delivery of anti-angiongenic factors remains a fertile area for strategic investment.

3.2. Glaucoma therapies

Glaucoma is triggered by elevated IOP, which can be corrected by either reducing the production of, or increasing the drainage of, aqueous humor from the eye [101–103]. Surgical strategies, such as trabeculectomy, create new openings to enhance aqueous humor drainage and lower IOP, but can result in abnormal wound healing and scarring. Although glaucoma progresses to posterior segment degeneration, drug treatments target the regulation of aqueous humor production or subconjunctival scarring, which necessitates the development of delivery strategies for the anterior segment of the eye. While not the focus of most glaucoma delivery strategies, it is worth noting that the delivery of neurotrophic factors to the posterior segment has been investigated to reduce retinal degeneration and slow the progression of glaucoma. For example, glial cell line-derived neurotrophic factor (GDNF) was loaded in biodegradable PLGA microspheres and shown to enhance the survival of retinal ganglion cells and axons [104], warranting further study. The delivery of hypotensive drugs or scar-inhibiting nucleotides constitutes the majority of the work dedicated to glaucoma treatment.

3.2.1. Hypotensive medication and delivery

Various categories of drugs have demonstrated the ability to reduce the production of aqueous humor, such as prostaglandin analogs (latanoprost, travoprost, unoprostone), beta blockers (metipranolol, timolol, propanolol) and carbonic anhydrase inhibitors (methazolamide, acetazolamide, ethoxzolamide) [105]. When administered via topical eye drops, factors such as lachrymation, nasolachrymal drainage, metabolic degradation and corneal impermeability lead to low drug residency and bioavailability [98]. To circumvent these issues, nanotherapies similar to those used for anti-angiogenic strategies have been developed. Xu et al. studied the delivery of methazolamide by different approaches. Methazolamide adsorbed to calcium phosphate nanoparticles or encapsulated into an in situ forming poloxamer gel showed significant decrease of IOP for up to 18 h [106,107]. More interestingly, chitosan-coated solid lipid nanoparticles of approximately 200 nm in diameter allowed for a sustained drug release, attributed to the highly adhesive nature of chitosan that prevents drainage [108,109], as confirmed by others [106,110]. Liposomes have been studied for the delivery of acetazolamide via eye drops [111] or latanoprost via single subconjunctival injection [112,113]. Although the eye drops may be preferable, subconjunctival injection reduces the IOP over 50 to 90 days versus only a few hours for topical application. The efficacy of the latter therapy, called LipoLat®, is currently compared to latanoprost ophthalmic solution in a randomized, phase 2 clinical trial (NCT02466399). Micellar subconjunctival delivery of ethoxzolamide [114] and metipranolol [115] were also reported as potential hypotensive medications. Interestingly, the majority of the work on drug encapsulation for treatment of glaucoma has been conducted in the past 5 years, and while nanocarrier characterization needs to be refined, the advances achieved pave the way for further investigation.

3.2.2. Inhibiting scar formation

In order to improve the efficacy of trabeculectomy, methods to reduce and/or block the post-operative scarring process with the delivery of nucleotides are being pursued. In particular, interest has been shown in the delivery of nucleotides that inhibit IκB kinase beta (IKKβ), which is thought to be involved in the activation of inflammation and cell proliferation [116,117], or transforming growth factor-β 2 (TGF-β2), the predominant TGF molecule thought to be an active component of conjunctival scarring [118,119]. Fattal et al. described sustained delivery of an antisense TGF-β2 phosphorothioate oligonucleotide (PS-ODN) that was complexed with polyethylenimine (PEI) to form a nanosized soluble complex, prior to encapsulation into PLGA microspheres. Subconjunctival administration in a rabbit model of post-surgical scarring resulted in continuous release over 35 days and improved bleb survival [120,121]. The same strategy, later named Trojan particles, was applied to dexamethasone encapsulation, but with no mention of in vivo efficacy [122].

3.3. Emerging concepts in ocular delivery

Within the last 30 years, the field of drug delivery has become one of the most multidisciplinary domains of research, relying on a greater understanding of biological processes coupled with advanced pharmaceutics, innovative materials and novel physicochemistry approaches. Here we highlight some of the most recent delivery strategies, including the most advanced synthetic materials, reactive oxygen species (ROS) formation inhibitors and some unprecedented concepts, as a preview to the future of ocular delivery.

3.3.1. Advanced synthetic materials

Advanced materials are playing an increasingly important role in ocular drug delivery and are one of the key features to versatile, tunable and controlled delivery systems. Despite often limited information about their intraocular toxicity, these innovative vehicles provide interesting new opportunities. For example, crosslinked hydrogels allow for sustained, controlled release by tuning the crosslinking and functionalization. A crosslinked PNIPAAm-based hydrogel was injected into the vitreous with no indication of unwanted side-effects [123] while a thiolated poly(aspartic acid) demonstrated in situ gelation for use as a potential ocular mucoadhesive drug delivery system, with a sustained, 24-h drug bioavailability [124]. Composite materials, comprised of nanoparticles and hydrogels, enable local, sustained release [125], as exemplified by the hybrid dendrimer hydrogel/PLGA nanoparticle composite that, after a single topical administration of anti-glaucoma drugs, led to a sustained and effective reduction in IOP over 4 days in normotensive rabbits [126].

