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Frontier applications of retinal nanomedicine: progress, challenges and perspectives

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Abstract

The human retina is a fragile and sophisticated light-sensitive tissue in the central nervous system. Unhealthy retinas can cause irreversible visual deterioration and permanent vision loss. Effective therapeutic strategies are restricted to the treatment or reversal of these conditions. In recent years, nanoscience and nanotechnology have revolutionized targeted management of retinal diseases. Pharmaceuticals, theranostics, regenerative medicine, gene therapy, and retinal prostheses are indispensable for retinal interventions and have been significantly advanced by nanomedical innovations. Hence, this review presents novel insights into the use of versatile nanomaterial-based nanocomposites for frontier retinal applications, including non-invasive drug delivery, theranostic contrast agents, therapeutic nanoagents, gene therapy, stem cell-based therapy, retinal optogenetics and retinal prostheses, which have mainly been reported within the last 5 years. Furthermore, recent progress, potential challenges, and future perspectives in this field are highlighted and discussed in detail, which may shed light on future clinical translations and ultimately, benefit patients with retinal disorders.

Keywords Retinal diseases, Nanomedicine, Eye drop, Therapeutic nanoagents, Theranostic, Gene therapy, Stem cell-based therapy, Retinal optogenetics, Retinal prostheses

Introduction

The specialized and photosensitive retina is located in the posterior segment of the eye. Functionally, the retina transmits and converts light into electrical signals for the optic and central nervous systems, contributing to visual acuity. Among the thin sophisticated architecture of ten retinal layers, the rod and cone photoreceptors are responsible for light collection and modification. The monolayer retinal pigment epithelium (RPE) forms the blood-retinal barrier to support the biological functions of the overlying photoreceptors. These fragile retinal cells are susceptible to various disturbances and can cause a wide range of sight-threatening retinal diseases. Clinically, they usually include age-related macular degeneration (AMD), diabetic retinopathy (DR), retinitis pigmentosa (RP), diabetic macular edema (DME), proliferative vitreoretinopathy (PVR), retinoblastoma (RB), glaucoma, and endophthalmitis. Conservative statistics based on prevalence data show that approximately 43 million cases of blindness occurred in 2020, and another 295 million people suffered from moderate to severe vision impairment, contributing to annual global productivity loss.[1, 2]

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Dysfunction and loss of the RPE or retinal neurons are the core pathological characteristics of retinal degeneration (RD). Glaucoma is a group of diseases that leads to irreversible vision loss and is characterized by the progressive loss of retinal ganglion cells (RGCs). Although not always elevated, intraocular pressure (IOP) remains the leading cause of irreversible blindness in patients with glaucoma [3]. The primary pathological characteristics of retinal diseases include oxidative stress, inflammation, neovascularization, ischemia, infections, and tumors [4]. These pathogenic processes do not occur in isolation; instead, they affect each other and interact during disease progression. Unfortunately, accurate diagnosis and treatment are currently limited in addressing these conditions.

Parallel visualization of the in vivo molecular composition, cellular structure, and function is crucial for retinal diagnosis, understanding the pathophysiology of retinal diseases, monitoring disease progression, facilitating timely interventions, and evaluating treatment outcomes. Broadly employed modalities for noninvasive retinal imaging include optical coherence tomography (OCT), OCT angiography (OCTA), photoacoustic microscopy (PAM), and magnetic resonance imaging (MRI) [5, 6]. However, because of aberration-induced insufficient resolution, limited penetration depth, and high background signal, these technologies are unable to specifically observe the retina at the molecular and cellular levels [7–9]. Therefore, there is an urgent need to explore theranostic alternatives to synergistically image, track, diagnose, and treat retinal disorders at early stages.

Pharmacotherapy is the most common intervention for the treatment of retinal diseases, as it targets different pathogenic mechanisms, with a low treatment burden and cost. In clinical practice, antibodies against vascular endothelial growth factor (VEGF), a critical pathological factor associated with retinal and choroidal neovascularization (CNV), have been considered to have the greatest potential to target retinal neovascular diseases [10]. Additionally, nonsteroidal anti-inflammatory and antioxidant agents and corticosteroids (e.g., triamcinolone acetonide [TA]) have been widely used for sight-saving therapies for various retinal diseases [11–14]. Intravitreal injection is a frequently used approach. However, this invasive route may cause complications such as infection, intraocular hemorrhage, and retinal detachment [15]. Accordingly, safer, noninvasive methods are preferred for retinal therapy [16].

Theoretically, eye drops used for drug delivery avoid invasive surgery and provide a more convenient option for stabilizing fundus lesions. However, non-invasive eye drops for the delivery of pharmaceutical ingredients into the posterior eye segment require passing through multiple ocular barriers, including the tear drainage, cornea, conjunctiva, blood-aqueous barrier, and blood-retinal barrier. Therefore, conventional eye drops suffer from considerable challenges, including low permeability and insufficient drug concentrations [17]. This necessitates innovative strategies to improve the effectiveness of eye drops for the management of retinal diseases.

Additionally, because of the short half-life and poor stability of conventional drugs, pharmacotherapy inevitably requires intensive dosing regimens, leading to a treatment burden, poor patient compliance, and even the discontinuation of treatment. Drug permeability and therapeutic bioavailability within the retina largely rely on the inherent physicochemical properties of the drug itself, especially its lipophilicity, hydrophilicity, and molecular radius. The development of novel therapeutic agents with satisfactory inherent physicochemical features remains a goal.

At the early stages of RD, retinal gene therapy appears to be one of the most important strategies before the complete loss of photoreceptors. Gene therapy generally involves the use of adeno-associated viral (AAV) vectors for gene delivery to retinal cells [18]. Although the efficacy of AAV delivery has been preliminarily verified in both preclinical and clinical studies, AAVs have some potential issues, particularly immunogenicity after repetitive utilization and inadequate packaging capacity [19, 20]. Thus, the design and application of different nonviral cargos may be an alternative strategy for gene delivery into the fundus.

Stem cell-based therapy aims to replace or repair degenerated native RPE or photoreceptors and may be the only effective strategy for visual restoration in progressive retinal degeneration [21]. However, the limited cell proliferation and retinal neuronal differentiation of stem cells pose major challenges in clinical practice. Additionally, traditional approaches for cell transplantation employ subretinal injections of bolus cell suspensions, causing low cell viability and potential side effects, such as retinal tears and hemorrhages. Therefore, novel strategies for regulating stem cell proliferation and differentiation, and facilitating in vivo cell delivery and survival are required.

In the late stages of RD, retinal optogenetics and retinal prostheses restore retinal light sensitivity and visual perception upon the integration of neuronal responses for transmission to the cortex. Retinal optogenetics involves the genetic introduction of light-sensitive optical proteins for ectopic expression in nonphotosensitive downstream neurons. Thus, they confer photosensitivity to the residual intact non-photoreceptor cells, irrespective of the genetic etiology of vision restoration. However, determining the optimal approach for retinal optogenetic

delivery is important in clinical practice. In contrast, retinal prostheses are direct wireless electrical stimulation materials or wiring electronic devices integrated with artificial synapses. Accordingly, photoactive synapses with excellent tunability and innate optoelectronic memory have been emphasized.

These challenges have motivated rapid progress in nanomedicine and revolutionized the management of retinal diseases. Compared to their micro- or macroscale counterparts, ultrafine nanocarriers undergo significant changes in their physiochemical structure, endowing them with diverse novel properties and functions. First, multifunctional nanomaterials have emerged as alternative theranostic contrast agents to traditional fluorescence probes for the real-time monitoring, diagnosis, and treatment of a series of retinal diseases [22, 23]. As a noninvasive delivery system, nanocarriers surmount ocular barriers and enhance penetration, prolong retention, improve solubility, promote drug release, decrease toxicity, and achieve targeted delivery of encapsulated agents to retinal tissues. Compared to traditional larger-sized drugs, nanoagents exert comparable or even better therapeutic outcomes because of their inherent therapeutic effects [24, 25]. Additionally, at different stages of RD, gene therapy, stem cell-based therapy, retinal optogenetics, and retinal prostheses present respective functions for visual rescue, which may be substantially assisted by nanomedicine [26, 27].

Most research on nanomaterials in the retinal field has focused on single aspect, e.g., drug delivery as a carrier, particularly via invasive intravitreal injection [28, 29]. However, the new trend in nanomaterial research is mainly the modification of traditional nanomaterials, the development of new biomaterials, and the combination of other disciplines or technologies to improve their performance and extend their applications. For the first time, we provide comprehensive and novel insights into state-of-the-art nanomaterial-based multiplatforms for frontier retinal applications (Fig. 1), predominantly based on publications from 2020 to 2024. We begin by introducing representative examples of topical noninvasive eye drops that rely on organic or inorganic nanomaterials. Subsequently, research on retinal nanomedicine involving nanoagent-based therapy is highlighted, with an emphasis on intelligent theranostic contrast agents derived from versatile nanomaterials for the tracking, imaging, diagnosis, and treatment of retinal diseases. Additionally, nanotechnology-aided gene therapy, stem cell-based therapy, retinal optogenetics, and retinal prostheses for prevalent retinal degenerative diseases are summarized. Finally, we elaborate on the current challenges and discuss the ongoing efforts and upcoming directions to overcome the bottleneck in retinal nanomedicine. The purpose of this comprehensive review is to promote multidisciplinary cooperation, share ophthalmology knowledge, and provide motivation and inspiration for the rational design of retinal nanomedicine in an attempt to accelerate its clinical translation, ultimately benefitting patients.

Retinal nanomedicine-based eye drops

To date, esculin and digitalis glycoside eye drops are the only commercially available drug to treat posterior segment diseases, confirming the feasibility of eye drops used in retinal fields [30]. Inspiringly, a variety of nanomaterial-constructed systems, including natural biomaterials (especially hyaluronic acid [HA], chitosan, and cyclodextrins), synthetic nanoformulations (particularly dendrimers, polymeric micelles, and lipid nanoparticles), and inorganic biomaterials (e.g., quantum dots [QDs], gold, and magnetic nanoparticles), have been widely utilized for the noninvasive delivery of retinal biologics [31–33]. They are advantageous over larger comparators for the management of multiple retinal diseases [34].

Natural organic nanomaterial-based drops

Natural polymers have distinct merits including high biosafety, improved membrane permeability, cell-activated proteolytic degradation, and bioactivity [28]. Representative natural organic biomaterial-based nanograde eye drops are mainly produced from natural polysaccharides (e.g., chitosan, HA, and cyclodextrins), biosynthetic materials (particularly peptide-based polymers), and cellulose derivatives [35, 36].

Chitosan-based eye drops

Chitosan, which contains a sugar backbone of β−1,4-linked glucosamine, is easily accessible and is the second most abundant natural polycationic polysaccharide produced from the deacetylation of chitin. Chitosan can interact with the ocular mucosa through ionic forces and temporarily open or widen the cellular tight junctions of the epithelial membrane [37]. Thus, chitosan can defeat the natural ocular defense mechanisms that delay drug permeation. Additionally, chitosan and its derivatives, especially chitosan-nanoparticle-based eye drops, have many favorable properties, such as biodegradability, biocompatibility, and a high mucoadhesive nature, and thus, they have had a tremendous impact on the advancement of retinal drug delivery systems for decades [38]. After topical administration, chitosan nanoparticles, as potent penetration enhancers for dual-drug delivery, present synergistic anti-reactive-oxygen-species (ROS), anti-inflammatory, and antimicrobial effects by significantly prolonging drug retention time, maintaining sustained drug release, and improving bioavailability in the choroid and retina [39–41]. More recently, Shen et al. designed

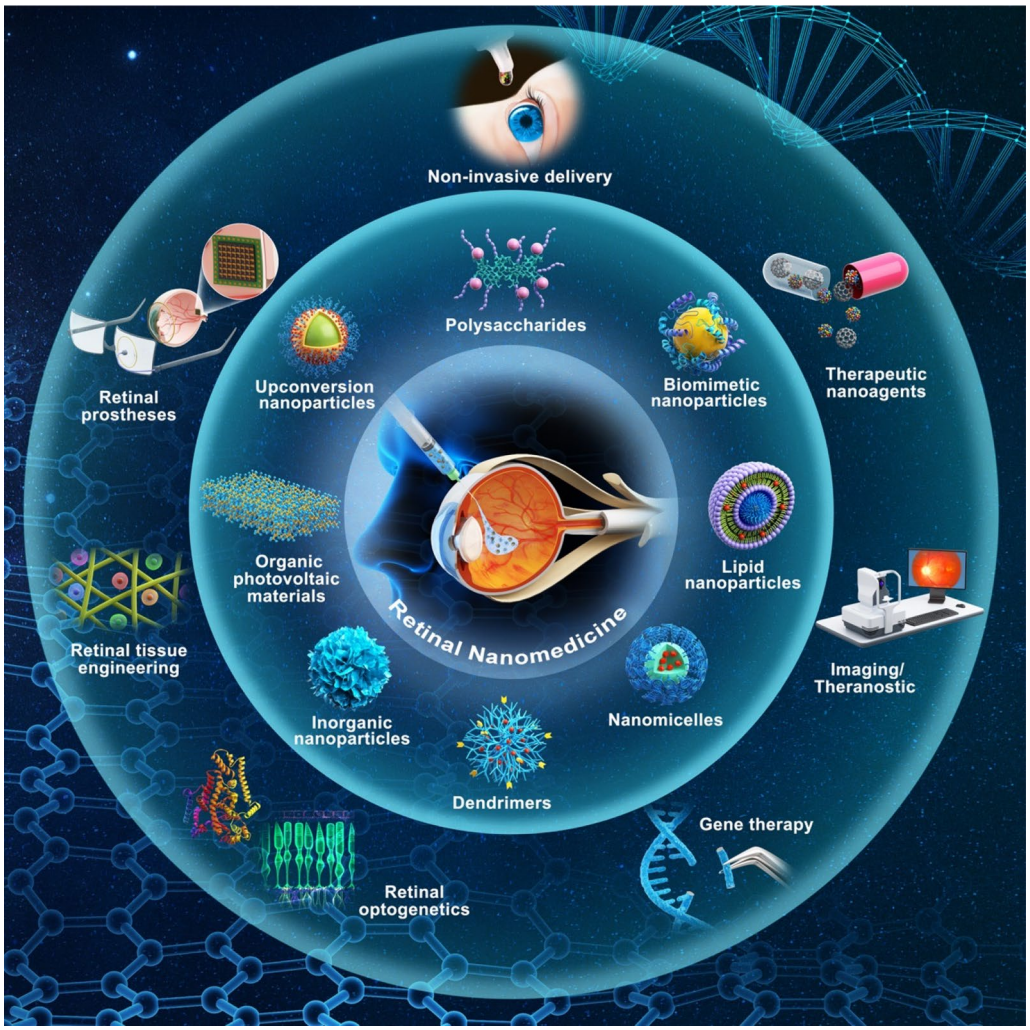

Fig. 1 Schematic illustration of representative retinal nanomedicine for frontier biomedical applications

fluorocarbon-modified chitosan (FCS)-based nanocomplexes by self-assembling anti-VEGFA antibodies for non-invasive administration. Consequently, high effectiveness at inhibiting vascular proliferation was observed in the CNV-bearing mouse and rabbit models. The developed eye drops successfully reached the fundus with an accumulated therapeutic dose via the conjunctiva-sclera/blood-choroid-retina route, where a rearrangement of the tight junction–associated proteins occurred in the corneal and conjunctival barriers (Fig. 2) [42]. Chitosan-based nanocomposites, such as organic–inorganic hybrid nanosystems and nanomicelles, have been rationally designed for the active delivery of agents into retinal tissues [43, 44]. Selected ligands, such as Valyl-Valyl-Valine,

(See figure on next page.)

Fig. 2 Representative chitosan-based eye drops for treatment of ocular fundus disease by macromolecular drug delivery. **a** Schematic illustration of fluorocarbon-modified chitosan (FCS) eye drops that enhanced the corneal and conjunctival penetration of macromolecules to reach the fundus by rearrangement of tight junction–related proteins. FCS/anti-PDL1 and FCS/anti-VEGFA nanograde eyedrops successfully treated choroidal melanoma tumor and laser-induced choroidal neovascularization (CNV), respectively. **b** Fundus fluorescein angiography (FFA) indicated the alleviated fundus lesions (square laser point) in FCS/Eylea treated CNV-bearing rabbits compared with other groups after treatment of 0 day, 15 days, and 30 days. Scale bar, 2 mm. **c** Immunofluorescence (IF) staining suggested that FCS successfully delivered Eylea to choroid and retina of rabbit eye to inhibit angiogenesis by images of CD31 (red) and VEGF (green). Scale bars, 50 μm. Reproduced under an open access Creative Common CC BY license [42]. Copyright 2023, American Association for the Advancement of Science

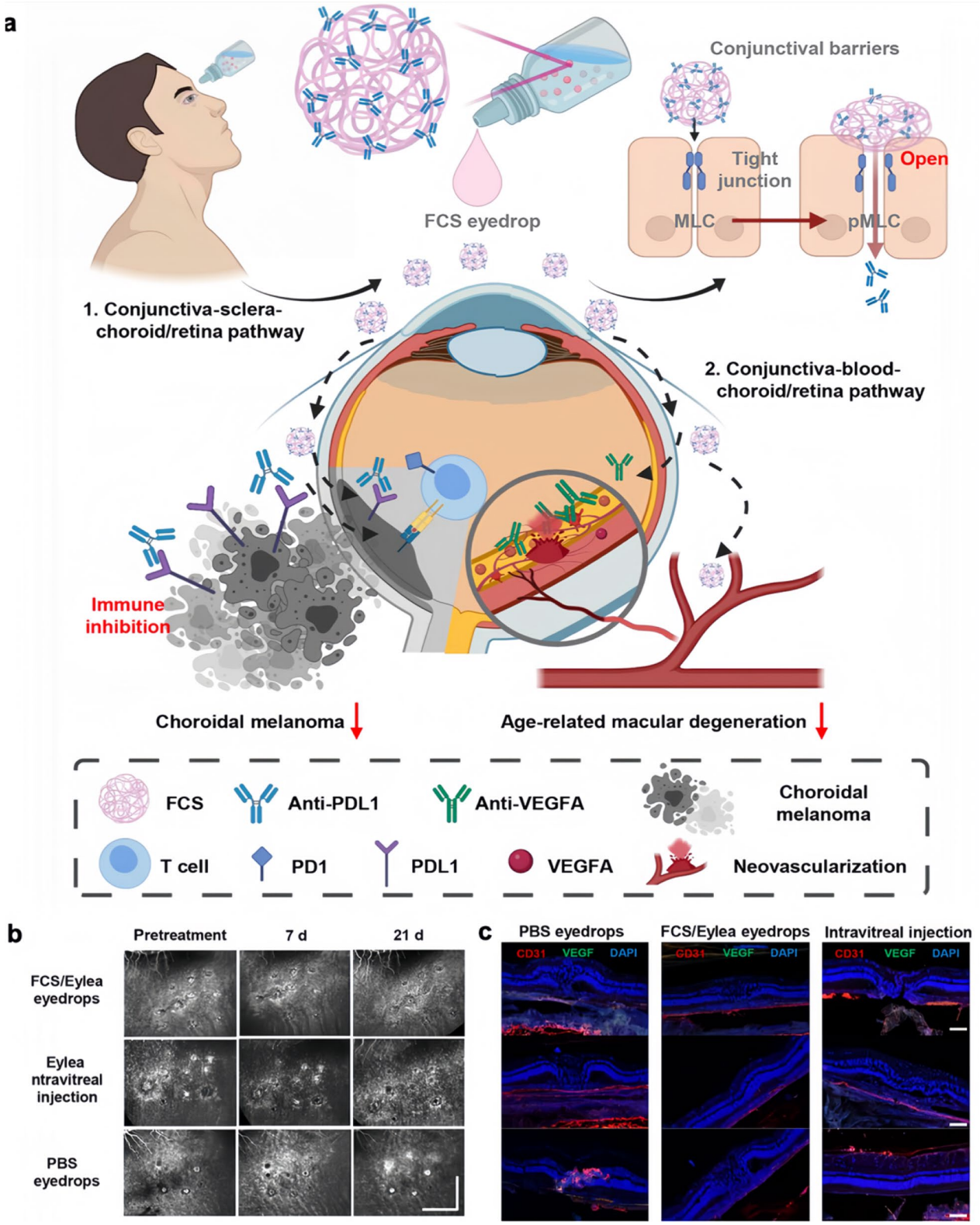

Fig. 2 (See legend on previous page.)

facilitate active targeting of the cell peptide transporter and enhance bioadhesive capacity. In addition, biostability and lysosomal escape of the synthesized nanocomposites have been evaluated using a typical membrane fusion lipid. After topical conjunctival administration, the mixed multifunctional nanocarriers significantly enhanced the cell permeability and maintained their micellar structure during transit. Chitosan has also been explored as a versatile modifier for the facile surface modification of various nanocarriers. Chitosan-based nanoparticles can be easily prepared and modified to change their charge and adhesion properties.