Triggered release from stimuli-responsive materials is an interesting strategy for ocular treatment as it offers on-demand, spatiotemporally-controlled drug bioactivity. Using the unique characteristic of transparency of the eye, a light-degradable polymeric nanocarrier has been used for minimally-invasive release of a tyrosine-kinase inhibitor, nintedanib, under low-power UV exposure. Although UV irradiation may damage retinal cells and should be used carefully [127], this system demonstrated release upon irradiation up to 30 weeks after intravitreal injection and long-term suppression of choroidal neovasculature in rats [128].

Advanced materials have begun to be pursued to provide new solutions to the challenge of targeted delivery to the eye. For example, while there is considerable enthusiasm for gene therapy, an appropriate delivery vehicle is needed to effectively target the tissue of interest. Recently, cationic lipid-based systems, which are known to facilitate endocytosis and endolysosome escape, were applied to ocular delivery and resulted in higher gene transfection efficiency, underlining the importance of understanding cell trafficking in the field of drug delivery [129,130]. This should, however, be carefully considered, as cationic surface charge may induce a strong inflammatory cell response [131]. Finally, as a proof-of-concept study for ocular imaging, an amphiphilic vinyl block copolymer modified with a single-strand collagen mimetic peptide (CMP) was co-nanoprecipitated with a semi-conducting polymer with good fluorescent properties. Stable nanoparticles of 40 nm were obtained and demonstrated selective binding to collagen in histology sections of mouse cornea tissue. This paves the way towards ocular theranostic approaches where the diagnostic and therapeutic agents can be combined into one system to better target and image the cells [132,133].

3.3.2. Innovative delivery concepts

Among the new mechanisms of action that have been explored as treatment strategies for age-related retinal degeneration, the prevention of excessive ROS formation should be highlighted. ROS formation is known to trigger oxidative stress which in turn damages retinal tissue and is thus a good therapeutic target [134]. Two systems have been designed to overcome the tissue damage associated with ROS by intravitreal injection of either human serum albumin nanoparticles containing a plasmid encoding a superoxide dismutase (SOD1) gene [135] or nanoceria crystallites comprised of cerium oxide. The latter strategy is particularly exciting because no excipients are required for delivery and it was efficacious in a rat model; angiogenesis-associated pathologies were prevented, including reduced levels of retinal ROS and VEGF, vascular lesions, subretinal neovascular tufts, light damage and blindness [136,137]. In a separate study, tyrosine was delivered via a peptide-modified chitosan nanocarrier with the goal of regulating RPE phagocytosis, which is known to be a key factor in photoreceptor survival [138]. Another study reports the inhibitory effect of gold nanoparticles on retinal neovascularization in a mouse model of retinopathy of prematurity (ROP) [139].

Beyond improved traditional implants and nanotherapies, novel concepts have been developed. Contact lenses as drug carriers for sustained release have been evaluated for the delivery of anti-glaucoma treatments. This complex system, in which coated nanodiamond clusters were successively embedded in chitosan spheres and a poly(hydroxyethylmethacrylate) (PHEMA) hydrogel matrix,

showed controlled and sustained release of encapsulated timolol maleate and prolonged drug activity on primary human trabecular meshwork cells from the cornea (see Fig. 4) [140]. Similarly, the development of microfabrication techniques now allows for the design of unusual delivery systems, such as micropatterned planar microdevices for drug delivery across RPE [141] or hollow microneedles for suprachoroidal particle injection [142]. A recent study demonstrated the use of an electroforming cobalt-nickel microtube designed to be loaded with drugs by capillary action before minimally-invasive intravitreal injection and wireless magnetic positioning within the eye. The so-called swiveling tubular magnetic microrobot is a good example of what could be the future of ocular delivery [143].

Despite major discoveries and progress in the treatment of age-related ocular diseases, ocular drug delivery systems remain somewhat invasive with limited duration of drug bioavailability in the posterior segment of the eye. Moreover, current therapies only slow the progression of vision loss rather than reversing the disease. Regenerative strategies require cell delivery and here, innovative combinations of cells, biomaterials and delivery vehicles are being pursued.

4. Cell delivery to the posterior of the eye

4.1. Cell transplantation

Broadly, cell transplantation aims to achieve: 1) the direct replacement of endogenous cell types lost due to degeneration, and/or 2) the delivery of cells that can secrete trophic factors to rescue degenerating cells. In order for transplantation to be successful in the former case, cells must survive and integrate into the host system. This requires migration to the target tissue, differentiation into the correct cell type for integration into the existing circuitry, and restoration of long-term function, all while being exposed to the hostile conditions of the aging retina. Although age-related degenerative diseases have different origins, they all culminate in the death of specific cell types of the retina, whether photoreceptors, RPE cells, or retinal ganglion cells (RGCs) [144]. To address this, cell delivery strategies include the transplantation of healthy photoreceptors, photoreceptor precursor cells, RGCs [145–147], RPE cells [148,149], or somatic cell types that secrete trophic factors [150,151].

4.1.1. Sources of cells for transplantation

The source of cells is a key component to the success and feasibility of a transplantation therapy. The ideal cell source has minimal ethical concerns, can be expanded and differentiated in culture in a minimal timeframe, originates from an autologous source, and has minimal costs associated with harvesting and maintaining cells in culture [152]. These idealized criteria form the basis of significant research strategies. There are currently four main sources of cells used for eye transplantation: 1) embryonic- or fetal-derived stem cells (ESCs), 2) fetal or early postnatal progenitor cells, 3) adult tissue-derived stem cells, and 4) induced pluripotent stem cells (iPSCs). ESCs are an attractive source of cells due to their ability to self-renew and differentiate into any cell type of the body [153]; however, these characteristics, while beneficial, also come with the risk of tumor formation [154]. While human ESCs remain an ethically challenging source, the establishment of several hESC lines within the last decade has overcome some of these issues. An alternative source are committed fetal or postnatal progenitor cells derived from the retina. The use of adult-derived stem cells includes those from the mammalian ciliary body [155,156], cell lines derived from Müller glia [157,158] and non-retinal cells such as mesenchymal stromal cells (MSCs) from bone marrow or adipose tissue [151]. MSCs are currently in clinical trials for other areas of cell transplantation research, and are being employed in a clinical phase I/II study for AMD as a source of factors providing neuroprotection [159]. Human induced pluripotent stem cells (hiPSCs) are a relatively new source of stem cells developed from the direct reprogramming of somatic cells to a pluripotent state [153,160]. The use of iPSCs is exciting because they can be derived from the patient's own tissue and are associated with fewer ethical concerns than embryonic or fetal cells [153]. Similar to ESCs, iPSCs can be differentiated using a combination of soluble factors into various cells of the retina, including rods, cones and RGCs [148,161–163]. While there may still be some risk of tumor formation with these cells, a recent safety study reported that iPSCs differentiated into RPE cell sheets and transplanted into the mouse subretinal space did not cause tumor formation up to 82 weeks post-transplantation [164], indicating that the risk is minimal.

4.1.2. Cell types used for transplantation

4.1.2.1. Retinal pigmented epithelium (RPE) cells. Due to the highly complex organization of the retina, replacing photoreceptors and associated circuitry is an extremely challenging task. An alternative target for cell transplantation studies is the rescue and preservation of photoreceptors through the replacement of trophic support provided by the RPE [149,165]. The use of an exogenous RPE source is not a new concept – in 1988 Li and Turner transplanted rat RPE cells in rats and demonstrated that grafted cells attached to Bruch's membrane and survived up to 3 months [166]. A later study confirmed that RPE cells can rescue photoreceptors by re-establishing metabolic processes of rods following transplantation [167]. Since these early experiments, RPE cells have been repeatedly demonstrated in pre-clinical studies to rescue photoreceptors in the retina and restore some visual function [149,168].

Importantly, RPE transplantation is being pursued in clinical trials as well. Two clinical studies initiated by Ocata Therapeutics are currently investigating the safety and tolerability of subretinal transplantation of RPE derived from human ESCs in patients with dry AMD (trial NCT01469832) and Stargardt's Macular Dystrophy (trial NCT01345006) [169,170]. Representing the first clinical study to use iPSC-derived cells for retinal delivery, RPE derived from autologous iPSCs have been transplanted in one AMD patient by Masayo Takahashi's group with success to date [171]. However, further transplantations have recently been halted due to a mutation found in the iPSCs derived from the second patient that will need to be addressed to ensure patient safety. A completed trial investigated the transplantation of intact sheets of human fetal retinal progenitor cells and RPE in AMD and retinitis pgmentosa patients, reporting improved visual acuity in seven out of ten patients; in one case this improvement was observed to last for five years [172]. Lastly, a trial completed in 2008 (trial NCT00401713) compared RPE-choroid sheet transplantation and RPE cell-suspension transplantation in patients with AMD. This study showed comparable anatomical and functional outcome for both surgical interventions and it was concluded that intrastructural irregularities of the sheet might be the cause of the rather limited visual gain in otherwise successful sheet transplants [173]. Although clinical trials involving biomaterials for retinal transplantation are not as prevalent as those without, a phase-1 trial has been granted approval which builds on the research of Pete Coffey [174,175], making use of human ESC-derived RPE cells that are grown as a monolayer on polyester membranes and then transplanted in the subretinal space (trial NCT01691261) [176]. While the surgical strategy is non-trivial, having the cells appropriately organized has resulted in positive pre-clinical data and enabled the strategy to be pursued clinically.