A clinical trial (NCT03192137) of DexaSite revealed favorable therapeutic effects on the suppression of pain and inflammation after ocular surgery. The system consists of dexamethasone and chitosan cross-linked with polyacrylic acid. The addition of chitosan primarily improved the viscosity for the effective delivery of dexamethasone [45]. However, the low solubility at physiological pH and the rapid elimination of chitosan and its derivatives by choroid capillaries may cause lower drug bioavailability in retinal tissues after topical instillation, which is an obvious shortcoming to be overcome [43, 44, 46].

HA-based eye drops

HA is a polymer chain containing repeating units of the disaccharide -(1–4)-d-glucuronic acid-(1–3)-N-acetyl-d-glucosamine. It is a typical polysaccharide derived from the extracellular matrix, such as the vitreous humor. Conventional approaches for nanoformulation preparation usually require large volumes of surfactants, chemical crosslinkers, and organic solvents, leading to significant toxicity. In contrast, HA-based nanoparticles are prepared through polyelectrolyte complexation, which is a mild method involving electrostatic interactions between opposing polyelectrolytes [47]. Accordingly, HA exhibits high viscoelasticity, good biocompatibility, excellent water solubility, and a strong binding force [48].

HA possesses a negatively charged carboxylic group that can be used to form nanoparticles with positive or negative surface charges at different concentrations to increase the mucus-cornea/conjunctiva interaction and retinal accumulation. For instance, HA-coated self-assembling nanoparticles made from gelatin-epigallocatechin gallate feature a positive surface and suitable size, facilitating the delivery of pharmacological ingredients into the retina [49]. In addition, the mucoadhesive ability of HA is closely linked to CD44 receptors expressed in the corneal epithelium and endothelium. Therefore, HA-based eye drops can delay drug permeation, despite the presence of natural ocular barriers. Based on this, Radwan et al. designed a natural nanopolymer (i.e., Apa-BSA-NPs) from HA-coated serum albumin nanoparticles for the delivery of the anti-VEGF drug Apatinib (Apa) for the treatment of DR. In vitro, the nanocarrier exerted no cytotoxicity, a high entrapment efficiency of 69 ± 1%, and a biphasic sustained release profile with an initial burst effect. Compared to the intravitreal injection of these nanoparticles, the retinal accumulation of Apa-BSA-NPs was improved by topical administration. Changes in the retinal micro- and ultrastructures were observed after topical treatment with HA-Apa-BSA-NPs in a rat model of DR. Nevertheless, the nanocarrier exhibited unique viscoelastic and mucoadhesive properties, and could serve as a guiding motif for actively targeting CD44-positive retinal cells [50].

Frequent blinking and tears decrease the residence time of soluble drugs on the ocular surface, whereas gelling drops generally form clumps and cause visual blurring. A typical method for prolonging drug retention is the use of excipients to enhance viscosity and/or mucoadhesion [51]. Because of their unique mucoadhesive characteristics, HA-cholesterol nanogels can be produced as ocular permeation enhancers via corneal and non-corneal pathways. The nanogel formulations firmly interact with the superficial corneal epithelium, facilitating the permeation of hydrophilic drugs or increasing the residence time of hydrophobic drugs [52]. More recently, Durak et al. developed a HA-based nanogel to deliver anti-VEGF agents for AMD treatment. The convenient incorporation of cholesterol and divinyl sulfone significantly controlled the size and improved the stability of the nanodrugs. After 192 h, the loading efficacy of the nanogel was 65% and the release of the anti-VEGF agent reached 34.72%. Importantly, the drug-encapsulating nanogel notably inhibited the excessive growth of blood vessels in an oxygen-induced retinopathy model, indicating that it is a potential candidate for the topical treatment of AMD [53].

HA and chitosan possess excellent mucoadhesive properties that can be further enhanced by mutual association. Theoretically, chitosan/HA nanocarriers can improve drug retention on the ocular surface and increase penetration and intraocular availability. Beatriz Silva et al. designed and investigated chitosan/HA nanocarriers for topical delivery of the neuroprotective and neuroregenerative agent, erythropoietin (EPO). As a result, the ocular bioavailability of EPO substantially increased, and EPO successfully reached the retina 12 h after topical instillation in Wistar rats and remained detectable 21 days later [54, 55].

Currently, HA-based eye drops for retinal diseases have not yet been applied clinically. Although HA is an excellent biodegradable and non-immunogenic comparator when used frequently in retinal diseases, a consensus

remains regarding the lack of optimization of drop tonicity, molecular weight, and concentration. Thus, it is necessary to determine an evidence-based standard for HA-derived eye drops in the treatment of retinal disorders based on more well-designed studies.

Fortunately, biomaterial-based transparent hydrogels with tamponading functions for retinal stabilization are emerging as vitreous substitutes for vision-threatening disorders. For instance, rhegmatogenous retinal detachment (RRD) often requires vitreous body removal and tamponade injections. Currently, the clinical use of silicone oil requires secondary surgery, which may cause patient discomfort. In contrast, expansive gases do not require surgical removal because they are naturally absorbed by the eye. However, during gas tamponade, the patient's vision is significantly impaired due to the difference in refractive indices between the gas and natural vitreous. Biomaterial-based tamponades, such as hydrogels, closely resemble the natural vitreous body and demonstrate potential as vitreous tamponade substitutes for future retinal applications [56]. One clinical trial involved HA-based patch (Healaflow®) has been conducted and completed for RRD treatment in China (NCT03542162). Healaflow® is a new type of HA and is a viscoelastic agent with strong crosslinking, slow absorption and self-degradation. Compared with silicone oil, Healaflow® promoted early visual recovery, caused less complications, and did not require prone position postoperation in the primary RRD repaired by 27G pars plana vitrectomy.

Peptide-based eye drops

Peptides with short amino acid sequences are crucial components in organisms and they participate in numerous biological processes. In contrast to other supramolecular materials, peptides can be produced at a low cost and are easily conjugated to relatively small molecules. A single function of peptides, either cell targeting capability or improved cell penetration, has been broadly used in peptide-based nanocarriers to transport drugs into targeted sites [57]. Accordingly, various peptide-mediated eye drops with good histocompatibility and considerable penetration through the ocular surface have been used to specifically target the fundus. Li et al. synthesized a smart supramolecular peptide-modified nanocarrier to shuttle an antivascular drug (axitinib) across dense scleral vessels to treat retinal neovascular diseases. Consequently, the targeting peptide nanostructure-formed eye drops displayed great transmembrane ability and significantly alleviated exudates and pathological angiogenesis in mice with DR by specific targeting and capture of a strongly pro-angiogenic and exudate factor, soluble semaphorin 4D [58]. Additionally, the co-assembled nano-transformer, consisting of a cationic peptide and glycopeptide with amphiphilic functions and an enzyme-responsive motif, triggered transformation upon legumain cleavage. The nanotransformer-based eye drops effectively penetrated the cornea and sclera to specifically enhance macrophage apoptosis in the fundus, leading to significant inhibition of pathological neovascularization in a mouse model of oxygen-induced retinopathy [59].

Cell-penetrating peptides (CPPs) such as penetratin are a family of short peptides containing 30 or fewer amino acid residues. They represent a class of excellent drug transport helpers [60]. The high bioavailability of ocular biomacromolecules, such as nucleic acids, proteins, and peptides, in ocular tissues is indispensable for penetration enhancers. Compared to other delivery systems, CPP-based vehicles exhibit better direct exposure to ocular absorption barriers and superior intracellular internalization. CPPs facilitate the intracellular internalization of hydrophilic biomacromolecules without interacting with receptors and they do not compromise cellular integrity or membrane stability. Usually, these cargos bind to CPPs by covalent or non-covalent complex formation without the requirement of chemical linkages with substances. Owing to their perfect biocompatibility and membrane modulation behavior, CPPs often serve as effective penetration enhancers across various barriers to drug absorption, such as epithelial tight junctions, for noninvasive drug delivery into the retina to treat retinal degeneration and optic nerve injury [61, 62]. For example, Shuai Shi et al. used a transmembrane peptide (i.e., PENE) to effectively deliver the anti-VEGF drug (i.e., Axitinib) to fundus. The developed PENE nanoparticle-based eye drops contributed to a wide drug distribution in retinal tissues and ocular veins, thus substantially reducing neovascularization (Fig. 3a) [63].

(See figure on next page.)

Fig. 3 Representative peptide-based eye drops for noninvasive retinal drug delivery. **a** Penetrating peptide-mediated non-invasive anti-VEGF drug (Axitinib) delivery for anti-neovascularization in fundus neovascular diseases. Reproduced with permission [63]. Copyright 2022, Elsevier B.V. **b** Topical instillation of cell-penetrating peptide conjugated melphalan blocks metastases of retinoblastoma. b1) 89WP-Mel in eye drops was absorbed in an "outside-in" manner. b2) Melphalan by intravitreal injection diffused in an "inside-out" manner. At 4 h after the instillation, IF staining of Cy5-89WP (red) treated b3) cornea, b4) sclera and b5) retina were shown in merged images. DAPI: cell nucleus. White arrows: diffusion directions. Scale bar, 100 μm in (b3, b4), 500 μm in (b5). Reproduced with permission [64]. Copyright 2022, Elsevier Ltd

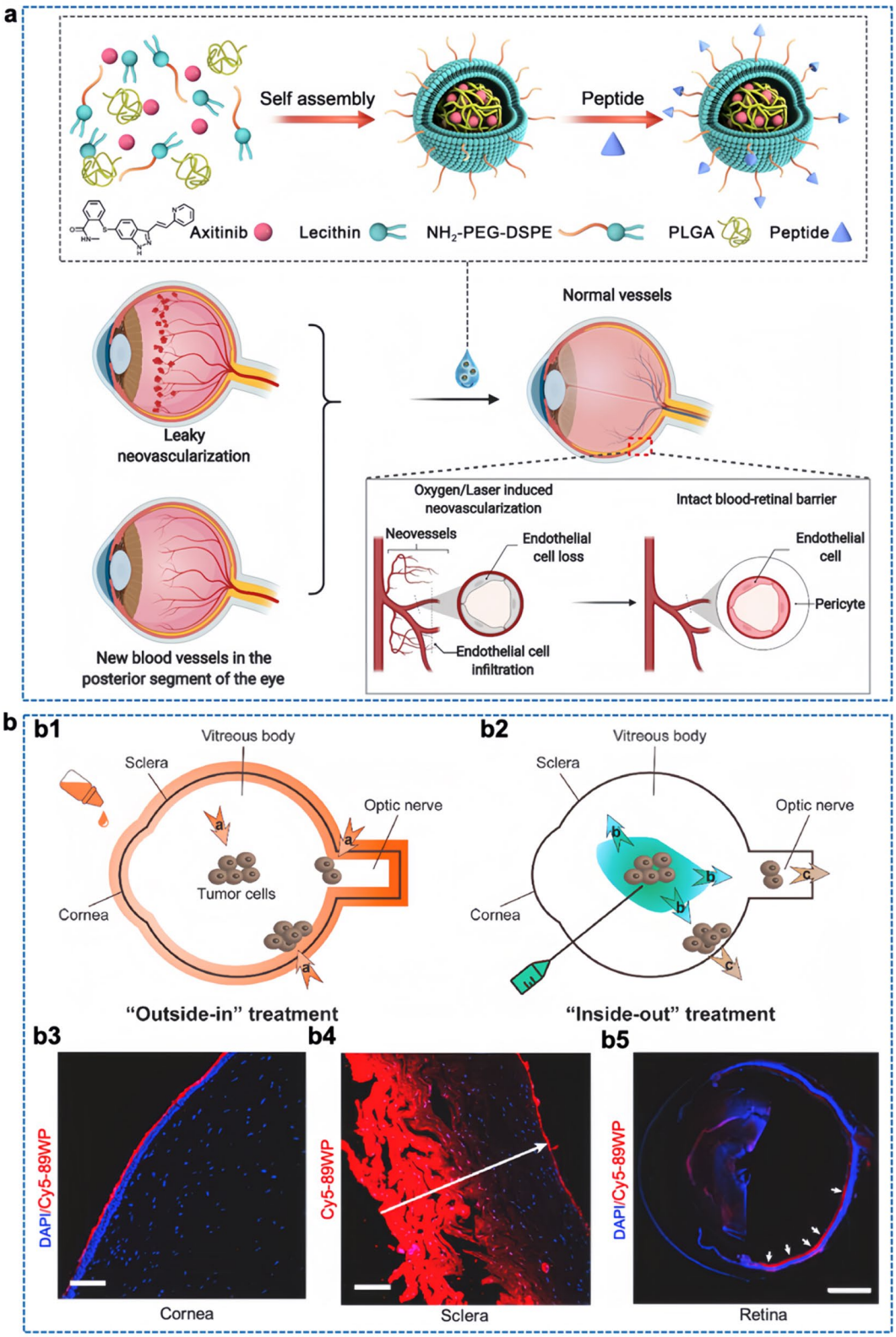

Fig. 3 (See legend on previous page.)

Currently, amphipathic and cationic penetratin are the best-known penetration enhancers for topical instillation. For the first time, 89WP conjugated with chemotherapeutic melphala (Mel) was used to formulate 89WP-Mel eye drops to improve the efficiency of intraocular drug delivery in a retinoblastoma-bearing mouse model. Upon electrostatic interactions between the anionic mucin on the ocular surface and cationic 89WP, the 89WP-engaged conjugate adhered to the ocular surface and markedly improved drug permeation into the retina. Notably, improved absorption of the instilled 89WP-Mel in the posterior segment formed a protective shield surrounding the ocular tissues, preventing extraocular tumor metastases. Importantly, enhanced retinal bioavailability of hydrophilic 89WP-Mel and other hydrophilic or hydrophobic small molecules was achieved through the conjunctival sac route, accompanied by increased residence duration in the retina (up to 24 h) and negligible cytotoxicity. This penetratin derivative-conjugation strategy paved the way for simultaneous tumor suppression and the prevention of extraocular metastases (Fig. 3b) [64].

Drug delivery vehicles can also be combined with multifunctional peptides possessing different pharmacological properties upon integration with drugs or drug-encapsulated cargo. Theoretically, the synthesis of multifunctional peptides based on a single sequence is challenging. Direct fusion of monofunctional peptides may increase peptide length and compromise the targeted properties of each component. Using machine learning, Hsueh et al. engineered multifunctional short peptide sequences with high biocompatibility, high cell penetration, and optimal melanin binding, prolonging the duration of peptide-drug conjugates for sustained drug release in the posterior ocular segment. The short CPPs allowed melanin conjugation to drugs, and a sustained drug system was synthesized without the need for a polymer matrix [65]. Sustained therapeutic sunitinib concentrations were detected after topical application of eye drops of a peptide-drug conjugate in a hypotonic gel (HR97-SunitiGel), thus effectively protecting RGCs in a rat model of optic nerve injury [66, 67]. This technology may benefit patients with retinal diseases, especially glaucoma. [67]

More than 80 peptide drugs have achieved Food and Drug Administration (FDA) approval, and more than 600 are in preclinical and clinical trials [68]. In the future, if CPP-based eye drops progress to clinical practice, they may be an alternative for improving patient adherence to the treatment of chronic retinal diseases. However, a facile and universal technology for peptide industrialization remains an unmet need, and there are continuous endeavors to optimize more applicable strategies.

Synthetic organic nanomaterial-based eye drops

Synthetic nanomaterials have been investigated to overcome the drawbacks of natural materials [69]. Currently, the most common and appealing components of synthetic organic biomaterials for the development of retinal-targeted eye drops include polyester nanoparticles, e.g., poly(lactic-co-glycolic acid) (PLGA); polymeric nanomicelles [70], dendrimer (Fig. 4a) [71], nanoemulsions, cyclodextrin [35], and lipid nanoparticles (LNPs) [70, 71].

Polyester nanomaterial-based eye drops

Polyester nanomaterials, mainly including PLGA, poly (ε-caprolactone) (PCL) and polylactic acid (PLA), are biocompatible and biodegradable in the human physiological milieu and have environmentally friendly attributes. As drug nanocarriers, polymeric polyesters possess several promising features, such as improved solubility of hydrophobic drugs and increased drug bioavailability and half-life [72]. An increasing number of studies have shown that polyester-based eye drops ranging from individual nanoparticles to block copolymers have a significant impact on retinal drug delivery [73]. However, PCL has many shortcomings, including hydrophobicity, poor bioactivity, and inadequate cellular recognition sites, whereas PLA is rapidly degraded by hydrolysis. These aspects hinder the further applications of PCL and PLA.