4.1.2.2. Retinal progenitors, photoreceptor precursors, and photoreceptors. Transplantation experiments have explored the use of the full developmental range of photoreceptor lineages, from retinal progenitor cells, through rod precursors, to mature photoreceptors. While photoreceptors can be successfully transplanted [145,146,177], their integration is lower when compared to precursor cells [147,178–180] and the ontogenetic timing of cells used for transplantation can have a significant impact on their ability to integrate and form functional connections [180,181]. Rod precursors have been shown to migrate into the ONL, form new synaptic connections and outer segments [145,147,182,

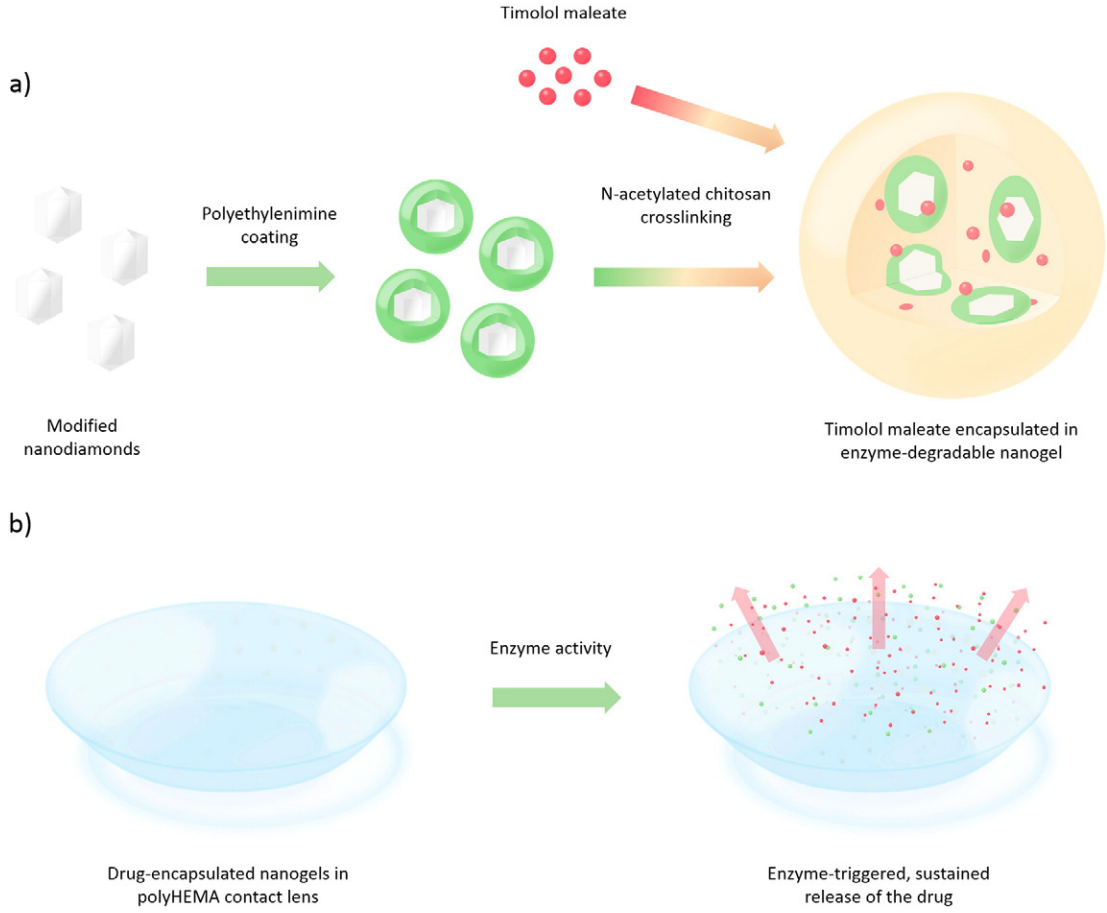

Fig. 4. Contact lenses as drug carriers for sustained delivery of anti-glaucoma treatment. a) Chemically modified nano-diamonds are successively coated with polyethylenimine (PEI) and co-encapsulated with an anti-glaucoma drug (timolol maleate) in crosslinked chitosan nanogels. B) Drug-encapsulated nanogels are then embedded in poly(hydroxyethylmethacrylate) (polyHEMA) hydrogel matrix and cast into contact lenses for enzyme-triggered delivery to the eye. Figure inspired by ref. [140].

183], and even restore rod-mediated vision in mouse models of retinal degeneration [145,146]. Despite the success with rod photoreceptor precursor cells, successful generation and transplantation of cone photoreceptors – the cells critical for daylight vision – remains elusive. The barrier for success with photoreceptor transplantation is significantly higher than that of RPE as the photoreceptors must integrate into the retinal circuitry in order to achieve functional repair, whereas the RPE cells provide more of a supportive role to the photoreceptors. For this reason and the difficulty in attaining a pure population of photoreceptors for transplantation, photoreceptor progenitors have not been tested clinically to date [184].

4.1.2.3. Retinal ganglion cells. The pathophysiology of glaucoma includes death of the retinal ganglion cells and subsequent degradation and retraction of axons from the optic nerve. The retinal ganglia form a complex axonal network whose organization, while likely necessary to restore complete function, is difficult to replicate with a transplant. Due to this, much of the glaucoma pre-clinical research has focused on attempts to rescue RGCs rather than directly replace them, including the transplantation of cells which secrete soluble factors such as mitogens, or cells that act as physical support for the endogenous cells [185,186]. However, despite the significant challenges associated with the tissue organization, the possibility of direct transplantation of RGCs and RGC precursors has been explored with some success in pre-clinical animal models [187,188].