Among the different types of polyesters, anionic PLGA has received FDA approval. The supramolecular structure of the versatile PLGA enables sustained drug release

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Fig. 4 Representative synthetic organic nanomaterial-based eye drops for noninvasive retinal drug delivery. **a** This hierarchical strategy of nano-in-nano dendrimer gel particles maximized the structural features of dendrimer, hydrogel, and particles, which efficiently delivered two first-line antiglaucoma drugs to decrease IOP in rodent with glaucoma. Reproduced with permission [71]. Copyright 2021. The Authors. Published by Elsevier B.V. **b** Nanoemulsion-based eye drops (i.e., LA@VNE later) encapsulated with lα-tocopherol (a potent antioxidant) and latanoprost (an IOP-lowering drug) prolonged drug ocular retention and improved retinal permeability. After topical instillation, effective glaucoma treatment was achieved by reducing ROS accumulation, RGC apoptosis, and inflammatory cell infiltration. Reproduced with permission [90]. Copyright 2023, Elsevier B.V. **c** Penetratin and HA dual-modified liposomes (PenHA-Lip) effectively penetrated the ocular barrier and non-invasively delivered anti-VEGF drugs (conbercept) to the targeted retinal pigment epithelium (RPE) for the treatment of CNV mouse model. Produced under an open access Creative Common CC BY license [100]. Copyright 2024. The Authors. Published by Dove Medical Press Ltd

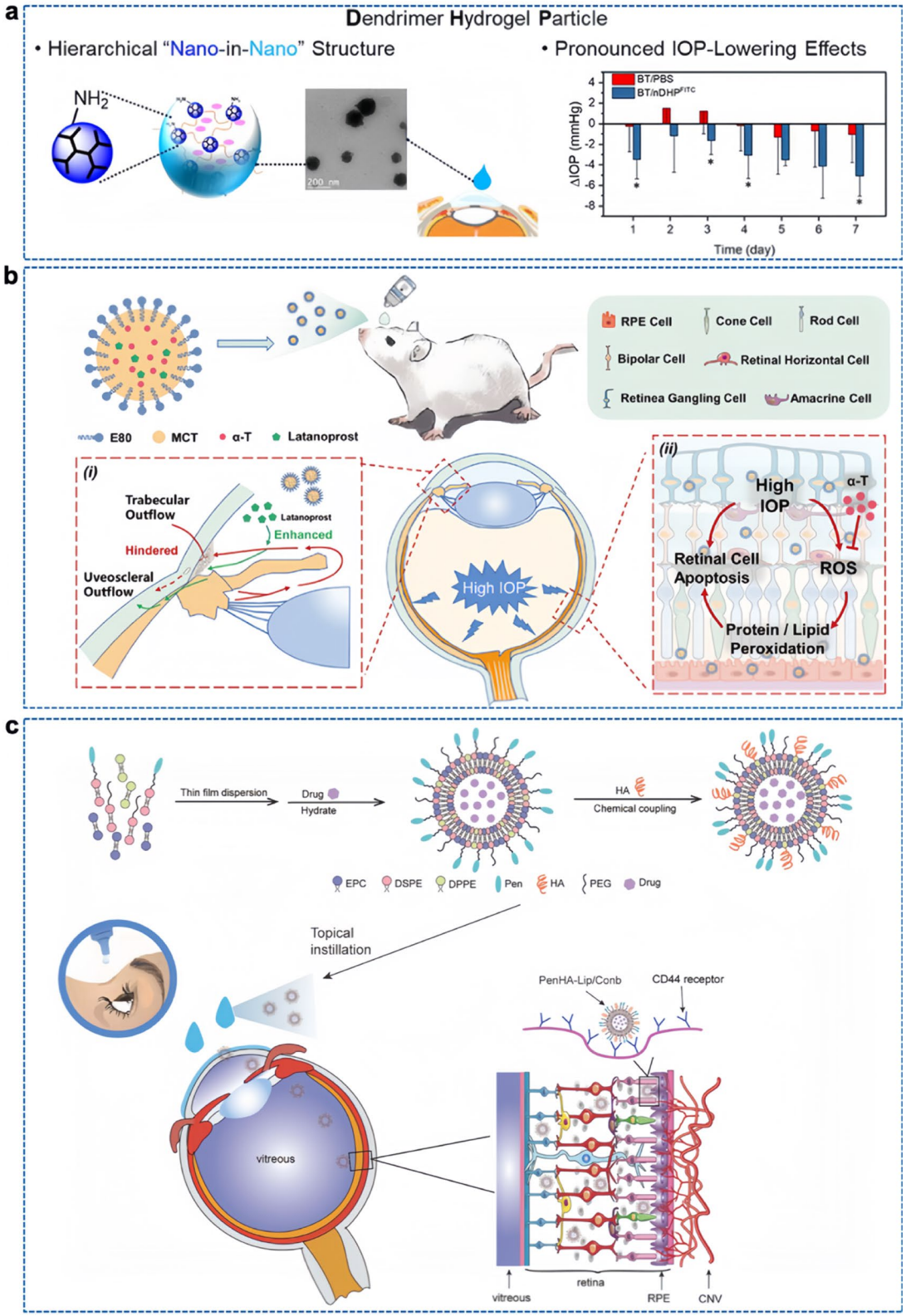


Fig. 4 (See legend on previous page.)

for the treatment of chronic retinal diseases, making it the most frequently applied eye-drop-based vehicle for the delivery of insoluble drugs and many macromolecules [74]. For instance, based on solvent displacement, PLGA nanoparticles effectively entrap the poorly water-soluble Riluzole (RLZ, a neuroprotective drug). The terminal carboxyl groups of PLGA cause RLZ to have a negative charge, which prevents the potential aggregation of RLZ. Thus, RLZ is uniformly dispersed and is suitable for PLGA. Following instillation, the long-term biosafety and biodistribution of fluorescently labeled nanoparticles in the fundus have been observed [75]. To serve as a drug vehicle, PLGA may also be used for the surface modification of various nanomaterials, such as nanorods and nanospheres, during the synthesis of eye drops. Surface modifications with PLGA have been well documented to help particles escape phagocytosis and have revealed high entrapment efficiency of the substance. Compared with traditional marketed eye drops, the developed nanocarrier-based eye drops demonstrated superior efficacy in retinal protection upon instillation [76]. For the long-term treatment of retinal-related diseases, a drug-dosage-controllable delivery nanosystem was developed using light-activated liposomes and a nanoporous biodegradable PLGA capsule. Upon near-infrared (NIR) irradiation, an on-demand drug-dosage-controllable profile and clinically relevant drug dosages were observed in the retina and choroid [77].

Although significant progress has been made in biodegradable polyester-based eye drops, clinical trials are still lacking. A clinical trial at Allergan Plc (Dublin, Ireland) was initiated using a rod-shaped biodegradable PLGA-polymer-based implant for the delivery of bimatoprost to treat glaucoma. The platform system contained a 10-μg dose of bimatoprost, and allowed long-term, non-pulsatile, consistent drug release in patients with glaucoma, overcoming adherence issues [65]. Although intraocular bimatoprost achieved a target duration of 3–4 months, the efficacy of the implant was not observed over a much longer period [78, 79]. In addition, the degradation of polyester nanoparticles generates some acidic products (e.g., lactic acid), which may cause inflammatory-response-associated retinal cell death [33]. PLGA faces other problems, such as non-uniform nanoparticle sizes, low efficiency of drug encapsulation, initial burst release, complicated fabrication, and a high cost of mass production, which pose challenges in clinical practice and should be addressed in future studies [80].

Nanomicelle-based eye drops

Nanomicelles are thermodynamically stable colloidal solutions formed by the self-assembly of hydrophobic cores and hydrophilic corona block copolymers in an aqueous environment. This attractive property facilitates improvement in the solubility of hydrophobic medicines [81]. Indeed, hydrophobic drugs can be encapsulated in the micellar core through a simple reaction procedure, that is physical entrapment, rather than chemical conjugation. The ability of polymeric nanomicelles to precisely discharge drugs with tailored size, molecular weight, and chemical composition provides additional advantages for drug delivery. For instance, artemisinin, which has poor solubility, can be encapsulated into nanomicelles with an average diameter of 41–51 nm by adjusting the concentrations of poloxamer 407 and polyvinylpyrrolidone k90 at varying ratios. Enhanced release and permeation of artemisinin from the nanomicelles were observed in excised rabbit eye corneas. Compared with the artemisinin suspension, the formulated artemisinin-loaded nanomicelles with clear aqueous solutions showed remarkable anti-angiogenic activities and avoided interference with vision [70]. Excellent mucoadhesiveness is another attractive property of polymeric micelles. With the assistance of bioadhesive features, polymeric micelles significantly extend the retention period on the ocular surface and allow the slow release of substances, thus preventing rapid elimination via tears and blinking. Polymeric micelles promote therapeutic efficacy by enhancing drug stability [82].

In addition to serving as vehicles, self-assembled polymeric nanomicelles have been shown to bypass efflux pumps and the reticuloendothelial system, thereby increasing the bioavailability of agents. Self-aggregating nanomicelles were prepared using a blend of polymers, polyoxyethylene-hydrogenated castor oil 40, and octoxynol 40, which were effectively internalized into cells. Topical administration of antiviral-prodrug-loaded nanomicelles significantly increased the transportation and subsequent cellular uptake of the prodrug [83]. Evasion by efflux transporters and mononuclear phagocytic systems renders polymeric nanomicelles superior to other nanocarriers. Recently, Zhao et al. reported a nanomicelle delivery platform derived from a copolymer EPC based on polyethylene glycol (PEG), poly (propylene glycol) (PPG), and PCL segments. Aflibercept-loaded nanomicelles allowed noninvasive penetration of the cornea-sclera and delivery of a therapeutic concentration of aflibercept into the diseased retina in a murine model of CNV. This nanomicelle showed inherent antiangiogenic properties, synergistically contributing to CNV regression. The fabricated dual-function nanomicelles are promising candidates for topical administration in retinal disorders [84].

Overall, the reverse, highly stable, and water-soluble characteristics of the unimolecular nanomicelles enable effective drug delivery to the targeted retinal tissues.

However, frequent dosing into ocular tissues may occur because of slow drug release from polymeric nanoformulations over a long period, which may harm the ocular tissues or trigger immune responses.

Nanoemulsion-based eye drops

Nanoemulsions (NEs) are liquid-in-liquid colloidal dispersive systems with nanosized droplets (10–200 nm). Compared to classical nanomicelles, lipid NEs have some merits, such as a transparent appearance, thermodynamic stability, decreased dose-associated side effects, reduced frequency of application, and ease of production. These attractive features make NEs a promising formulation option for retinal drug delivery, particularly for poorly water-soluble compounds. To evaluate the efficiency of NE-based carriers, Su et al. developed an NE-formulated, doped hydrogel for the co-delivery of drugs to the fundus. Consequently, the deep penetration into the retina lasted for 21 days after a single administration. Sustainable retinal drug release substantially reduced CNV and mitigated oxidative-stress-induced damage in a wet AMD model. The findings revealed that the NE system has the potential for controllable drug release and deep tissue penetration with minimal side effects [85, 86].

Topical eye drops of NEs are a convenient and simple approach for the effective treatment of retinal diseases with negligible immunogenicity. Indeed, through electrostatic interactions, cationic NEs can penetrate and remain on the anionic ocular surface for a long period, thus providing a suitable choice for non-invasive drug delivery into the posterior ocular segment and increasing drug bioavailability. For instance, Delgado-Tirado et al. used an NE system as eye drops for the non-invasive delivery of a lipophilic small-molecule RUNX1 inhibitor. Upon topical administration, a sufficient therapeutic dose within the vitreous cavity was detected, leading to inhibition of the progression of proliferative vitreoretinopathy in a novel rabbit model [87].

To further enhance the efficacy of drug delivery to the retina, an NE-based nanocarrier for hydrophobic fenofibrate delivery to the retina was formulated. Theoretically, it is difficult to use a fenofibrate formulation as a classic eye drop because of its low aqueous solubility. In contrast to the systemic route, eye drops resulted in significantly higher concentrations of fenofibrate in the vitreous humor and retina [88]. Importantly, the therapeutic potential of the delivered fenofibrate remains following a topical non-invasive approach, which significantly reduces retinal inflammation and vascular leakage in DR and wet AMD [89]. Similar to co-delivery NEs using invasive injection, Guo et al. designed a novel nanoemulsion for noninvasive co-delivery of α-tocopherol and latanoprost for glaucoma treatment. Through localized administration, prolonged ocular retention and improved retinal permeability of nanoemulsions were achieved, which enabled the sustained release of the encapsulated drugs. Additionally, α-tocopherol as a potent antioxidant effectively decreased ROS accumulation, inflammatory cell infiltration, and RGC apoptosis (Fig. 4b) [90]. The possible mechanism of drug delivery into the fundus through NEs as eye drops may be a noncorneal pathway, that is, by means of the sclera, which has higher permeability, a higher surface area, and easier accessibility.

Usually, the preparation of emulsions and drug delivery systems requires specialized high-cost equipment to monitor critical processes, such as the drug dissolution rate, intensity, and duration of drug mixing. In contrast, nanoemulsion-derived self-nanoemulsifying systems (SNEDDS) may be a simpler and more convenient strategy for improving the drug dissolution rate or affecting the permeability of the ocular surface barrier. Furthermore, Accordingly, Dehghani et al. developed TA-loaded SNEDDs to improve the bioavailability of lipophilic drugs and ocular delivery. Upon topical treatment of albino rabbit eyes for 2 weeks, the dosage was detected in different ocular tissues, including the cornea, sclera, retina, and optic nerve, with high biosafety [91].

Despite the efficient retinal drug delivery of NEs, clinical trials associated with retinal NE-based eye drops are currently lacking, and several clinical trials of NE eye drops for dry eye symptoms have been conducted [92, 93]. Therefore, more efforts are required to facilitate the translation of NE findings.

LNP-based eye drops

Three types of LNPs (with nanosizes ranging from 50 to 1,000 nm), namely, liposomes, solid LNPs (SLNs), and nanostructured lipid carriers (NLCs), have emerged as potential nanocarriers for noninvasive delivery of a wide range of drugs [94, 95]. Similar to cell membranes, liposomes are phospholipid vesicles composed of a circular bilayer structure to confine distinct aqueous sites. Liposomal technology can incorporate both water-soluble and water-insoluble compounds, thus facilitating the loading of a wide range of molecules, including proteins, peptides, RNA, DNA, and diagnostic agents [96, 97]. Hydrophilic cargoes can be introduced into the aquatic core, while lipophilic compounds are enclosed in the biocompatible lipid shell. Recently, liposome-based nanocomposite eye drops have emerged as carriers with the greatest potential to co-deliver ellagic acid (EA) and oxygen to the retina [98]. Within the nanocarrier, EA removed excess ROS to protect retinal cells against apoptosis, and suppressed retinal angiogenesis by blocking the VEGFR2 signaling pathway. Oxygen effectively ameliorated hypoxia and improved anti-neovascularization

efficacy in the diabetic retinal microenvironment. In a hypoxic cell model, eye drops significantly reversed retinal cell hypoxia and decreased VEGF expression levels. After eye dropping, the retinal vascular network and central thickness improved in a mouse model of DR [99]. Additionally, through a dual modification of penetratin and the retina-targeting ligand HA, the ophthalmic liposome eye drop effectively penetrated the ocular barrier through corneal and non-corneal pathways and safely delivered anti-VEGF therapeutic drugs to the targeted retinal sites. A single topical administration of liposomes had an effect equivalent to a single intravitreal injection of anti-VEGF drugs in a mouse model of CNV, providing a promising therapeutic option for neovascular retinal disease (Fig. 4c) [100].

Currently, a few cationic liposome-based nanocarriers have been designed for nonviral gene delivery to retinal tissues. Theoretically, positively charged liposomes can trap anionic genes via electrostatic interactions, thereby promoting intracellular gene delivery and preventing nuclease degradation in vivo. Liposomes with surface modifications improve intraocular delivery of biomacromolecules. For the non-invasive delivery of small interfering RNA (siRNA) to the retina, liposome-based eye drops were prepared and further optimized with a cytoplasm-responsive stearylated peptide. These multifunctional peptides exhibited a superior ability to improve the intracellular dynamics of siRNA, cell permeation, and complexation. By modifying the surface of liposomes with peptides, intracellular uptake was enhanced, regardless of the surface charge of the liposome. After instillation into rat eyes, the nanocarrier significantly enhanced the intraocular migration of siRNA into the retina [101].

SLNs (10–1,000 nm) derived from lipids are solid at either room temperature or in the body. They are characterized by good biodegradability, favorable biocompatibility, and low toxicity. These nanoparticles are spherical nanostructures characterized by a solid lipid-core matrix that can solubilize lipophilic substances. Thus, SLNs are attractive delivery systems for the effective encapsulation of water-soluble medicines and corrective dynamic medication. A critical advantage of SLNs is their restricted drug mobility, which extends the duration of drug release. In addition, the SLN matrix has an optimal osmotic pressure, refractive index, and viscosity, making it a potential candidate for the development of eye drops for the treatment of retinal diseases [102]. Following eye instillation, SLNs stream through the vitreous body, cross the inner limiting membrane, and ultimately reach the outer retinal layers [103]. However, because of their highly ordered crystalline structure, SLNs have disadvantages, such as low stability, insufficient loading capacity, and rapid drug expulsion during storage [104].

As the next generation of SLNs, NLCs are composed of liquid and solid lipids at ambient temperature. Because the mixture of liquid and solid phases produces a sufficient gap, NLCs present a less-structured crystalline arrangement, in contrast to SLNs. Furthermore, the increased available space results in improved drug-loading capacity, and a disordered structure decreases drug leakage, while improving stability. These attractive properties render the NLCs viable candidates for efficient retinal drug delivery. Topical administration of NLCs can prolong the corneal retention time, improve ocular penetration to obtain a sustained release profile, and minimize the dosing frequency of therapeutic drugs, thereby leading to an overall enhancement of bioavailability in the retina [105, 106].

Among the three types of LNPs, liposomes possess the longest tolerance for administration and perfect colloidal properties. Moreover, their relatively low release kinetics and high bioavailability make them the most commonly used FDA-approved nanocarriers. Early clinical studies showed that liposome-based eye drops efficiently transport TA and ranibizumab into the vitreous and retina of patients with DME and neovascular AMD, respectively [107, 108]. However, manufacturing-related cautions regarding liposomes, such as process controls, impurity profiling, and scale-up of batches, must be exercised prior to achieving regulatory approvals for clinical observations. Importantly, the instability of liposomes in physiological media should be noted, and this may be improved by multifarious preparation processes using additional materials.

Inorganic nanomaterial-based eye drops

At some circumstances, inorganic nanomaterials are chosen over organic nanoparticles thanks to their easy modification and precise alteration in terms of shape, size, surface area, and crystallinity [109]. Upon reasonable design, a diversity of inorganic nanomaterial-derived nanocarriers has been developed for non-invasive drug delivery into retinal lesions.

Some inorganic nanoparticles, including non-metallic (such as corbon dots and silicon oxide), and metallic nanoparticles (e.g., ceria, gold, silver, iron oxide metallic) have been widely studied in the retinal diseases. They possess unique biomedical bioactivities, special physic and chemical properties, including magnetic, electrochemical, thermodynamic and catalytic properties [110–112]. Magnetic nanomaterials facilitated loaded drug permeation through various ocular barriers without damage, meanwhile magnetic targeting assists drug release at retina. A pioneering work validated that the silicon oxide magnetic nanoparticles-based cargo could non-invasively deliver two drugs with anti-unfolded

protein response towards retina. Through topical administration, the delivered nanoparticles were tightly integrated with photoreceptors in vivo, broadening the therapeutic applications of magnetic nanoparticles [113].

Mesoporous nanoparticle-derived delivery systems have arisen enormous concentration on retinal drug delivery due to their controllable porosity, abundant active sites on the surface and large surface ratio. However, they typically present a high initial burst and inadequate drug loading performance. In order to improve drug encapsulation capability meanwhile decreasing burst release, ongoing efforts are needed paid to develop the mesoporous nanosystem with hollow architectures. To obtain customizable shell thicknesses and sustained drug release characteristics for pharmacological intervene of intraocular diseases, chitosan-functionalized hollow mesoporous ceria nanoparticles (CNPs) with tailorable shell thicknesses were synthesized. Following instillation, the chitosan-modified hollow mesoporous CNP-based eye drops effectively opened the tight junctions of corneal epithelium, and sustained delivery of therapeutic drug to targeted lesion sites for 7 days (Fig. 5a) [114]. To further develop long-life nanograde eye drops, the CNP-based eye drops with solvothermal-aid deposition and surface modification have been designed. The moderate shelled CNPs displayed desirable thickness (~20 nm) and thin (~10 nm), enabling regulation of drug release profiles and revealing the most sustained drug release profile (over a period of 10 days). In a rabbit model with glaucoma, a single instillation of the optimized CNP-based eye drops effectively restored the decreased thickness of outer nuclear layer to normal, and rescued the impaired photoreceptors (Fig. 5b) [115]. These studies highlighted a crucial role of nanostructural engineering in developing the long-acting nanograde eye drops for the pharmacological management of intraocular diseases.