4.1.2.4. Non-retinal cell types. Non-retina associated cell types such as mesenchymal stromal cells (MSCs) [151,159,189], neural progenitor cells [190,191], and even dental pulp cells [150] have been transplanted to the retina in order to provide trophic support to the endogenous cells. There are several ongoing clinical trials using adipose stem cells, neural stem cells, and bone marrow stem cells but to date these have not yet yielded results. This strategy is advantageous because, unlike biomolecule delivery strategies, transplanted cells secrete many factors that can target multiple pro-survival signaling pathways [192]. The challenge, however, as with other cell transplantation strategies, is the burden associated with cell survival. Another possible method of using these cells is to drive their differentiation to a retinal phenotype, as has been recently demonstrated using human bone marrow stem cells [151].

4.1.3. Challenges with cell transplantation

Despite encouraging results with retinal transplantation, there remain a number of challenges that must be overcome for long-term functional recovery. The method of delivery must be carefully considered as the degree of trauma caused by the delivery of cells can affect the inflammatory response and thus the success of the transplantation [145,184]. Currently there are two locations in the eye used for delivery: the subretinal space, which is more technically challenging and potentially disruptive, but is the location where the cells are lost; and the vitreous, which is less invasive and not as technically challenging, but requires cells to survive in the vitreous and then migrate to the retina. Ideally, cells injected as a suspension into the subretinal space should migrate and distribute along the retina as a monolayer. However, following a bolus injection of cells in saline aggregation is often observed, resulting in cell death and limited (if any) host tissue integration [178, 193–195]. Introducing the use of materials to support cells and provide

proper distribution in the subretinal space increases cell survival following transplantation [178,193,196].

Another major concern for cell transplantation is the survival and integration of cells. It is unclear how many cells survive in many cases, as quantification of cell survival is not often reported, but it appears that the majority undergo apoptosis [180,194,197]. One reason for this is the problem of anoikis, an apoptotic cascade initiated by lack of cell anchorage [197,198]. This is supported by the observation that RPE cells transplanted as a whole sheet survive better than as a suspension [199,200]. An additional contributing factor to cell death is the hostility of the micro-environment, which includes the presence of apoptotic signals, inflammatory cells, and damage to the surrounding architecture [146,201,202]. To compound this issue, any cells that fail to integrate and undergo apoptosis secrete pro-apoptotic signals and create debris, causing further damage to the surrounding tissue [145,202].

4.2. Cell delivery systems

Scaffolds for cell delivery have been designed to promote cell survival and integration (see Table 2) [203,204] by protecting cells from the hostile host environment [205,206]. Scaffolds can support uniform cell distribution and direct the differentiation of transplanted stem cell progeny [207]. To rescue aging ocular tissues, RPE cells have been transplanted on a synthetic Bruch's membrane and photoreceptors within an injectable hydrogel to the subretinal space [208].

4.2.1. Synthetic Bruch's membrane for RPE delivery

As the RPE lacks the capacity to regenerate, age-related diseases such as AMD and diabetic retinopathy result in degeneration of the RPE and blindness. RPE degeneration is accompanied by pathological changes to Bruch's membrane, such as thickening, collagen crosslinking, calcification and drusen deposition [6,209]. Transplantation of RPE cells to the aging posterior segment promises to reverse disease progression and rescue damaged tissues. Success is measured by tissue repair where RPE cells express mature markers, such as CRALBP, RPE65 and bistrophen, and functional repair with re-gained vision.

Direct RPE transplantation onto aged Bruch's membrane results in poor cell survival, adhesion and organization [201,210,211]. Given the highly organized cell structure of the RPE, successful RPE cell implantation appears to require replacement of the damaged Bruch's membrane as well [6]. For this reason, RPE cells are transplanted as a pre-cultured sheet on a support membrane and transplanted as a monolayer. This necessitates a complicated surgery and poses a biomaterial challenge in the design of an optimal artificial Bruch's membrane onto which RPE cells are cultured and then transplanted. To overcome the difficulty in transplantation of an ultra-thin membrane, a platform device made of parylene can be loaded with a graft containing the desired cells for transplantation [212].

Recognizing the importance of the porous nature of the Bruch's membrane, various materials have been studied as potential candidates for the development of porous membranes for the culture and delivery of RPE cells. For example, a porous polycaprolactone (PCL) thin-film (vs. polyester transwell and a non-porous PCL thin-film) enhanced maturation of fetal human RPE (fhRPE) monolayers as demonstrated by improved tight junction localization and cellular density, and expression of RPE-associated genes such as RPE65, RLBP1 and BEST1 [213]. Interestingly, a porous polyimide membrane coated with cell-adhesive proteins, such as laminin and collagen I, promoted the adhesion of hESC-derived RPE [5]. By simply using porous collagen membranes [214], a functional RPE was achieved where phagocytosis of photoreceptor outer segments was demonstrated in vitro [215]. Preliminary tests for potential subconjunctival or subretinal transplantation of a similar collagen-based scaffold were performed in rabbits and showed no inflammatory or immune response [216]. Post-transplantation cell survival has also been demonstrated with the use of a polyester membrane that has properties similar to the native Bruch's membrane to transplant human RPE stem cells into the rabbit retina [217].