In terms of a higher targeted drug distribution in retina and RPE cells, Laradji et al. designed HA-coated gold nanoparticle (in a small size at 15–20 nm)-based eye drops by an easy gold-thiol reaction. HA coating significantly improved cell internalization and biocompatibility of gold nanoparticles, allowing gold nanoparticles deliver larger cargo into targeted retinal cells [116]. The convenient surface functionalization and easy attachment of high-density surface ligands make inorganic nanomaterial an excellent candidate to deliver agents to targeted retinal sites. However, the biological toxicity and poor degradability remain awkward.

Nanomaterial-based retinal contrast agents

Early diagnosis and treatment of retinal diseases can save patients' vision and lives. OCT, OCTA, PAM, and MRI are the most widely used techniques for noninvasive retinal imaging. OCT is a non-contact optical imaging device for the cross-sectional imaging and reconstruction of deep tissues. OCT usually employs multiple scatterings of light reflection through endogenous scatters, such as mitochondria and cell nuclei, with micrometric resolution. OCTA is another retinal optical imaging technique that uses backscattered light in the target tissue. Advanced non-invasive PAM is a hybrid real-time imaging technology that integrates ultrasound detection and contrast agent-enhanced optical excitation. MRI is a non-invasive cellular imaging technique that enables the tracking and visualization of transplanted cells in host tissues and allows researchers to evaluate cell survival, migration, and functional integration. Many experimental studies and clinical practices have explored the sole utilization of imaging devices. Combining different imaging technologies, such as OCT/PAM, provides the complementary advantages of each device in a single examination. Through this combination, OCT can provide valuable functional and structural information, while PAM can provide comprehensive molecular details. Theranostic nanomedicine and nanotheranostics are cutting-edge strategies that integrate diagnostic and therapeutic approaches into one device and are emerging in the field of retinal disease treatment [117–119]. However, differentiating pathological retinal molecules, cells, and

(See figure on next page.)

Fig. 5 Representative inorganic nanomaterial-based eye drops for noninvasive retinal drug delivery. **a** Therapeutic hollow ceria nanoparticles (hCe NPs) by dual-functionalization of chitosan and ZM241385 were designed for intraocular delivery of antiglaucoma drug pilocarpine. Single topical instillation of the nanocarriers effectively opened corneal epithelial tight junctions and delivered drug to the targeted ciliary body. Meanwhile the nanocarriers possessed potent anti-inflammatory and anti-oxidant capabilities, leading to a simultaneous mitigation of glaucomatous damage for 7 days. Reproduced with permission [114]. Copyright 2020, Elsevier Ltd. **b** Hollow mesoporous ceria nanoparticles (CNPs) with tunable cavity enhanced intraocular delivery of Y-27632 (an anti-ocular hypertension drug). b1) Representative transmission electron microscopy (TEM) images of CNPs with a thickness of 10 nm and 20 nm. Scale bars: 20 nm. b2) Representative histological images of glaucomatous retinas in healthy (Pre), glaucomatous (GL), untreated (Ctrl), and treated Y/CNP20 nm. Compared with Pre group, the whole retinal thickness was reduced, and TUNEL positive nuclei were increased in the GL, which were reverted by the Y/CNP20 nm treatment, suggesting that Y/CNP20 nm prevented photoreceptor cell apoptosis and mitigated progressive glaucoma. Scale bars: 80 μm. Reproduced under an open access Creative Common CC BY license [115]. Copyright 2021. The Authors. Published by Dove Medical Press Ltd

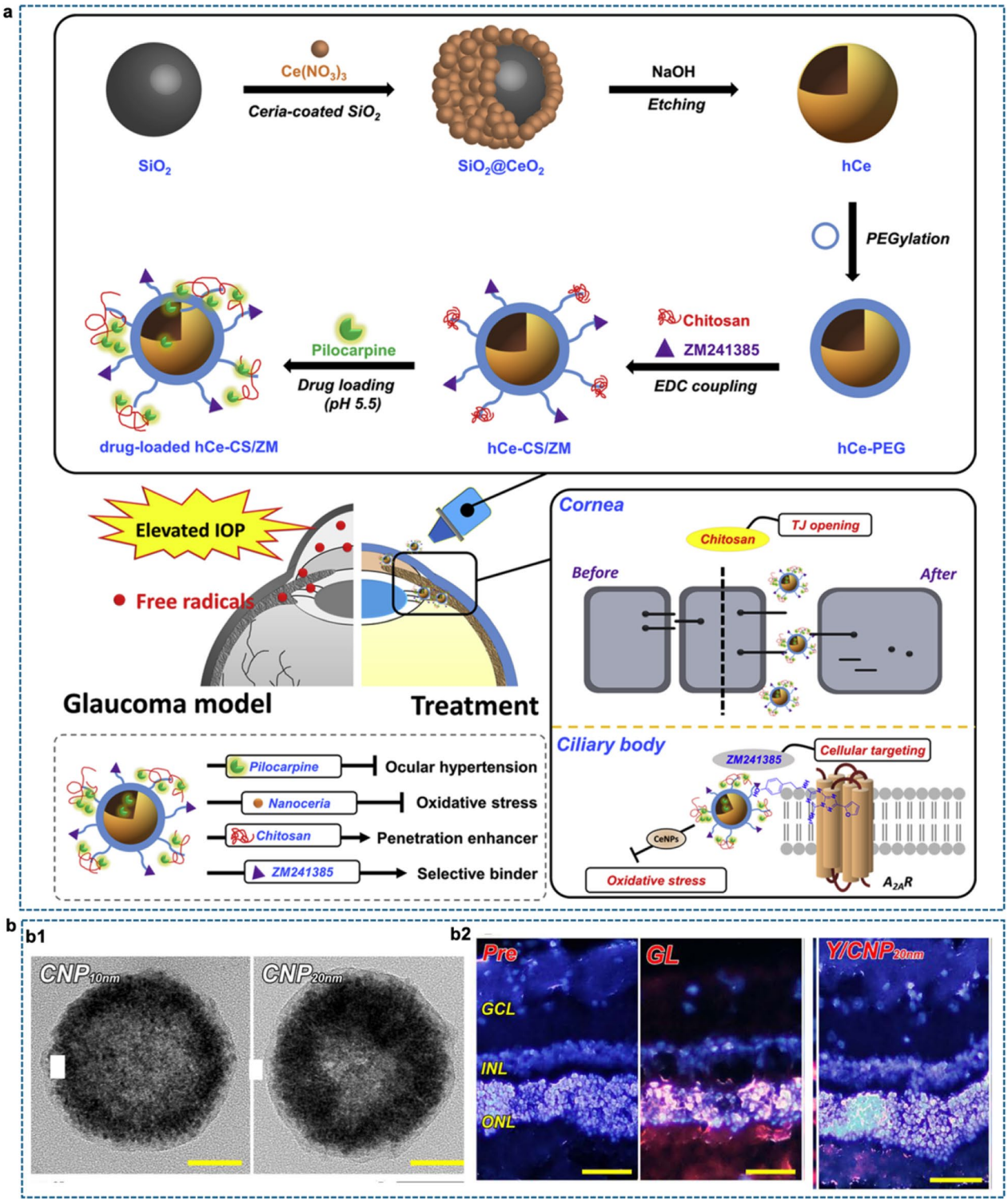


Fig. 5 (See legend on previous page.)

vessels from healthy tissues remains a major challenge for existing imaging technology. To obtain a higher spatial resolution and sensitivity, several types of nanomaterials, including metallic nanomaterials, especially gold and magnetic nanoparticles, and non-metallic nanomaterials, such as silica and carbon, have been proposed as

exogenous contrast agents. Accordingly, this section discusses various nanomaterial-based imaging and nanotheranostic agents with the assistance of molecular and cellular imaging tools for imaging, early diagnostics, and therapeutics of retinal diseases.

Metallic nanomaterial-based retinal contrast agents

To obtain highly accurate and sensitive imaging, several metallic nanomaterials such as gold, silver, magnetic nanoparticles, and upconversion nanoparticles (UCNPs) have been introduced as valuable contrast agents.

For example, silver sulfide nanoparticles (Ag_2S) as semiconductor materials allow for low-toxicity thermal sensing, remote heating, and in vivo NIR biological imaging. To achieve both OCT and NIR imaging, Coro et al. assembled Ag_2S nanoparticles with amphiphilic block copolymers, which exhibited extraordinary biocompatibility and colloidal stability over time. Biocompatible copolymers protect the photoluminescence properties of Ag_2S nanoparticles by offering an extra protective layer, instead of exchanging classical ligands that may create surface traps because of insufficient replacement of surface sites. Importantly, this process guarantees the controlled fabrication of submicrometric scattering centers. The introduced Ag_2S nanoparticle-based probe improved OCT contrast and NIR-II imaging [120]. In contrast, UCNPs are rare-earth-based actinide- or lanthanide-doped transition metals that sequentially absorb low-energy photons and emit high-energy photons. The bright upconversion luminescence of UCNPs can be used to accurately assess the severity and prognosis of retinal angiogenesis upon NIR irradiation [121].

Gold-based retinal contrast agents

Over the past two decades, significant advancements have been made in the development of gold nanomaterials as contrast agents for PAM and OCT imaging. Unlike traditional organic dyes, gold nanomaterials guarantee rich surface chemistry for versatile functionalization, easy synthesis, and scattering of up to five orders of magnitude. Notably, gold nanomaterials possess high size/shape-dependent optical absorption and photostability, as well as superb molar extinction coefficients. A series of gold nanomaterials with different morphologies and sizes has emerged as contrast agents for retinal imaging, including spherical gold nanoparticles (GNPs), colloidal GNPs, gold nanostars (GNSs), gold nanorods (GNRs), chain-like GNP clusters (GNCs), and gold nanobipyramids (GNBPs).

To image the small-molecule dopamine in the retina using surface-enhanced Raman scattering, the surfaces of the GNPs were modified with N-hydroxysuccinimide ester. The functionalized GNPs reacted specifically with dopamine. Dopamine elicited the aggregation of the designed GNPs to form plasmonic hot spots, which significantly increased the Raman signal of dopamine and facilitated retinal dopamine imaging. This technology platform can be expanded to visualize other key retinal biomolecules to understand the biochemical mechanisms involved in the progression of retinal diseases [122]. With the advent of stem cell transplantation in the retinal field, a non-invasive imaging approach to longitudinally track and label transplanted cells to monitor cell viability, integration, and function in the host is urgently needed. Following GNPs labelling of photoreceptor precursors, multimodal imaging approaches, including OCT, fluorescence fundus, and computed tomography, enabled high-resolution imaging and long-term tracking of transplanted photoreceptor precursors in rats for more than 1 month, emphasizing the applicability of GNPs for retinal cell labelling and monitoring in experimental settings [123]. However, these traditional spherical GNPs have several deficiencies, especially their complex leakage from vessels, accumulation in the liver and spleen, and overlapping absorption peaks in the visible window (approximately 520 nm) with that of hemoglobin.

To overcome these shortcomings, ultrapure GNSs, GNCs, and GNRs with red-shifted peaks in the NIR window (approximately 650 nm) were synthesized by altering the morphologies and sizes of the GNPs [124–126]. In particular, ultraminiature GNCs with an average width of 20 nm exhibit excellent photostability. By conjugating GNCs with arginine-glycine-aspartic acid (RGD) peptides in a quantitative control, these functionalized GNCs could combine with αvβ3 integrin expressed on activated endothelial cells of newly formed blood vessels, leading to an increased signal in PAM and OCT. Multimodal imaging precisely visualizes and monitors the targeting capabilities of nanoprobes in a clinically relevant CNV rat model (Fig. 6a) [127]. In addition, GNCs provide significant fluorescence signals for in vivo longitudinal tracking of RPE with high spatial resolution. Following the subretinal injection of RPE in rabbits, OCT and PAM selectively imaged the migration of GNC-marked ARPE-19 cells (RPE cell line) for 3 months. Accurate anatomical information was provided to visualize the exact retinal layer where the transplanted cells were present in complex in vivo retinal environments [128]. Although these GNCs can disassemble to GNPs with a smaller size, long-standing biosafety concerns remain. Refinement of the clearance of GNC with different shapes, sizes, and formulations is required prior to clinical translation. Similar to GNC, GNR-based contrast agents have contributed to signal improvement in PAM and OCT, as they have a high sensitivity of optical excitation to changes in hemodynamics [129]. Meanwhile, GNRs are restricted by poor

biocompatibility, potential biotoxicity during production, and rapid elimination from the body [130].

The dependence on nanoparticle motion dramatically limits labeling strategies and causes static detection of nanoparticles. However, the depolarization of oriented nanoparticles, such as GNRs, is difficult for multiplexed detection and lacks pronounced spectral dependence. To achieve specific detection and multiplexing of exogenous contrast agents in scattering tissue, Keahey et al. combined spectral measurements and depolarization of GNBPs using a polarization-sensitive OCT system. Polarization-sensitive OCT reveals the polarization state of backscattered light and the subsurface microstructure of biological tissues. By combining spectral contrast OCT and polarization-sensitive OCT devices, the location of various GNBPs in lymphatic vessels can be distinguished from those in retinal vessels and surrounding tissue in a living mouse model. This technique advances OCT vessel imaging, and can be used to detect various anisotropic nanoparticle-dependent OCT contrast agents [131].

Magnetic nanoparticle-based retinal contrast agents

Magnetic nanoparticles, particularly superparamagnetic iron oxide (SPIO) nanoparticles with outstanding magnetic properties, have proven to have great potential for diagnosis and therapy; that is, theranostics in retinal diseases. SPIO nanoparticles serving as multifunctional ferrofluids are highly stable in aqueous solutions and can be used as MRI-negative contrast agents by enhancing T2 imaging signals. Moreover, SPIO is capable of targeted aggregation upon the application of an external magnetic field. For example, SPIO nanoparticles have been used for targeted labeling of photoreceptor precursors derived from human embryonic stem cells. MRI successfully tracked the cell biodistribution of labeled photoreceptor precursors after subretinal transplantation in rat models, providing abundant information on cell viability and functional behavior [132]. The good targeting ability of SPIONs is not influenced by differences in specific receptor-antibody binding or the receptor expressed levels among individuals, resulting in high efficiency and low toxicity [133]. To target pathological angiogenesis, M1-polarized macrophage-secreted exosomes were induced using extremely small iron oxide nanoparticles (ESIONPs). Subsequently, macrophages were co-incubated with ESIONPs to form ESIONP-engineered exosomes (ESIONPs@EXOs). In vitro and in vivo results showed that ESIONPs@EXOs targeted and attenuated pathological angiogenesis by inducing ferroptosis and immunotherapeutic ability, while presenting an excellent T1-weighted contrast feature of MRI for retinal angiogenesis imaging. Generally, engineered ESIONPs@EXOs may be a feasible theranostic strategy for imaging and therapy of pathological retinal angiogenesis (Fig. 6b) [134].

RB is the most severe intraocular malignancy that commonly occurs in children and seriously threatens their survival and quality of life. Early-stage RB rarely affects visual function, but delays in diagnosis and treatment increase the likelihood of visual impairment, necessitating timely diagnostic imaging and intervention [135–137]. MRI is the most commonly recommended device for RB theranostics because it can precisely discern surrounding tissue infiltration and metastatic lesions with the assistance of functional nanomaterial-based contrast agents [138], such as SPIO nanoparticles, which can produce heat after exposure to an alternating magnetic field. Dextran-coated SPIO nanoparticles were prepared to selectively kill RB cells in a magnetic hyperthermia paradigm [139]. The core of SPIO nanoparticles comprises Fe_3O_4 nanoparticles, which are easily conjugated to different entities, including hydrophilic/hydrophobic drugs. Sadri et al. synthesized an Fe_3O_4 magnetic nanoparticle-based nanoplatform for the delivery of the anti-tumor drug vincristine by the functionalization of two ligands,

(See figure on next page.)

Fig. 6 Representative nanomaterial-based retinal contrast agents. **a** Ultraminiature chain-like gold nanoparticle (GNP) cluster (GNC)-assisted optic coherence tomography (OCT) and photoacoustic microscopy (PA) distinguished CNV. a1) Scheme of the physical characteristics of renal clearable GNP spheres with 7–8 nm diameter by pulsed laser ablation (PLA) approach. a2) RGD ligand-loaded GNCs combined ICG dyes to fabricate ICG-GNC-RGD. a3) Scheme of subretinal administration of VEGF followed by intravenous (IV) injection of ultraminiature GNC cluster to target CNV in rabbits. a4) Color fundus photos of CNV and indocyanine green angiography (IGCA) performed at early (a5), middle (a6), and late (a7) stage before injection of GNC. The fluorescent images at early and middle stage exhibited the morphology of choroidal vessels, while CNV (white dotted circle) was detected in the late stage of ICGA. a8, a9) PAM images of CNV (indicated as white arrows) were obtained at 578 nm and 650 nm, respectively. Injection of GNC to target CNV in rabbits led the strong PA signals and achieved PAM images at 650 nm, allowing easy distinguishing CNV from the adjacent healthy retinal and choroidal vessels. Reproduced under an open access Creative Common CC BY license [127]. Copyright 2023. The Authors. Published by Wiley–VCH GmbH. **b** Macrophage-derived exosomes engineered by extremely small iron oxide nanoparticle (ESIONPs) for targeted treatment of pathological angiogenesis. Scheme of cell bioreactor aided exosome modification and exosome-incorporated ESIONP (ESIONPs@EXO) fabrication. The ESIONPs@EXO demonstrated targeted pathological angiogenesis, magnetic imaging, immunotherapy and ferroptosis. Reproduced under an open access Creative Common CC BY license [134]. Copyright 2024, American Chemical Society

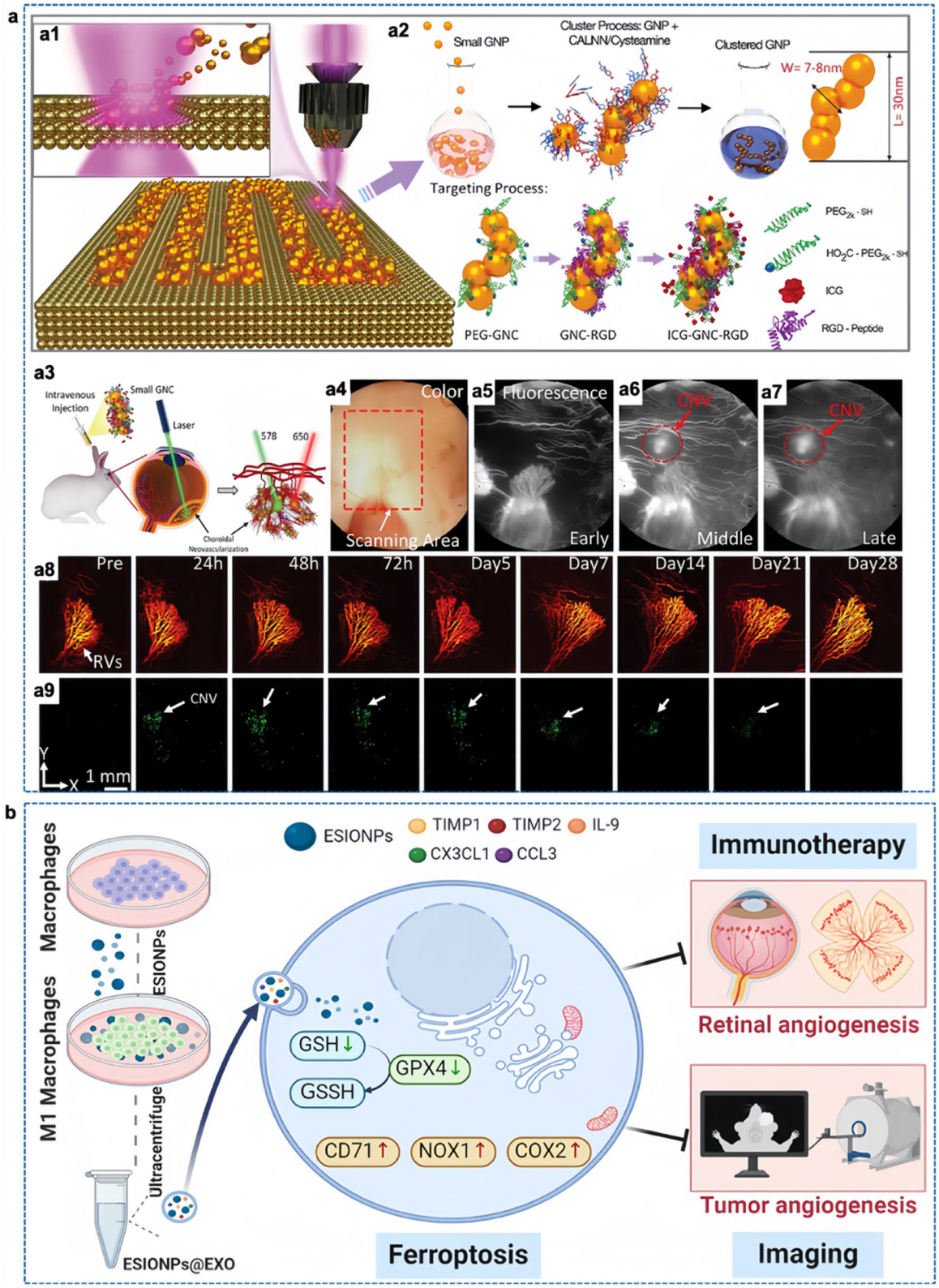


Fig. 6 (See legend on previous page.)

transferrin and folic acid. These nanoparticles showed a high absorption peak upon exposure to an alternating magnetic field and conferred greater toxicity to RB cells [140].