Recently, materials have been developed that closely mimic the native membrane. Although the Bruch's membrane has a complex pentalaminar structure, it is the inner collagenous layer that is targeted for mimicry. It consists of a porous, mesh-like architecture made of collagen fibers with a diameter of 60 nm and a packing density of 48%, which allows for nutrients and oxygen transfer [6]. Using electrospinning,

Table 2
In vivo studies of biomaterial-supported cell/stem-cell delivery to the posterior segment of the eye.

Cell type	Material	Disease model	Outcome	Reference
Retinal pigmented epithelium (RPE) cells				
Adult and fetal human RPE stem cells	Polyester matrix membrane	Wild-type rabbit	Cell survival up to 4 weeks with polarity markers maintained; no retinal scarring	[217]
Human ESC[a]-derived RPE cells	Parylene plate	Royal college of surgeons rat	Successful implantation of intact synthetic monolayer seeded with cells; loss of less than 2% of cells after 7 days	[212]
Human ESC[a]-derived RPE cells	PET[b] or P(LA-co-CL)[c]	Wild-type rabbit	Subretinal biocompatibility over 14 days, some migration of native RPE cells into scaffold	[222]
Retinal Progenitor Cells (RPCs)				
Primary mouse RPCs	nanowire PCL[d] scaffold	rhodopsin null mouse	Supported cell growth in vitro, some migration and differentiation in vivo after 30 days	[223]
Primary mouse RPCs	thin-film PCL[d] scaffold	Rhodopsin-null C57Bl6 mouse	Localized to ONL and expressed photoreceptor markers in vivo	[224]
Primary mouse RPCs	PGS[e] scaffold	Rhodopsin-null and wild-type C57Bl6 mice	Transplanted cell migration into retina and maturation, cells survived for 1 month	[225]
Mouse RPCs	Hyaluronic acid hydrogel	Rhodopsin-null mice	No damage during injection; cell distributed evenly in subretinal space; cell survival up to 3 weeks	[226]
Retinal stem cell-derived rods	Hyaluronic acid/methylcellulose hydrogel	Adult albino CD10 and TKO[f] mice	Cell survival and migration significantly greater in gel than saline; improvement in pupillary light response	[178]
Retinal stem cells	Hyaluronic acid/methylcellulose hydrogel	CD10/Gnat2 −/− mice	Cell survival for 4 weeks in vivo, superior cell distribution in subretinal space	[193]

[a] Embryonic stem cell.
[b] Polyethylene terephthalate.
[c] Poly(L-lactide-co-ε-caprolactone).
[d] Polycaprolactone.
[e] Poly(glycerol sebacate).
[f] Triple knock-out.

various nanofibrillar delivery systems have been designed to mimic the Bruch's membrane for RPE delivery. Different materials have been investigated: silk and PCL [218], polyimide [219], a combination of silk and poly(ethylene glycol) (PEG) [220], and a RGD-functionalized poly(methyl methacrylate-co-poly(ethylene glycol) methacrylate) (P(MMA-co-PEGMA)) [221]. RPE cells seeded on 200 to 300 nm nanofibrous scaffolds formed the expected poly(hexagonal) structure with a striking resemblance to native RPE, and expressed markers typical of RPE [6]. Surprisingly, the key distinguishing material property was the nanofibrous property regardless of the material used. This was demonstrated independently in two studies comparing different nanofibril supports, one comparing PLGA and collagen, and the other polyethylene terephthalate (PET) and poly(L-lactide-co-ε-caprolactone) (P(LA-co-CL)) [6,222]. While the nanofiber structure enables RPE survival and organization, implantation requires the use of a relatively rigid backing [222]. Notwithstanding the complex material design and consequent surgery, the nanofibrous strategy holds great promise, yet the influence of restored RPE on aging ocular tissues remains to be evaluated in these strategies.

4.2.2. Photoreceptor and retinal progenitor cell delivery

Regenerative strategies that include photoreceptor replacement promise to overcome vision loss due to RPE degradation and photoreceptor death. Successful transplantation of photoreceptors relies on their integration into the neural circuitry of the retina. Biomaterial scaffolds designed for photoreceptor delivery must enhance both their survival and migration out of the scaffold to enable cell integration. Biodegradable (or bioresorbable) scaffolds with high porosity (permeability) contribute to photoreceptor survival by regulating nutrient and oxygen diffusion [222] and have shown the most success to date [224,227,228].

The first generation of degradable scaffolds for RPC delivery consisted of porous membranes of PLA/PLGA blends, the porosity of which was adjusted using different PLA/PLGA ratios and phase inversion/separation techniques [182]. In vitro, cells migrated into the porous scaffolds, attached therein and showed down-regulation of immature markers and up-regulation of differentiation markers [229]. Cell attachment to the material was correlated with cell differentiation. In vivo, RPCs transplanted on these degradable scaffolds into the mouse subretinal space showed greater survival than RPCs transplanted as a single cell suspension. Importantly, grafted RPCs migrated into the host retina and expressed several mature markers (neurofilament-200, glial fibrillary acidic protein, protein kinase C-α, recoverin and rhodopsin), demonstrating in vivo differentiation [194]. Importantly, a similar observation was made when RPCs were transplanted into porcine retina [230].