Conventional therapeutics for RB, such as surgery, usually lead to aesthetic deformities, severe pain, potential complications, and recurrence. The major shortcomings of chemotherapy include low bioavailability and potential side effects. Emerging minimally invasive therapies involve the integration of various therapeutic modalities, such as photothermal therapy (PTT), immunotherapy, photodynamic treatment (PDT), ultrasound-enhanced treatment, and chemotherapy, which may be a translational strategy to maximize their therapeutic effects in RB, uveal melanoma, and AMD [141–144]. PTT is an attractive treatment that depends on photothermal nanoparticles to transform light energy into heat to damage targeted cells, whereas immunotherapy is a method involving activation of the immune system to change the cellular microenvironment to rapidly kill cells. To obtain a more real-time, accurate, and comprehensive image of RB, a combination of SPIO nanoparticle-based MRI with ultrasound (US) imaging and PAM has been proposed. For instance, the conjugation of magnetic hollow mesoporous gold nanocages with Fe_3O_4 nanoparticles has been used to encapsulate immune polypeptides, such as perfluoropentane and muramyl dipeptide. because of their inherent hollow mesoporous structure, gold nanocages improve low-intensity focused US (LIFU) treatment through acoustic absorption. Muramyl dipeptides enhance the activation of dendritic cells and promote their ability to identify and kill tumor cells. Perfluoropentane not only serves as a contrast agent for US, but also as a synergistic factor to enhance LIFU therapy. These nanoparticles are sensitive to the release of perfluoropentane and muramyl dipeptide under LIFU triggers, improving the synergistic antitumor effect via LIFU/immune therapy and simultaneously reducing tumor recurrence. Overall, the multifunctional Fe_3O_4 magnetic nanoparticle-based nanoplatform improved MRI/PAM/US imaging and LIFU/immune therapy both in vivo and in vitro, facilitating the biosafety of RB theranostics [145]. However, the inability to improve cellular active uptake and abundant accumulation of SPIO nanoparticles is a limitation of the single magnetic target, but this can be compensated by the superb targeting of modification substances, such as folate and cationic cholesterol. Superparamagnetic/folate dual-target theranostic cationic nanoliposomes can encapsulate perfluorohexane and indocyanine green for synergistic therapy of RB upon PTT/PDT guided by combinational multimodal MRI/PAM/US imaging, resulting in almost complete tumor regression [146].

Although various ingenious nanomedicines provide options for the efficient diagnosis and treatment of tumors, they often involve complicated preparation processes, premature drug leakage, and potential toxicity because of rigid encapsulation or covalent conjugation [147].

Non-metallic nanomaterial-based retinal contrast agents

Silica-based nanomaterials possessing large porosities, tunable and uniform pore sizes, and controllable biodegradability in biological media have attracted considerable attention in the field of retinal disease for use in drug delivery, biosensing, and theranostic applications [148]. For example, mesoporous silica nanoparticles (MSNs) made have pores in the 2–50 nm range and a high surface area, endowing them with unique physicochemical features. By tailoring pore sizes, volumes, and surface areas, MSNs of diverse sizes and shapes have been developed, including nanoribbons, nanozigzags, nanohelices, and nanotubes. In addition, MSNs are easy to functionalize, making them perfect candidates as surface hosts for various metals. In parallel with advanced metallic materials, vanadium also demonstrates intrinsic optoelectronic and thermal properties that serve as an electron-conducting tunnel. Optimized synthetic vanadium/silica hybrid-assisted laser desorption/ionization mass spectrometry (LDI MS) was developed for the precise diagnosis and progression monitoring of DR. Vanadium core–shell nanorods were constructed using mesoporous silica nanorods to support vanadium oxide on the surface for metabolic detection by LDI MS, and plasma metabolic fingerprints were extracted with improved LDI efficacy. Consequently, global metabolic changes in the DR plasma were monitored to facilitate the successful diagnosis of DR in healthy individuals. A panel of metabolic signatures was identified to evaluate the progression of DR. This strategy will shed light on the advancement of tailored materials for noninvasive and real-time metabolic detection, providing novel tools for personalized medicine [149]. In contrast to other nanomaterials, it is difficult to optimize the performance of Si nanomaterials as powerful contrast agents by controlling their shapes and sizes. Accordingly, the investigation of a synthetic strategy is important for developing silica-based nanomaterials with precisely tunable dimensional control in the NIR biological imaging window. Recently, Ki et al. synthesized visualization materials containing biodegradable silicon-derived optical nanodisks to evaluate blood vessels in the retina. The contrast probe imaged blood vessels in vivo in a retinal phantom by mimicking retinal blood vessels [150].

Overall, these findings emphasize the applicability of engineered nanoparticles as contrast agents for labeling,

detecting, tracking, and imaging molecules, cells, and blood vessels in the retina, and ultimately for the noninvasive therapy of retinal diseases. However, these material-dependent theranostic nanoplatforms face several challenges, particularly in terms of long-term biosafety, drug resistance and random drug release, thermodynamic instability, and difficulty in interactions with biomolecules and biological processes, such as gene and protein expression, which need to be addressed prior to their clinical translation [151].

Nanomaterial-based retinal therapeutic agents

The nanomaterials discussed in the "eye drops" section is used as drug delivery systems, but exert no therapeutic effects themselves. In contrast, this section focuses on the inherent active ingredients of nanomaterials as therapeutic substances, but not as drug nanocarriers. Some nanomaterials, especially inorganic nanoparticles possess direct therapeutic capabilities specific to retinal pathological disorders, including oxidative stress, inflammation, neovascularization, ischemia, infections, and tumors.[152] However, these disorders do not exert effects individually; instead, they affect each other and interact during disease progression. For example, oxidative stress is the primary trigger for neovascularization by upregulating VEGF expression in CNV, and inflammation inevitably occurs in oxidative-stress-related retinal diseases [153]. These nanomaterials predominantly include inorganic metallic nanoparticles (particularly nanoceria, gold, silver, and platinum), inorganic nonmetallic nanomaterials (e.g., silica and biomimetic nanoparticles), and organic nanomaterials.

Inorganic nanomaterial-based retinal therapeutic agents

Reformulating inorganic nanomaterials to target retinal pathological molecules, include nanoceria wafers, graphene QDs, antibody-conjugated gold nanoparticles, and platinum nanozymes. These pathological molecules consist of ROS, hypoxia, inflammatory factors, mitochondrial O_2•-, and VEGF [154–159].

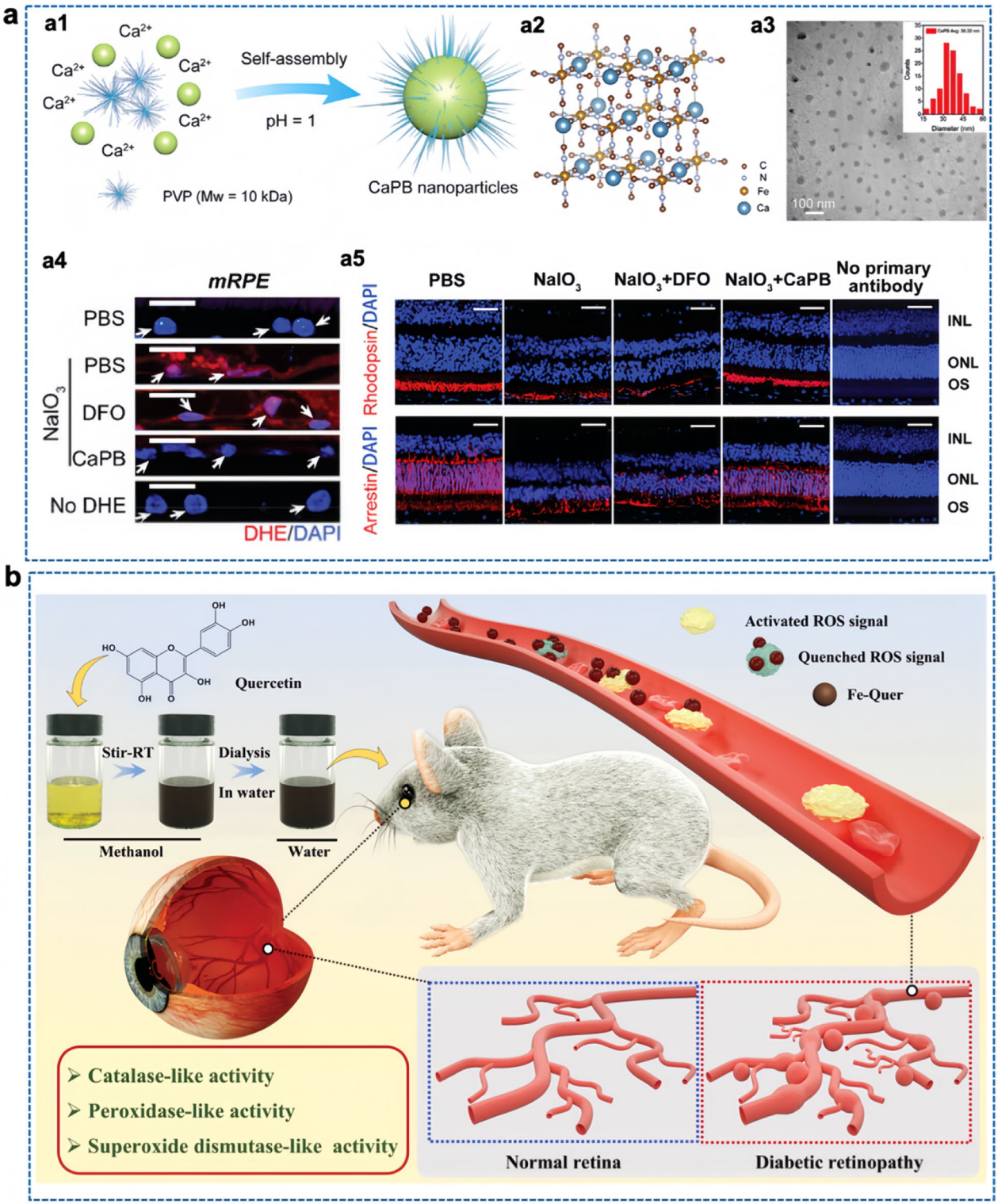
Nanoceria, a rare-earth nanoparticle, is a powerful antioxidant that supports retinal structure and normal function by inhibiting noxious oxidative stress. For example, Sudipta Seal et al. proved that nanoceria significantly alleviated iron-induced ROS generation and supported RPE cell viability in vitro [160]. To further investigated the in vivo effects of nanoceria, Rita Maccarone et al. intravitreally injected nanoceria into the acute light damage-treated rat model that mimics AMD features. The nanoceria distributed in RPE cytoplasm, and protected RPE from death and degeneration. In terms of mechanism, nanoceria affected autophagy by downregulating key protein expression levels of autophagy-related makers. These results reveled that nanoceria represents an eligible candidate to delay RPE degeneration in AMD. [161] Despite their promise, the elimination of nanoceria and potential biosafety concerns limit their clinical applications.

Overloaded ferrous ions play an important role in ROS accumulation and are involved in RPE degeneration. With the goal of effectively chelating ferrous ions, our team rationally designed a nanoscale calcium-ion-based prussian blue analog (CaPB). The easily fabricated CaPB with spherical particle diameter of 30 nm displayed potent iron binding and high biocompatibility. In a mouse model of AMD, a single intravitreal injection of CaPB significantly prevented RPE death and subsequent photoreceptor degeneration, ultimately providing superior rescue of retinal structures and visual function (Fig. 7a) [162].

Nanozymes (NZs) are catalytic nanoparticles that mimic the bioactivity of natural antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and peroxidase (POD) [144]. Relative to their natural counterparts, NZs have several merits, including durability, superior stability, cost-effective scale-up manufacturing, and ease of synthesis, making them a preventive or curative strategy for a series of retinal diseases. Gold-, iron-, and platinum-based NZs have attracted significant interest from ophthalmologists for the treatment of various retinal diseases, particularly retinal vasculopathies, DR, and AMD [163–166]. For example, Gui et al. rationally designed ultrasmall Fe-Quer NZs by coupling quercetin with metal iron ions for vascular protection. Because of

(See figure on next page.)

Fig. 7 Representative inorganic nanomaterial-based therapeutic nanoagents. **a** Prussian blue analogue nanoparticles (CaPB) protected against retinal degeneration. a1) Scheme of the synthesis of CaPB. a2) Scheme of Ca^{2+}-substituted prussian blue framework. a3) TEM image and nano-size of CaPB (insert). a4) DHE staining showed that CaPB decreased ROS in oxidative stress-induced RPE. Scale bars, 20 μm. a5) The CaPB rescued the protein expression levels of photoreceptor markers Arrestin and Rhodopsin by IF staining. Scale bars, 50 μm. Reproduced under an open access Creative Common CC BY license [162]. Copyright 2021, Wiley-VCH GmbH. **b** Schematic illustration of coordination polymer nanodots Fe-Quer nanozymes (NZs) to prevent and impede the progression of diabetic retinopathy (DR). The synthetization of ultrasmall Fe-Quer NZs. Fe-Quer NZs possessed excellent water dispersibility and multifunctional nanoenzyme properties, e.g., catalase (CAT), peroxidase (POD), and superoxide dismutase (SOD), for efficient reactive oxygen species (ROS) scavenging, anti-microangioma, anti-microvascular leakage, and antiangiogenic capabilities in DR mouse model. Reproduced under an open access Creative Common CC BY license [164]. Copyright 2023, Wiley



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the low toxicity of ions and natural products with artificial NZ activity, Fe-SANzyme significantly scavenged ROS, eliminated oxidative stress, and inhibited inflammation and microvascular leakage, thereby alleviating pathological angiogenesis with high biosafety in DR (Fig. 7b) [164].

More recently, biocompatible platinum-based nanoparticles (PtNPs) have been shown to be potent NZs with high ROS-scavenging activity without specially prepared ligands, demonstrating great potential for the treatment of retinal diseases [167–169]. Cupini et al. first demonstrated that the intravitreal injection of PtNPs in a rat model of AMD effectively ameliorated the inflammatory response and mitigated photooxidative retinal damage. Ultimately, retinal morphology and function, including the number of photoreceptors, ERG activity, and RGC responses, were preserved. These results suggest that PtNP disrupts the vicious cycle of inflammation, ROS generation, and degeneration with higher efficacy [170]. Although NZs attempt to mimic the catalytic function of natural enzymes, their structure and composition are different from those of natural enzymes, which leads to lower catalytic efficiency and specificity. Currently, the research and applications of NZs mainly focus on oxidoreductase and hydrolase, largely limiting their application range and affecting their ability to handle complex biomolecular reactions. Additionally, insufficient recycling and reuse of NZs remain during the design and manufacturing process. These problems should be taken into consideration in practical applications to decrease cost and complexity.

Organic nanomaterial-based retinal therapeutic agents

Organic radical scavengers, especially natural products, such as melanin, nanovesicles, and cell membrane-derived nanoagents, are superior for retinal protection against oxidative stress [171, 172].

Nanovesicle-based retinal therapeutic agents

Nanovesicles are nanometer-sized extracellular vesicles (EVs) with lipid bilayer structures. Compared to synthetic nanocarriers, such as liposomes, EVs are naturally biomimetic nanomaterials secreted by almost all cell types, making them safer, nontoxic, less immunogenic, more precise, and more inherently stable in vivo. Additionally, EVs can rapidly diffuse throughout ocular tissues by overcoming natural barriers, such as the blood-retina barrier, and they have been detected in tears, the aqueous humor, the vitreous body, and the retina [173]. According to their size and biogenesis, EVs are classified into exosomes (40–100 nm), microvesicles (100–1,000 nm), and apoptotic bodies (500 nm–2 μm); however, the exact sizes vary greatly among studies [174].

Although exosomes are the smallest secretory EVs with a relatively uniform nanoscale size, they consist of various substances, such as lipids, cytosolic proteins, cytokines, and RNA. These therapeutic substances are retained and are not altered by the pathological microenvironment, suggesting their great therapeutic value in a variety of retinal diseases, such as AMD, DR, retinal ischemia, and optic nerve crush. [175, 176] Exosomes released from different cells have various biological effects. In particular, the therapeutic potential of mesenchymal stem cell (MSC)-derived exosomes have received considerable attention [177]. Intravitreal injection of engineered MSC-derived exosomes significantly ameliorated retinal inflammation, apoptosis, and angiogenesis in a mouse model of DR and AMD, ultimately leading to the protection of photoreceptors and retinal function [178]. Mechanistically, MSC exosomes exert anti-oxidative pharmacological activities mainly by downregulating hypoxia-inducible factor-1α (HIF-1α) [179].

Similarly, ADSC-secreted exosomes are endowed with easy access to target cells, a low probability of abnormal growth, and low immunogenicity. Intravitreal injection of ADSC-EXOs markedly mitigated glutamate-induced damage to retinal morphology and function [180]. The intravitreal injection of engineered exosomes from regulatory T cells in conjunction with an anti-VEGF antibody substantially suppressed CNV in mouse and non-human primate models [181]. Recently, Yin et al. found that retinal-organoid-derived human retinal stem cells effectively secrete exosomes and subsequently transfer them into Müller cells to regulate stem cell and glial cell fate. Subretinal transplantation of these exosomes decreased gliosis, improved early dedifferentiation of Müller cells in rats with RCS, and delayed photoreceptor degeneration for retinal neuroprotection and development [182]. These results reveal the inherent advantages of exosomes, including good intercellular communication and strong cell or tissue targeting. Additionally, exosomes can be encapsulated into degradable PLGA microcapsules with multi-cavity interiors. Intravitreal injection of these stable formulations sustainably released therapeutic exosomes for over 1 month in mice with retinal ischemia–reperfusion injury, resulting in sustainable rescue of retinal thickness and function (Fig. 8a) [183]. Because of the expansive cargo of exosomes, they possess multifactorial mechanisms of action. Characterization of their mechanisms of action, including the mRNA, miRNA, and proteins responsible for the myriad of therapeutic targets, is required in further studies.