Notwithstanding the positive results attained with the transplantation of photoreceptors on these PLA/PLGA scaffolds, there is a mismatch in modulus and flexibility between the scaffold and the subretinal space, resulting in tissue damage [231]. Moreover, the acidic degradation products of PLA- and PLGA-based supports may lead to a chronic inflammatory response in the confined subretinal space [222,232]. Consequently, both slow-degrading porous membranes [223] and more flexible systems [225] were developed.

To overcome these issues, bioresorbable/biodegradable hydrogels have been pursued for cell delivery to the subretinal space. Indeed, the tunability of injectable hydrogels, which allows the viscosity, composition and degradation rate to be adjusted, allows for minimally-invasive surgery and limited tissue damage [178,193]. Hydrogels provide a protective environment and an even distribution of RPCs within the retinal tissue [226]. An injectable hydrogel comprised of hyaluronan/methylcellulose (HAMC) promoted greater survival and distribution of both transplanted RPCs and retinal stem cell (RSC)-derived rods, than the identical cells delivered in conventional saline to the subretinal space (see Fig. 5) [178,193,204]. The HAMC hydrogel is particularly well-suited for delivery into the subretinal space as it is minimally swelling, bioresorbed within one week and gels rapidly on injection [207,233,234]. An alternative strategy uses fibrin glue to promote cell adhesion, via an integrin-RGD-mediated mechanism [235]. These pioneering studies on hydrogel-based systems pave the way for future ocular regenerative therapies.

4.2.3. Retinal ganglion cell delivery

Unlike RPE and photoreceptor transplantation, retinal ganglion cell (RGC) transplantation has had limited attention to date [236,237] because regeneration of optic nerve cells likely requires a more complicated strategy. For example, the arrangement of the transplant should recapitulate the radial organization of the native nerve fibers in order to facilitate proper impulse conduction. An electrospun scaffold composed of densely packed, radially aligned PLA nanofibers was coated with laminin, and resulted in enhanced in vitro cell adhesion, survival, and preserved RGC electrical properties within a radial pattern of RGC axons [238]. Although promising for the treatment of age-related ocular diseases, efficacy of this strategy remains to be shown in vivo.

5. Outlook

Despite the promising results of anti-angiogenic (anti-VEGF) antibody treatments, such as bevacizumab (Avastin™) and ranibizumab (Lucentis™), all attempts of controlled antibody delivery showed enhanced bioavailability, yet no improvements in visual acuity. Given the safety concerns of current repeated intravitreal injections, there is great opportunity for local delivery strategies to be developed to achieve sustained release. Nanoparticulate systems, which have been long-studied for cancer therapies and diagnosis, may be a rich source of inspiration [239,240]. As a promising example, nanocarriers loaded with common anticancer drugs, such as paclitaxel [241] or doxorubicin [82], have been recently reported for the treatment of choroidal neovasculature. However, the blood-retinal barrier may limit the use of intravenous delivery of nanocarriers, and intravitreal injections may result in undesirable complications. Thus, topical administration of eye drops for drug delivery to the posterior segment of the eye constitutes a non-invasive approach that may provide significant benefit, but remains challenging due to multiple drainage and biological barriers, including blinking and rapid dispersion of eye drops. To counteract the fast clearing of eye drops, nanoparticles have been modified on the surface with phenylboronic acid and shown to sustain the release of cyclosporin-A for up to 5 days [242]. Solutions might also come from annexin-functionalized nanocarriers which have demonstrated significant uptake and transcytosis of liposomal drug carriers across corneal epithelial barriers [88]. In addition, emerging techniques are currently being evaluated for better penetration of the nanoparticles through the sclera and to the retina. For example, transscleral delivery can be enhanced with either iontophoresis where penetration is enhanced with a low electric current [243,244] or ultrasound [245,246]. Implants are an interesting alternative to nanoparticles for prolonged drug release. Currently under investigation, transscleral, refillable implants may provide an innovative strategy for sustained drug release [247,248].

Cell delivery constitutes a more ambitious, yet still emerging, approach for ocular treatments. The need for artificial Bruch's membranes to support RPE cell transplantation has prompted the development of original nanofiber-based, degradable scaffolds, which have already demonstrated beneficial properties in vitro and a good biocompatibility in vivo [6,218]. However, the nanofibrillar system necessitates the use of an additional support material with appropriate permeability, flexibility, bioresorption and biocompatibility. A micropatterned porous thin-film co-carrier [213] coated with nanofibers may provide the solution; however, in vivo efficacy of transplanted RPE has yet to be demonstrated. RPC transplantation is an alternate strategy which obviates the need for a supportive membrane yet requires injection into the subretinal space, followed by in situ differentiation and tissue integration. Injectable, bioresorbable hydrogel delivery vehicles hold great promise for