The clinical application of EVs is promising, given their unique properties. Clinical trials of EVs for the treatment of retinal diseases are currently underway. A phase I study was conducted in China to investigate intravitreal

injection of human umbilical MSC (HUMSC)-derived EVs for healing large, refractory macular holes. This clinical trial is still underway, and preliminary results have already been published (NCT03437759). Intravitreal HUMSC-EV therapy was found to be safe in four patients, while an inflammatory reaction occurred in one patient, but a reduced dose avoided this risk [184]. More recently, a phase II/III study was performed in Turkey using HUMSC-EVs for the treatment of retinitis pigmentosa via injection into the subtenon space (NCT05413148). To determine the onset and progression of DR, a Chinese team plans to investigate differentially expressed exosomal miRNAs in serum samples from patients with or without DR, but recruiting has not yet occurred (NCT03264976). It is anticipated that more clinical trials will focus on the therapeutic potential of EVs, rather than on their monotonous role as biomarkers. However, despite the tremendous therapeutic potential of EVs, some challenges remain in the field, including poor recovery and purity, low extraction yields, low encapsulation efficiencies, and lack of standardized storage and preservation protocols that should be considered prior to introduction into clinical practice.

Other organic nanomaterial-based retinal therapeutic agents

Specifically, as a type of natural pigment, melanin is widely distributed in the human body, including the RPE in the retina. Melanin is a well-known radical scavenger and thus, provides retinal protection. However, melanin cannot be constantly synthesized in the RPE, and its radical scavenging and photoprotective efficacy decline with increasing age. A recent study reported the fabrication of therapeutic PEGylated synthetic melanin-like nanoparticles fabricated to enhance the antioxidative and photoprotective effects of melanin. Of note, a single-dose intravitreal injection of nanoparticles led to long-term nanoparticle accumulation in the RPE for at least 3 months. Further results showed that melanin-like nanoparticles substituted for natural melanin in the RPE and effectively scavenged radicals (Fig. 8b) [185].

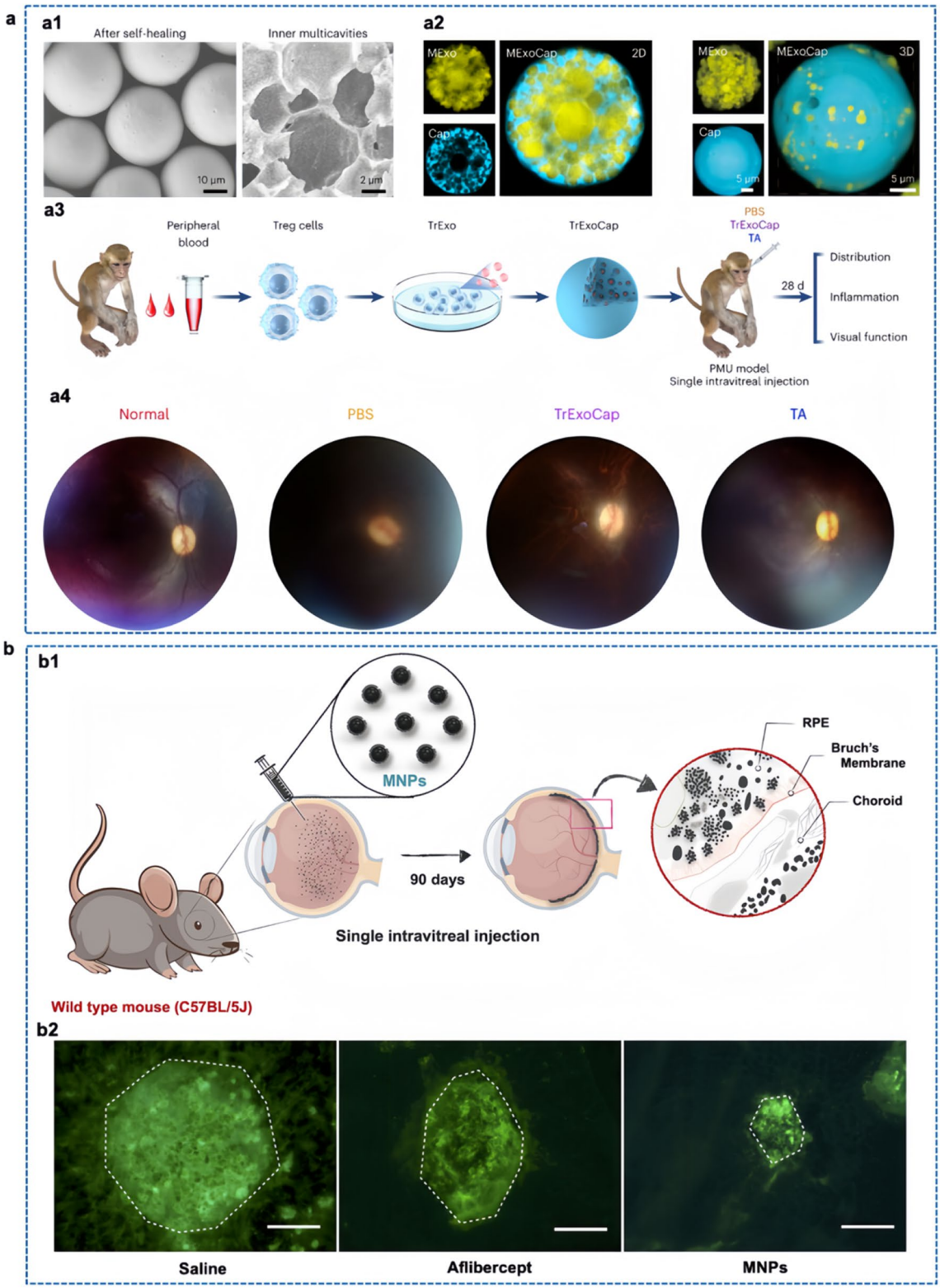
Similarly, polydopamine (PDA) is a melanin-like polymer that is generated from the natural neurotransmitter dopamine and displays ROS-scavenging properties because of its abundant phenolic groups. PDA nanoparticles have been used to efficiently attenuate multiple types of ROS-mediated oxidative injuries, protect neuronal and endothelial cells, and suppress retinal microglial activation. In a mouse model of optic nerve crush, a single intravitreal injection of pure PDA nanoparticles or multifunctional PDA-based nanocomposites efficiently mitigated RGC loss through ROS elimination and inflammatory suppression, thereby maintaining retinal structure and function [186, 187]. Together with desirable biodegradability, biocompatibility, and photothermal transfer effects, PDA-based therapeutic nanoplatforms may be a potential strategy for the management of retinal diseases.

Another type of biomimetic alternative composed of cell-membrane-derived nanoagents has attracted extensive attention in the field of retinal disease treatment [74]. In particular, the cell membrane layer with an intrinsic antigenic function can be incorporated into synthetic cores, allowing these biomimetic nanoparticles to participate in cell interactions and intercellular communication in the pathological microenvironment. For example, Li et al. developed a retinal endotheliocyte-membrane-based nano-agent that targets VEGF. Further fusion of red-blood-cell-membrane-coated PLGA nanoparticles effectively prevented macrophage phagocytosis. Following intravenous injection of the hybrid cell-membrane-derived nanoagent, an excellent reduction in CNV regions and leakage of CNV were observed in a wet AMD mouse model [188].

Collectively, these biomimetic nanocomplex-based nanoagents provide novel remedies for vitreoretinal

(See figure on next page.)

Fig. 8 Representative organic nanomaterial-based therapeutic nanoagents. **a** Degradable polymeric microcapsules delivered exosomes to effective treat vitreoretinal diseases. a1) Scanning electron microscopy (SEM) images of MExoCap after the self-healing and the inner multicavities. a2) Confocal laser scanning microscope (CLSM) images of MExoCap in two-dimension (2D) cut view (left) and three-dimension (3D) reconstruction (right). Yellow, MExo; blue, Cap. a3) Treg cell-derived exosomes (TrExo) were collected from monkey blood, and then loaded TrExo to form the TrExoCap by the diffusion and self-healing. A single intravitreal injection of PBS, TrExoCap or TA into the primed mycobacterial uveitis (PMU) monkey model was performed, then the safety and therapeutic effects were evaluated on day 28. a4) Color fundus images suggested that PBS group presented severe inflammatory response in the vitreous cavity of PMU monkey model, which was significantly ameliorated by TrExoCap treatment. Reproduced with permission [183]. Copyright 2023. The Authors, under exclusive licence to Springer Nature Limited. **b** PEGylated melanin-like nanoparticles (MNPs) were synthesized to substitute the natural melanin in retinal pigment epithelium (RPE) for AMD treatment. b1) Schematic for biocompatible MNPs that can selectively target ROS, traffic and accumulate in the cytosol of RPE for at least 3 months upon a single-dose intravitreal injection. b2) Representative images of endothelial-cell-specific marker IB4-stained (green) RPE/choroid/scleral flat mounts from saline-, aflibercept-, and MNPs-treated retina. Compared with the saline- and aflibercept-treated retina, MNPs-treated group markedly reduced the size of IB4-labeled CNV outgrowths. Scale bar, 100 μm. Reproduced with permission [185]. Copyright 2022, American Chemical Society



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diseases by modulating the retinal microenvironment. However, the relatively low yield and additional invasiveness of the extraction process make its application problematic [189]. These limitations should be addressed in future studies.

Retinal nanomedicine-based strategies for RD at different stages

A common pathology of RDs, mainly AMD, RP, and Stargardt's disease, is the deterioration of the RPE and the resultant degeneration of photoreceptors [190]. No existing therapies can completely halt progressive degeneration or reinstate visual function. In the early stages of RD, retinal function is characterized by mild deficits, and the retinal structure is preserved and grossly intact. Retinal protection via pharmacotherapy may prolong cell life at this stage, whereas gene therapy may reverse cellular functional deficits and attenuate the progression of retinal degeneration. Moreover, stem cell-based therapy appears to be critical for treating RD before the complete loss of photoreceptors. As RD progresses, the retina presents with an advanced loss of cone and rod photoreceptors, accompanied by subsequent degeneration of second-order neurons. In the late stages, retinal optogenetics and retinal prostheses restore retinal light sensitivity and visual perception upon the integration of neuronal responses for transmission to the cortex. All these strategies for vision restoration can be enhanced by nanomedical interventions to some degree.

Retinal nanomedicine-based gene therapy for early RD

AAV-assisted delivery systems have off-target risks, a lack of specificity, and low editing efficiency [191]. Developed non-viral nanomaterials, including organic LNP; HA; peptide-conjugated nanoplexes; polymers; and inorganic nanoparticles, such as mesoporous silica-based nanocarriers, may be alternatives to AAV [192, 193].

LNP-derived gene nanocarriers are the forefront replacements for viral delivery systems that improve biosafety and cellular specificity. Previously, Patel et al. reported that ionizable LNP with unsaturated hydrocarbon tails exhibited the highest efficiency for gene delivery into the RPE. Following mRNA delivery by the SLN, sustained gene expression in the RPE lasted for up to 5 days [194]. Unfortunately, RPE cell-specific targeted LNP-based delivery systems are limited to retinal neurons and Müller glia. To overcome these barriers, pH-sensitive self-assembled LNPs have been formulated for the effective delivery of the therapeutic gene *ABCA4* (a key gene mutated in macular Stargardt's disease) into the photoreceptors of Abca4-/- mice by incorporating a rhodopsin promoter into the plasmids. The multifunctional nanosystems were stable in vivo, depending on the nucleic acids and pH-sensitive amino lipid structures, allowing for endosomal escape and efficient internalization in targeted retinal cells. As a result, significant expression levels of ABCA4 were detected in photoreceptors for at least 8 months [195, 196]. In contrast, the developed top-performing peptide-conjugated LNPs rapidly targeted photoreceptors by decorating them with a combinatorial bacteriophage-based heptameric peptide and dye-conjugated peptides. This delivery system effectively delivered mRNA to RPE and neural retina in mice and nonhuman primates. Subsequently, robust protein expression was observed in the RPE, photoreceptors, and Müller glia, expanding the potential of biosafe LNP-based nanocarriers for gene therapy of inherited blindness.[197] The innovative gene-editing technology CRISPR-Cas9 has been widely employed as the next generation of gene therapeutic tools. Gautam et al. developed LNP variants to package mRNA for gene editing in mouse retinas. LNP variants were generated through surface modification of PEG-lipids with negatively charged carboxyl (LNPz), carboxy-ester (LNPx), and positively charged amine (LNPa) functional groups. LNPa and conventional unmodified LNPs retained gene expression in the RPE, whereas LNPx and LNPz allowed unexpected photoreceptor transfection. Further modifications of LNPx enabled co-delivery of *Cas9* mRNA and the single guide RNA (sgRNA), resulting in successful gene editing in the RPE and Müller glia. These results demonstrate that the LNP surface functionalized with PEG variants changed the cellular tropism of mRNA and allowed for the correction of genetic mutations. This novel system represents a successful paradigm for various retinal gene-editing therapeutics (Fig. 9a) [198].

Dendrimer-based gene delivery systems have also been reported to improve gene transfection efficiency. A core–shell nanocarrier composed of two external layers and a core has been designed. The inner core of the lipid bilayer contains amino-acid-modified dendrimers and a nuclear localization signal facilitates nucleic acid complexation and cellular uptake [199]. To achieve optimal co-delivery of the Cas9-sgRNA plasmid complex and the therapeutic gene, a dual vector of supramolecular nanoparticles was developed. Upon small-scale combinatorial screenings, three molecular building blocks, i.e., β-cyclodextrin-modified branched polyethyleneimine, adamantane-coated PEG, and polyamidoamine dendrimer, were integrated. Following intravitreal or subretinal administration, the therapeutic gene was precisely integrated into the targeted site in the mouse retina and was highly expressed in retinal cells. Thus, this study provides a revolutionary curative strategy for nanomaterial-aided CRISPR/Cas9 gene therapy [200].

Another obvious shortcoming of AAV delivery is its limited packaging capacity (plasmid DNA is usually less than 5 kb). Silica-based nanoplatforms have been extensively studied as non-viral gene delivery vehicles because of their high porosity and sufficient packaging capacity. The most frequently investigated silica-based nanoplatforms, MSiNPs, are characterized by a tunable pore size (2–20 nm), high nanopore volume (0.6–1.0 $cm^3\ g^{-1}$), and large surface area (400–1,000 $m^2\ g^{-1}$), thus they are especially attractive for expanding the vehicle capacity to load targeted nucleic acids. Additionally, the textural properties of the MSiNPs can be adjusted by controlling the synthesis parameters. Silica chemistry allows surface modification and the incorporation of different elements to achieve various features [201]. Typically, MSiNPs combine with anionic nucleic acids upon functionalization via surface amination. Valdés-Sánchez et al. designed amino-functionalized MSiNPs with radially oriented nanopores of 3.5 nm, ideal diameters (approximately 150 nm), and homogeneous spherical shapes. This system has a potent capacity to encapsulate plasmid DNA. Subretinal injection of these nanoparticles correctly delivered the exogenous therapeutic transgene into the nucleus of the RPE cell layer and no adverse effects were detected in the retinal tissue of the mice [202]. Although it is challenging to translate MSiNPs into clinical applications, MSiNPs with hydrolytic biodegradability, nontoxic degradation products, and high biocompatibility are considered the most promising alternatives to viral vectors.

The application of non-viral nanosystems also encounters a major problem: the encapsulated contents are insufficiently stable in vivo and prone to premature release and even degradation. Accordingly, stimuli-responsive silica nanoparticles were fabricated using a facile water-in-oil microemulsion method that prevented premature payload release [203]. The silica nanocapsules achieved glutathione-triggered degradation and on-demand payload release at the targeted sites via conjugation with a disulfide-bond-containing crosslinker. Both subretinal and intravenous injections of silica nanocapsules effectively delivered CRISPR gene editors to the targeted retinal cells without vehicle integration into the genome, resulting in high gene transfection and editing efficiencies (Fig. 9b) [204]. Furthermore, these silica nanocapsules effectively carried therapeutic mRNA and sgRNAs to correct gene mutations in mouse RPE precisely. In a mouse model of Leber's congenital retinal degeneration, the edited retinal region at the injection site primarily exhibited electrical activity.

These preclinical findings reinforce the efficacy of non-viral nanocarrier-assisted genomic interventions for inherited retinal disorders [205]. Although clinical trials of gene therapies are in progress, almost no related results of non-viral nanocarrier-mediated gene therapy translate into clinical practice. The extent of current outcomes is probably a long way from the permanent restoration of vision, and more attention should be paid to the biosafety and practicability of nanomaterial-based non-viral vehicles.

Retinal nanomedicine-assisted stem cell-based therapy for RD progression

As RD progresses, stem cell-based therapy is effective for visual restoration by replacing or repairing the degenerated RPE or photoreceptors [21]. Currently, RPCs, embryonic stem cells (ESC), induced pluripotent stem cells (iPSC), and MSCs are the predominant cell types used for RD treatment. However, limited cell proliferation and retinal neuronal differentiation of stem cells pose a major challenge in clinical practice. Additionally, traditional approaches to cell transplantation usually involve subretinal injections of bolus cell suspensions, resulting in low cell viability and potential side effects. These challenges have been addressed using a series of organic and inorganic biomaterial-derived cell delivery systems.

(See figure on next page.)

Fig. 9 Representative nanomaterial-based strategies for genome editing. **a** PEG-variant surface modifications of LNP mediate genome editing in the mouse retina. a1) Scheme of different LNP structure by loading mRNA cargo. a2) The PEG modification was emphasized in the lipid composition of LNP variants. DSPE-PEG2k-M stands for PEG composing various functional groups. a3) After PBS and LNPx treatment of 2 to 3-month-old mice, IF staining of photoreceptor-expressed tdTomato (red) and co-localized with photoreceptor marker recoverin (green). a4) Fundus imaging indicated that the Cas9-sgAi9-LNPx mediated editing events. Dotted line depicted the treated retina and white arrow indicated the optic nerve head. a5) RPE flatmount images presented the RPE gene editing events. Reproduced under an open access Creative Common CC BY license [198]. Copyright 2023, Springer Nature Limited. **b** Glutathione (GSH)-responsive silica nanoparticles (SNP) enabled targeted delivery of nucleic acids and CRISPR genome editors in vivo. The well-controlled SNP with the size of ~ 50 nm encapsulated nucleic acids and CRISPR genome editors in a high efficiency. The SNP with surface functionalization of PEGylated and different targeting ligands can deliver various biomolecular, including nucleic acids (e.g., mRNA and DNA) and CRISPR genome editors (e.g., Cas9/sgRNA ribonucleoprotein (RNP)). Subretinal injection of SNP conjugated with targeting ligands of all-trans-retinoic acid (ATRA) and intravenous injection of SNP conjugated with targeting ligands of GalNAc effectively delivered mRNA and RNP to murine RPE and liver cells, respectively, resulting in efficient genome editing. Reproduced with permission [204]. Copyright 2021, Elsevier B.V

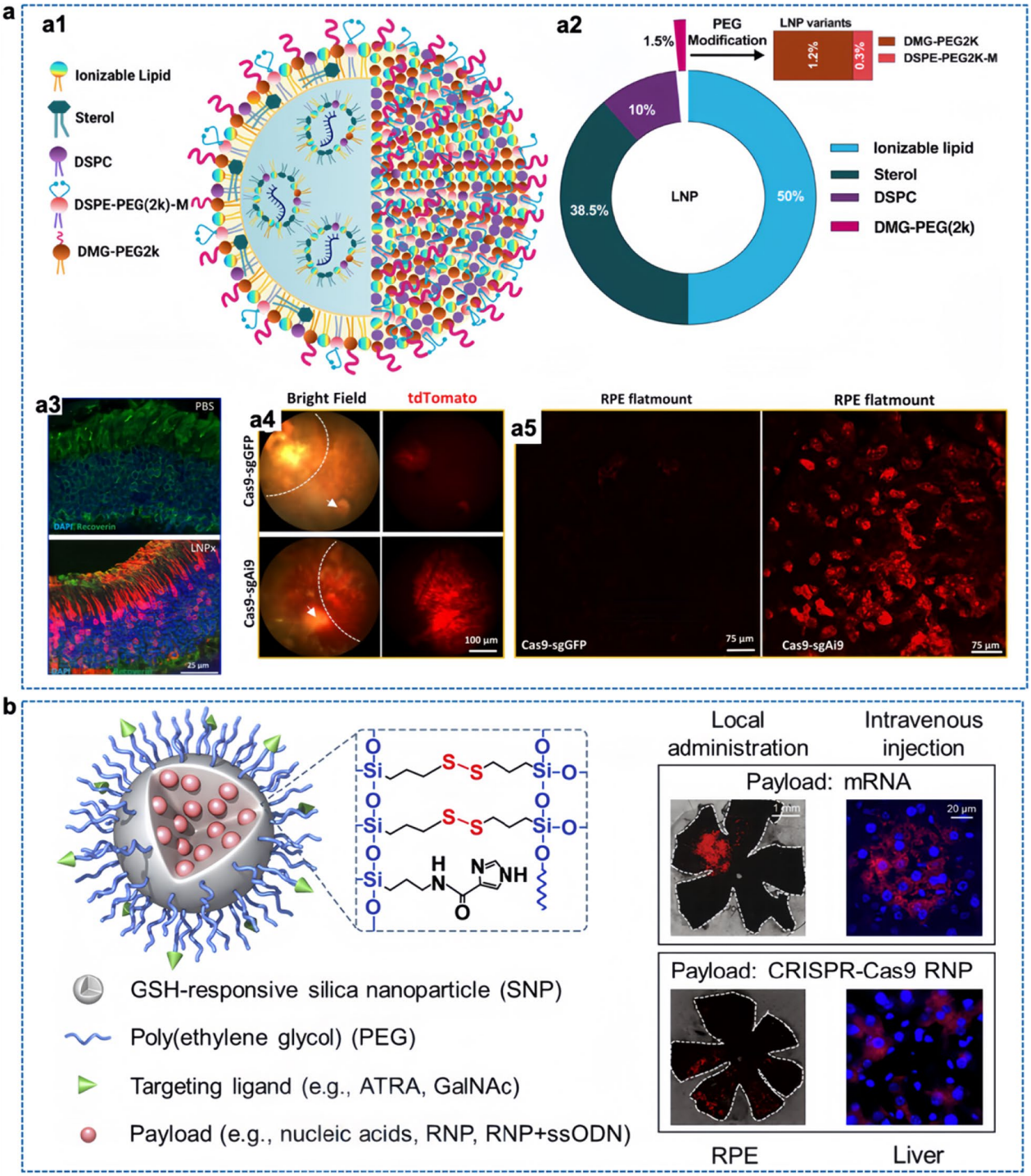

Fig. 9 (See legend on previous page.)

The biophysical and biochemical cues of the extracellular microenvironment (ECM) are crucial for mediating cell fate, particularly cell survival, proliferation/differentiation, and immigration/integration.[206, 207] Hydrogels featuring an abundant porous structure, rich in water, and tunable shapes and sizes perfectly mimic the natural ECM. Numerous natural biomaterials, such as HA, chitosan, gellan gum (GG), silk sericin (SS), and agarose are widely used to fabricate hydrogels [208, 209]. Minimally invasive injectable hydrogels avoid complicated surgical

processes, providing a convenient and safer approach to deliver donor cells and improve cell viability. Donor cells can be loaded into a pregel solution and transplanted into targeted retinal sites through in situ injection and fast gelation. For instance, with the assistance of an HA-methylcellulose hydrogel, the co-transplantation of RPE and photoreceptors has also been achieved for vision restoration in a mouse model of retinal degeneration [210]. Superior to injectable hydrogels, self-healing hydrogels, such as chitosan hydrochloride crosslinked with oxidized dextran, are more tolerant to adverse mechanical damage during injection, which better protects the encapsulated cells and expands the lifespan of hydrogels [211]. To provide a biomimetic retinal niche for RPC proliferation, our group demonstrated suitable mechanical stiffness, interconnected porosity, and intrinsic functional groups such as carboxyl, hydroxyl, and amino groups in gelatin-HA (Gel-HA)-based hydrogels. The introduction of PDA into Gel-HA significantly enhanced RPC adhesion and guided the RPCs to preferentially differentiate into retinal neurons [212]. HA has the potential to improve graft cell survival through a CD44-mediated mechanism. Importantly, RPC-expressed CD44 resulted in increased HA-CD44 interactions to further promote RPC adhesion and migration [213].

Because of its adjustable mechanical characteristics, thermosensitive gelling properties, and excellent biocompatibility, the natural anionic polysaccharide GG has been extensively applied in stem cell-based therapy. However, GG gelation at high temperatures makes it difficult to distribute it homogeneously in the targeted region following injection, and it is challenging to load cells at physiological temperatures [214, 215]. Cell growth and viability are suppressed by the insufficient cell affinity of GG. To overcome these shortcomings, a dopamine-modified GG hydrogel was developed as a favorable vehicle for cell delivery via nonionic cross-linking of the carbodiimide reaction. The hydrophilic properties of dopamine provide a beneficial microenvironment for cell attachment and growth. Consequently, the physically crosslinked GG hydrogel presented the highest degradability and associated cell-releasing capability after 28 days of cell culture. Overall, accumulating evidence has identified time-dependent stress relaxation as a crucial mechanical clue for the regulation of cellular functions [216].

In addition to natural biomaterial-based soft hydrogels, biodegradable or nondegradable solid polymeric scaffolds have also been widely used to support stem cell-based therapy.[217] The effects of solid scaffolds on cell survival remain unclear. Solid scaffolds typically result in low cell viability via subretinal delivery. The underlying explanations may be their unmatched stiffness modulus to that of the retina and insufficient flexibility required for cell delivery. Some evidence has shown that solid scaffolds activate physical environmental signaling and simultaneously provide structural support for planted cells by forming intact cell monolayer-/sheet-implants [218]. Such implantable grafts enable ex vivo cell immobilization prior to intraocular delivery, and support cell survival and integration in vivo. For instance, poly (glycerol sebacate) (PGS)-derived biopolymer scaffolds provide a suitable medium for the diffusion and premature release of biomacromolecules, such as ciliary neurotrophic factor (CNTF). Recently, the covalent immobilization of CNTF on electrospun PGS/poly(ε-caprolactone) (PGS/PCL) scaffolds demonstrated promising results in supporting RGC regeneration. As a 3D model of the rodent optic nerve, an ex vivo RGC explant cultured on a CNTF-immobilized scaffold exhibited significantly extended neurites after 20 days of culture. Importantly, improved cell survival, proliferation, and differentiation were observed, ultimately promoting the overall efficacy of RGC regeneration (Fig. 10a) [219]. Additionally, planar scaffolds with nanoscale structures have been introduced to optimize RPE monolayer delivery and are currently being evaluated in early stage clinical practice. Lee et al. successfully constructed an ultrathin micromolded 3D "ice cube tray" PGS scaffold for high-density photoreceptor layer reconstruction. The ultra-lightweight biodegradable PGS had optimized mechanical properties, cell survival, cell-to-biomaterial load and integration rates, allowing generation of a multicellular photoreceptor layer prepared for the reconstruction of the outer retina (Fig. 10b) [220].

Inorganic nanomaterials with hierarchical architectures and unique properties are popular in stem cell-based therapies. Unlike photoreceptors, RGCs, which are characterized as long-range neurons, require complicated synaptic activity and are myelinated in the optic nerve. Yang et al. developed a carbon nanotube (CNT)-retinal sheet consisting of PLGA for intraocular RGC transplantation. Compared with the PLGA sheet alone, the CNT-PLGA retinal scaffold showed more tunable mechanical characteristics, electrical conductivity, and biodegradation [221]. After incorporation into this sheet, the engrafted RGC exhibited improved cell viability and regeneration along the optic nerve. Recently, our group engineered bifunctional MXene nanomaterials, i.e., ultrathin niobium carbide (Nb_2C), to regulate the fate of RPC during RD treatment [222]. We found that Nb_2C MXene significantly enhanced the retinal neuronal differentiation of RPCs upon photothermal treatment in mice with retinal degeneration and protected RPCs from oxidative-stress-induced damage by scavenging free radicals. Bifunctional nanomaterials provide an intriguing

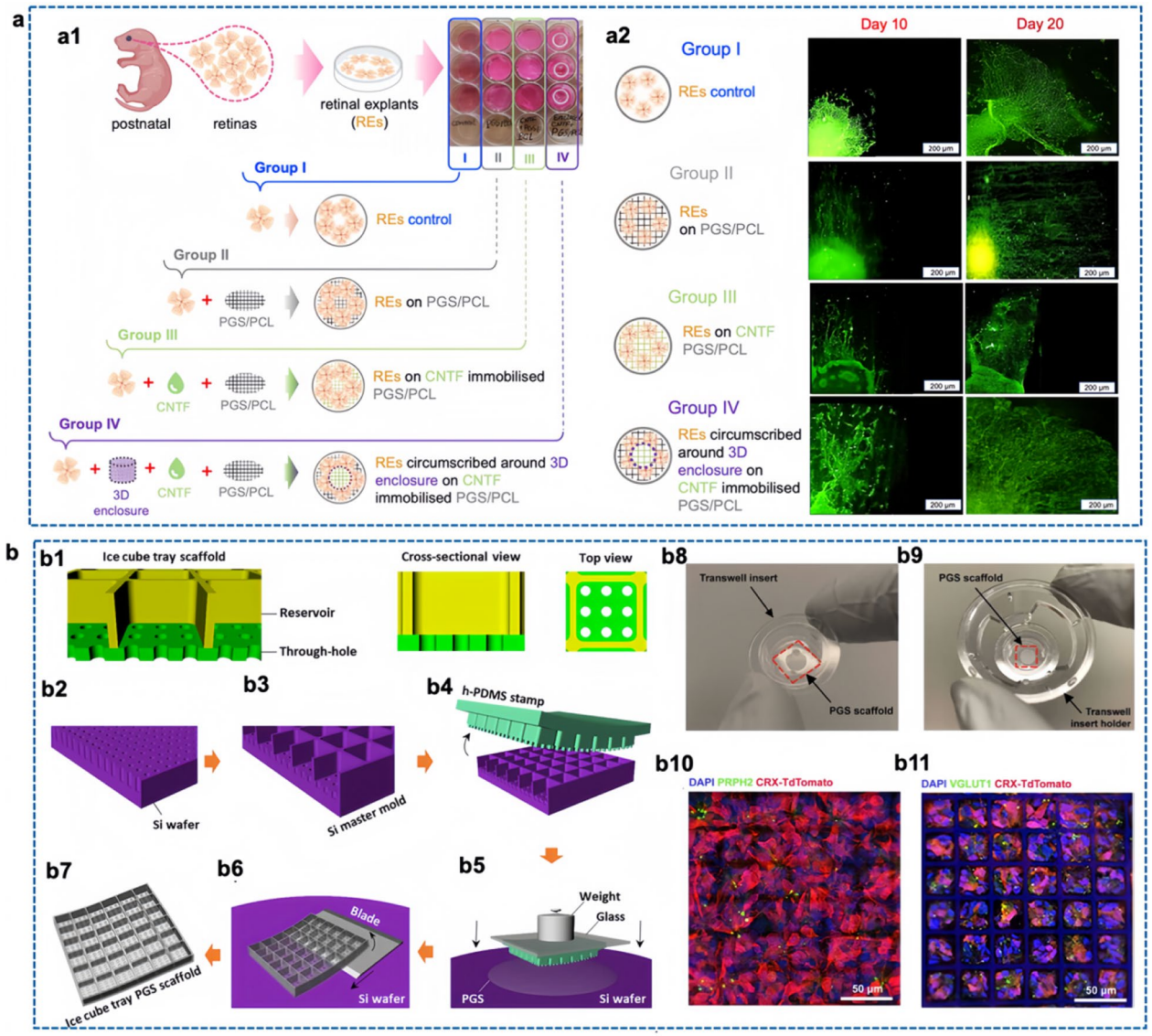

Fig. 10 Representative biomaterial-mediated cell transplantation in retinal degeneration. **a** Ciliary neurotrophic factor (CNTF) regulated growth of retinal ganglion cell axons on electrospun poly (glycerol sebacate)/poly(epsilon-caprolactone) (PGS/PCL) scaffolds. a1) Experimental groups including Group I–IV: retinal explants (REs) cultured on TCP, PGS/PCL, CNTF immobilized PGS/PCL and REs circumscribed around the 3D PVA enclosure on PGS/PCL in the presence of CNTF gradient, respectively. a2) IF staining of MAP2 showed the RGCs neurite outgrowth of the REs on all four Groups cultured for 10 and 20 days. The REs on PGS/PCL revealed that CNTF mediated environment improved the average neurite lengths and extensions after 20 days of cell culture. Reproduced under an open access Creative Common CC BY license [219]. Copyright 2024. The Authors. Published by IOP Publishing Ltd. **b** High-density photoreceptor layer reconstruction based on ultrathin micromolded 3D scaffolds. b1) Scheme of the ice cube tray scaffolds with a reservoir layer for photoreceptor capture and a through-hole layer for exchange of waste products, nutrients, fluid. b2-b7) Scheme of the process to synthesize the ice cube tray photoreceptor scaffolds applying a PGS prepolymer. b2) Through-hole based on Si wafer and b3) reservoir etching processes of a Si master mold. b4) Si master mold for a hard-polydimethylsiloxane (h-PDMS) stamp and their molding and demolding processes. b5) Mounting and demounting processes of the h-PDMS stamp for developing a PGS ice cube tray PR scaffold. b6) A razor blade for delamination of the scaffold. b7) Ice cube tray PGS scaffold was developed. b8) Transwell insert with scaffold below. b9) The scaffold mounted into a transwell insert. b10, b11) Maximum intensity projections of scaffold where whole mounts plated with red CRX + /tdTomato-PRs suggested that PRs seeded on scaffolds expressed m) green PRPH2, and n) green VGLUT1. Blue: PGS autofluorescence and DAPI-labeled cell nuclei. Reproduced under an open access Creative Common CC BY license [220]. Copyright 2021. The Authors. Published by American Association for the Advancement of Science

paradigm for stem cell-based therapy and broadening the multifunctional horizon of inorganic nanomaterials.

Generally, biomaterial-derived delivery systems are advantageous for improving cell survival, regulating cell fate, and promoting axonal polarization of implanted cells, while reducing cell reflux and off-target delivery. It is worth noting that the transfer of donor cells delivered by biomaterials may change protein expression for cell functional restoration. Recently, HA and methylcellulose hydrogels have been shown to significantly reduce material transfer and neurite formation in transplanted rod photoreceptors by suppressing cell–cell contact. HA is largely nonadhesive to cells and decreases material transfer, leading to an unlikely or limited extension of photoreceptor nanotubes [223]. Thus, modification of biomaterials to tune material transfer is important for mediating the fate of transplanted cells. However, the effects of most biological materials on material transfer have not yet been evaluated. Therefore, improvements in cell–cell contact and tunable control of material transfer in biomaterial-mediated cell transplantation should be further elucidated in future studies.

Retinal nanomedicine-based strategies for late RD

In the late stage of RD, RGC and bipolar cells are preserved and remain intact to convey information to the brain. Under such circumstances, the only and most suitable option may be a restorative strategy aimed at improving light sensitivity of the remaining retinal cells by directing electrical stimulation.

Retinal nanomedicine-based retinal optogenetics

Retinal optogenetics, as a frontier technology, is becoming a powerful tool for the precise restoration of neuronal circuitry [224]. Retinal optogenetics genetically introduces light-sensitive optic proteins for ectopic expression in non-photosensitive downstream neurons, conferring photosensitivity to residual intact non-photoreceptor cells, irrespective of the genetic etiology, thereby restoring vision [225].

Mammals are typically unable to perceive light of long wavelengths (> 700 nm) [226, 227]. Recently, nanomaterial (e.g., UCNPs and metal-oxide semiconductors)-mediated retinal optogenetics has emerged to remotely manipulate deep-tissue signaling pathways and protein functions under irradiation with NIR light (> 900 nm) [228, 229]. Nelidova et al. first proposed a dual nanosystem containing a nanomaterial component (gold nanorods) and a genetic component (temperature-sensitive transient receptor potential [TRP] channels). Gold nanorods capture NIR light and generate heat to open the TRP channels in the proximity of the nanorods. Retinal cells are targeted by TRP channels and are sensitive to infrared radiation. By expressing snake or mammalian TRP channels in the photoinsensitive cone photoreceptors of mice with RD, NIR stimulation improved the activity of retinal cones, RGC neurons, and the cortical layer. Interestingly, the mice exhibited light-driven learned behaviors. After targeting TRP channels in the postmortem human retina, light responses in photoreceptors were recorded using NIR-light-evoked activity, providing a new methodology for visual rehabilitation (Fig. 11a) [230]. Yang et al. engineered a TRP-like biohybrid sensor by combining UCNPs and optically engineered cells on a graphene transistor for NIR sensing and imaging. The tailored UCNPs, as light transducers and retinal optogenetic actuators, enabled the indirect activation of classical optogenetic proteins (e.g., channelrhodopsin-2). The UCNPs convert NIR light into blue light and induce a transmembrane photocurrent by detecting a biocompatible graphene transistor (Fig. 11b) [231]. Overall, these nanomaterial-based retinal optogenetics approaches show the potential for local, temporal, and optical modulation of selected cells in vivo with minimal invasion.

(See figure on next page.)