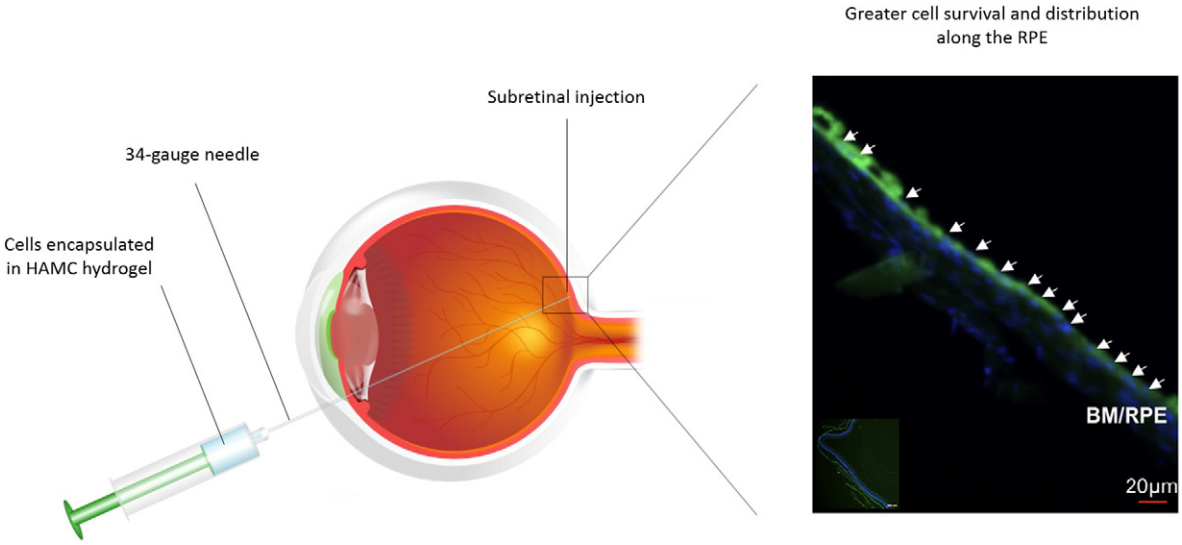

Fig. 5. Delivery of retinal progenitor cells (RPCs) to the subretinal space of a damaged retina, using hyaluronan/methylcellulose (HAMC) hydrogel as biomaterial support. HAMC allows for in situ rapid gelation and results in greater cell survival and distribution. Adapted with permission from ref. [193].

cell delivery to the retina as the surgical strategy is less invasive than implantation of a solid scaffold. Moreover, the hydrogel can be designed to have a modulus that matches that of the retina and chemical properties that enhance cell survival/integration after transplantation [165,204,205] and direct stem-cell fate in situ [206,207]. While side effects and complications from subretinal injection need to be assessed, advanced hydrogel design for RPC or precursor cell delivery provides tremendous opportunity for successful ocular cell delivery [249].

Despite being a leading cause of visual impairment and blindness, glaucoma has not yet been a focus of sustained drug delivery and cell transplantation research. More research on intravitreal sustained drug delivery and RGC-coated patches is expected.

Whether for drug or cell delivery, the choice of material constitutes one of the major challenges for the future. Since regulatory approval is a long, laborious process, most of the materials presented herein have a long regulatory history, including natural lipids (mainly for liposomes), polysaccharides (such as chitosan, hyaluronan, cyclodextrins) or synthetic polymers (typically PLA, PLGA, PCL). But, the confined space in which ocular delivery systems are administered may require further material toxicity studies, as the acidic degradation products of synthetic polyesters may be harmful to the tissue [222,232]. The tremendous progress in synthetic materials should provide advanced properties to these delivery systems. In particular, functional polymers for drug/peptide grafting and delivery may lead to innovations in controlled and targeted drug release to the posterior segment of the eye. Well-documented strategies and advanced designs of stimuli-responsive and functional polymer-based nanocarriers for other biomedical applications may serve as examples [250,251]. However, for these materials to be useful, they (and their degradation products) must be biocompatible and bioresorbable [252]. Therefore, intraocular toxicity of any innovative material should be investigated early.

Another exciting potential strategy to explore for vision repair is the combination of delivery techniques, such as nanoparticle-encapsulated hydrogels, for sustained release of multiple therapeutics, co-delivery of cells and drugs or multifunctional delivery systems [195,253].

Improvements of in vitro and in vivo models will be required for better translation to the clinic. Indeed, creating an accurate animal model of retinal degeneration is challenging. Diseases such as AMD and diabetic retinopathy are the culmination of complex genetic and epigenetic factors and, while current models can mimic several pathological characteristics of degeneration, none of these fully recapitulate all anatomical features. Furthermore, because of this variation in models, it is difficult to translate results from one study to another; an investigation of 6 different genetic mouse models of degeneration found that photoreceptor transplantation success varied widely depending on the model used [146]. This underlines the importance of testing strategies in different animal models of disease and ideally in different laboratories, similar to the way a clinical trial would be executed at multiple sites.

Ultimately, to overcome the challenges associated with age-related or degenerative ocular diseases, collaboration between scientists, engineers and clinicians in academia and industry is required for successful translation of innovative strategies to the clinic. Advances in each discipline – cell biology, drug discovery and delivery, and surgical strategies – are required to overcome these daunting challenges to repair and restore vision.

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