Fig. 11 Representative nanomaterial-based strategies for retinal optogenetics. **a** Tunable near-infrared sensors restored light sensitivity. a1) Scheme of the NIR light sensor consisting bind antibody-conjugated gold nanorods (yellow) and engineered transient receptor potential (TRP) channels (blue) expressing protein epitope tags (orange) in extracellular domains. a2) Left: Wild type (WT) healthy retina. Outer segments (OS) of photoreceptors captured photons. Right: Cell bodies of rod are lost but cone persist in the retinal degeneration 1(rd1) mouse retina. ONL, outer nuclear layer; INL, inner nuclear layer; GCL, ganglion cell layer. a3, a4) Scheme of the structure of rTRPV1 channel. a3) Top view: orange arrows depicted a 6x-His epitope tag in each of the four subunits of the TRPV1 tetramer (yellow, blue, gray, and green), and red asterisk indicated the channel pore. a4) Right: side view. Left: 6x-His epitope tag (orange) within the first extracellular loop in blue subunit was amplified. a5) Scheme of the location of TRP channel–expressing, infrared light-sensitive pit organ. Optic tectum received the information. a6) Scheme of behavioral test. NIR stimulation (915 nm, 200 ms) of one eye cues water presentation for water-restricted, head-fixed rd1 mice. Mice respond by licking before (anticipation) or after water appearance. Reproduced under an open access Creative Common CC BY license [230]. Copyright 2020. The Authors. Published by American Association for the Advancement of Science. **b** Scheme of the upconversion optogenetics-inspired biohybrid sensor for NIR sensing and imaging with high response frequency. b1) TRP-triggered infrared vision of pit-bearing snakes. b2) Biohybrid NIR sensor mediated NIR imaging by the response frequency, which is significantly higher than that of cell lines expressed heterologous TRPs. Reproduced with permission [231]. Copyright 2023, Elsevier Ltd

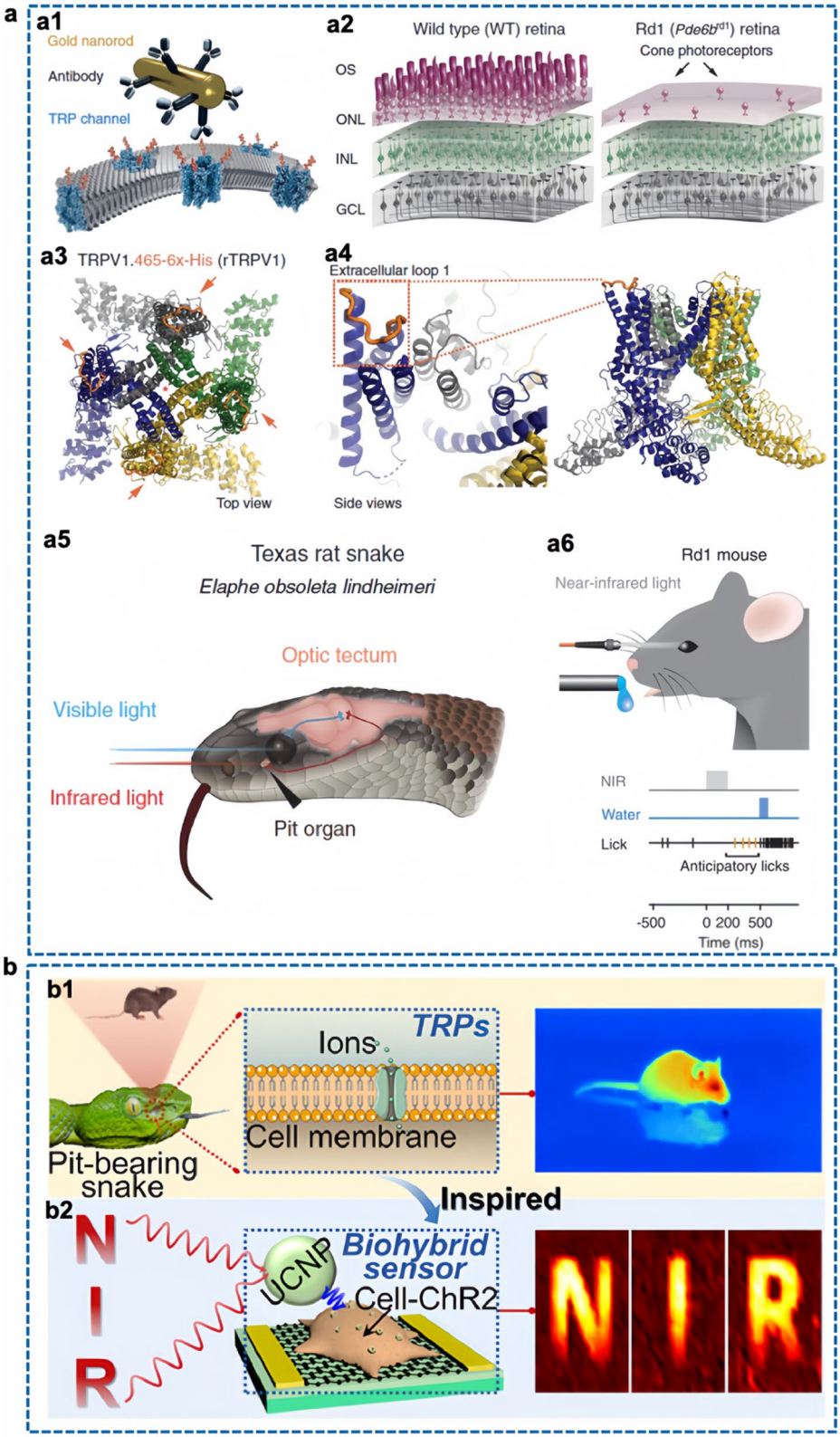

Fig. 11 (See legend on previous page.)

Considering that multiple emission peaks cause chromatic crosstalk, independent activation of distinct neuronal populations is not feasible using conventional UCNPs or their mixture with the sensitizer Yb^{3+}/Nd^{3+}. To realize responsive dichromatic emission, UCNPs were decorated with different types of sensitizers; that is, Er^{3+}, Yb^{3+}, and Nd^{3+}. Based on controllable UCNPs, NIR trichromatic retinal optogenetics separately activates three specific neuronal populations. After switching the excitation wavelength, the red, green, and blue light emissions were selectively regulated to match the respective optogenetic proteins. This activation, with tunable intensity, selectively manipulated specific neuronal populations and transracially modulated motion in awake mice. This strategy opens a promising path for multichromatic upconversion-mediated retinal optogenetics.[232] The utilization of engineered retinal optogenetic modules and nanomaterial-based actuators, particularly functional UCNPs, has advanced bio-combined nanoscale devices and broadened their utility in retinal diseases.

To effectively prevent pathological CNV and oxygen-induced retinopathy, a CRISPR-dCas9 optogenetic gene nanocarrier comprising light-controlled UCNPs and VEGF transcriptional inhibitors was introduced. Upon activation by external blue light, the opto-CRISPR nanosystem demonstrated controllable and targeted repression of VEGF gene expression. Any gene of interest can be designed by merely replacing the gRNA sequences [233]. Most retinal optogenetics approaches depend on blue light irradiation to activate the photoswitch, during which relatively strong phototoxicity may damage corneal and retinal tissues. More recently, Ding et al. constructed a biomimetic camouflage nanoparticle-based platform that contained PEGylated liposomes and macrophage membranes for optogenetic therapy of retinoblastoma. In contrast to external blue light stimuli, the developed optogenetic nanosystem enabled significant suppression of tumor growth with high efficacy by in situ bioluminescence-triggered apoptosis, while avoiding corneal neovascularization and retinal damage [234]. This nanotechnology provides a safer strategy of a "cool" light source for bioluminescence-controlled retinal optogenetics to target various retinal diseases.

Although elegant studies involving UCNPs have been conducted, the inorganic metal contents of UCNPs, such as erbium, ytterbium, yttrium, and thulium, are problematic for biodegradation. This poses a potential long-term nanotoxicity issue in biological medical applications [235]. Practical strategies to circumvent the toxicity issues of UCNPs include the fabrication of ultra-small nanoparticles to increase biological elimination, surface functionalization with bio-biocompatible ligands or detoxifying reagents, and enhancement of the upconversion efficiency of UCNPs to decrease light dosage in practice. Further investigation is required to determine which of these strategies will bring more benefits. The number of retinal optogenetics-based therapeutics has shown an exponential increase. Two dose-escalation clinical trials are currently ongoing to evaluate the safety and efficacy of retinal optogenetics in patients with advanced RD (NCT02556736 and NCT04278131) [236]. However, they have no relationship to nanomedicine. These outcomes confirm the promise of nanomaterial-assisted retinal optogenetics to restore vision at clinically relevant levels. Determining the optimal approach for optogenetic delivery through nanomaterial-based strategies is another goal of clinical trials.

Nanomedicine-based retinal prostheses

Similar to retinal optogenetics, retinal prostheses are another alternative for RD treatment. Direct wireless electrical stimulation (ES) of residual RGCs without photoreceptor activation by optoelectronic and semiconductor nanomaterials presents positive effective in late RD. These nanomaterials, such photoelectric phosphenes, inorganic semiconducting QDs and organic semiconducting polymer poly[3-hexylthiophene] nanoparticles (P3HT NPs), have been be engineered to emit light in response to ES. Phosphenes can serve as visual perceptions elicited by light and other stimuli, e.g., electrical currents. Inspiringly, the noninvasive determination of electrically evoked phosphene thresholds (EPTs) provided a safe strategy to evaluate electrical excitability in patients, representing a promising candidate of retinal prostheses. Additionally, the short-term stimulation of EPTs showed a positive effect on the visual field in a clinical study (NCT00804102) [237]. Attributing to the safe, fast and reliable practicability of EPT testing, a clinical trial enrolled 52 participants with RP to treat with either 30 min once a week of transcorneal ES for 52 weeks or sham (NCT01837901). Compared with sham, higher power setting of transcorneal ES with good tolerance significantly improved the retinal function and greatly preserved visual field area. The long-term safety and visual protection of self-administered TES by patients at home was lasted for 1 year [238]. Similarly, it has been well documented that the photovoltaic response of QDs achieve light activation of neurons. Thus, J. Olson et al. conducted a first-in-human phase I clinical trial (NCT04008771) to evaluate the safety of QDs in patients with advanced RP. Intravitreal injection of QDs exerted no adverse events, and seemed beneficial to vision recovery [239]. However, these existing prosthetic procedures show a limited spatial resolution lower than that allowed by foveal cones. To circumvent these problems, Fabio Benfenati et al. designed a novel light-sensitive interfaces

with retinal neurons using P3HT NPs. One P3HT layer is contacted on an underlying conductive layer (e.g., indium tin oxide), and the other layer is bathed by the electrolytic extracellular medium. Upon a single subretinal injection, P3HT NPs showed a persistent and even distribution throughout subretinal space without retinal toxicity. More importantly, P3HT evoked retinal responses in high spatial resolution for up to 8–10 months in degenerate retina [240, 241]. The developed P3HT NPs (about 300 nm) can be a liquid retinal prosthesis for the effective treatment of late RD.

Different from nanomaterial-based wireless ES in retinal prostheses, the nanomaterial-based artificial photoelectric synapses often require wiring or external cameras. The role of artificial photoelectric synapses in retinal prostheses is also to restore the sensitivity of remaining retinal neurons to light. To date, a variety of highly photoactive nanomaterials with excellent tunability and innate optoelectronic memory, such as carbon-originated nanomaterials (QDs, carbon nanotubes, graphene, and graphene oxides), molybdenum disulfide (MoS_2), black phosphorus, organics, metal oxides, transition metal dichalcogenides (TMDs), and halide perovskites, have been widely applied in the formation of sophisticated artificial optoelectronic synapses [242–250]. The artificial synapse amplifies the electromagnetic fields generated by light through a structure called a plasma nanochannel and interacts with retinal neurons at the nanoscale. Once in contact with postsynaptic retinal neurons, the device is charged with a smart polymer that releases neurotransmitters in response to light stimulation, thereby mimicking physiological release processes. Additionally, the device was coated with appropriate presynaptic adhesion molecules to reconstruct the synaptic environment, thereby forming an appropriate synthetic synapse. Specifically, the device can activate retinal neurons in the presence of light at a resolution of approximately 5 mm, which is comparable to the resolution achieved by cone cells in the center of the human retina, which is responsible for high-resolution vision. The goal of this technique is to help restore vision in patients with RD, and it represents a potential technological breakthrough in retinal prostheses.

The natural retinal system senses objects panchromatically for chromatic adaptation. Therefore, single/dual functions and monotonic light perception in retinal prostheses restrict their clinical applications [251]. Compared to monochrome sensing systems, full-color-sensitive synapses with highly sophisticated panchromatic imaging abilities are more attractive and advantageous [252]. Recently, Long et al. demonstrated the use of retinal prostheses for efficient and intelligent panchromatic imaging. This system contains an inorganic CsPbI3/NiO core nanowire and a wavelength-dependent color-sensitive SnO2/NiO double-shell nanotube. The bidirectional photoresponsive SnO2/NiO synapses enabled panchromatic imaging by adjusting the color selectivity with bias. The CsPbI3 nanowire generated a self-powered photocurrent, significantly decreasing the systematic energy consumption. The developed retinal prostheses, based on the positive surrounding gate effect of NiO, obtained either negative or positive photocurrents under longer-wavelength (red and green) or shorter-wavelength (blue) illumination, respectively, structurally and functionally mimicking the biological retina [253].

Despite some promising findings observed with retinal prostheses, they inevitably have deficiencies, including limited visual resolution, problems with integration with complicated biosystems, and mechanical mismatch with the soft retina. Rigid electrodes may damage the soft retina and display limited selectivity with poor proximity to the target degenerative retinal cells. The most advanced nanomaterials readily applicable to retinal prostheses are smaller, softer (e.g., ionogel photosynaptic retinas), more biocompatible, and more efficient [254]. More recently, Chung et al. designed low-modulus soft liquid–metal (LM) electrodes in a flexible artificial retina for visual restoration. Soft LM electrodes based on a eutectic gallium-indium alloy were combined with photosensitive transistor arrays, and the tips of these electrodes were decorated with platinum nanoclusters to reduce the impedance of the stimulation electrodes. These microelectrodes significantly improved the proximity to the target RGC and evoked retinal neural activity through effective charge injection. This liquid form contributes to a low Young's modulus, minimizing damage to retinal tissues. Of note, selective local illumination of light triggered the spatiotemporal responses of RGC in a mouse model of RD, implying visual restoration in degenerated mice (Fig. 12) [255]. However, the exploration of LM as a biointerfacing biomaterial remains in the early stages and requires more effort in future work to obtain safer and higher resolution stimulation.

Wiring retinal prostheses have significant clinical benefits. Three prominent devices have achieved market authorization: the Argus II epiretinal device (Second Sight), Alpha AMS subretinal implant (Retina Implant AG), and the new Prima subretinal prosthesis (Pixium). They have been approved for clinical application or are being evaluated in clinical trials for the treatment of advanced AMD or RP [256, 257]. The Argus II is the first FDA-approved wiring retinal prosthesis for surgical implantation on the retinal surface. However, among 47 patients tested, 8 suffered common side effects, including conjunctival dehiscence, corneal opacity, corneal melt, and retinal tear [258]. Due to financial difficulties,

the product will be discontinued in 2023. More than 500 patients with profound vision loss have been implanted with retinal prostheses in clinical trials [259]. A subset of these patients was able to detect and discriminate motion, localize and identify objects, and perform limited reading, simple orientation, and basic mobility tasks in realistic conditions. Specific device problems include overstimulation or delamination of the implanted components. Adverse events mainly include conjunctival erosion and retinal detachment, although these are rare. Recently, the first open-label single-group feasibility clinical trial (NCT03333954) recruited five patients with atrophic AMD to evaluate the outcomes of photovoltaic substitutes of photoreceptors using subretinal implantation. This device allows patients to simultaneously utilize their remaining peripheral natural vision and central prosthetic vision under room-lighting conditions [260].

Challenges and perspectives

Conventional ophthalmic formulations and therapeutic strategies have limited efficacy in the management of retinal diseases. Emerging retinal nanomedicines provide options for various frontier applications (Table 1). Although retinal nanomedicine has demonstrated overwhelming advantages over large-scale congeners, it still faces challenges in practice. The key advantages and challenges of different nanomedicines for the treatment of retinal diseases are discussed (Table 2). Furthermore, various perspectives have been proposed.

1) Retinal nanomedicine-based eye drops, as non-invasive tools, have improved topical biological delivery by effective penetration across defensive ocular hurdles. However, because of their natural variability, natural nanomaterials present batch-to-batch discrepancies among materials produced from the same ingredients. Moreover, the transmission of pathogens or potential immune reactions may occur with the use of eye drops. Despite the low cost of generating natural nanomaterials, their manufacturing process is relatively slow because of the challenges in regulating environmental manufacturing factors. Therefore, these concerns must be addressed before their use in clinical practice. Compared to natural nanomaterials, the manufacture of synthetic organic nanomaterials is remarkably repeatable, ensuring their expected physical and chemical properties [261]. Therefore, it is relatively simple to change their properties to obtain predicted outcomes. In addition, the reproducible and controllable manufacturing processes of synthetic nanomaterials result in a high level of purity, which decreases the risk of toxic reactions. These appear to be more advantageous than natural nanomaterials and they permit broad application in the formation of eye drops. Additionally, despite efforts dedicated to the development of more efficient inorganic nanomaterial-based eye drops, few have been approved for clinical use. Inorganic nanomaterials are characterized by small particles and large surface areas, resulting in a high drug-loading efficiency. However, the biological toxicity and poor degradability of these materials cannot be ignored. Overall, synthetic organic nanomaterials may be a better choice for the efficient and safe preparation of eye drops. In addition, synthetic organic nano-

(See figure on next page.)

Fig. 12 Biomaterial-mediated retinal prostheses for vision restoration. **a** Scheme of retinal prostheses incorporated with the soft 3D liquid metals (LMs) stimulation electrodes in close proximity to the locally non-uniform retinal surface caused by the degenerated photoreceptors. **b** Scheme of the device layout. To achieve the stimulation electrodes at room temperature, the micropillar array of 3D eutectic gallium–indium alloy (EGaIn) was directly printed on the drain electrode surfaces of photosensitive transistors. Then, the parylene C layer loaded the pillars' sidewalls, and the pillars' tips were opened applying the anisotropic O2 reactive ion etching (RIE) serving as the charge injection sites to the retina prior to the electroplating of platinum (Pt) nanoclusters, i.e., platinum black (PtB). **c** Photograph of the artificial retina compose of the 3D LM microelectrodes incorporated with a high-resolution phototransistor array. Scale bar, 1 mm. **d** SEM image of the 3D LM microelectrodes of 20 μm diameter and 60 μm height that were integrated with every drain electrode of this transistor array. Scale bar, 100 μm. **e** SEM image of the 3D LM microelectrode's tip locally coated only with PtB. Scale bar, 1 μm. **f** Photograph of the artificial retina implanted into the live rd1 mouse. The inset shows the fundus photo of the implanted device that was adhered to the retinal surface without bleeding and damage. Scale bar, 1 mm. **g** Scheme (left) and image of optical coherence tomography (right) of artificial retina implanted-rd1 mouse retina. Scale bars, 100 μm. The mouse retina was conformally surrounded with the 3D LM stimulation electrodes. **h** Scheme of 470 nm full-field blue-light illumination of artificial retina implanted mouse eyes at the intensity of 1.80 mW cm^{-2}, and the inset indicated the fundus image. Scale bar, 200 μm. **i** Potential train and firing rate of the evoked RGC spikes were recorded during the continuous visible blue-light illumination. Scale bars, 200 ms (horizontal); 100 μV (left, vertical); 40 Hz (right, vertical). **j** Contour plot of firing rates were spatially mapped under illumination. **k** Scheme of the constant 415 nm wavelength of light-illuminated live rd1 mouse at the intensity of 1.80 mW cm^{-2} using an ellipsoidal-patterned shadow mask, and the inset indicated the fundus image. Scale bar, 200 μm. **l** Potential train and firing rate of the evoked RGC spikes were recorded during the light illumination using the shadow mask. Scale bars, 200 ms (horizontal); 100 μV (left, vertical); 40 Hz (right, vertical). **m** Contour plot of firing rates was spatially mapped under illumination. Reproduced under an open access Creative Common CC BY license [255]. Copyright 2024. The Authors. Published by Nature Publishing Group

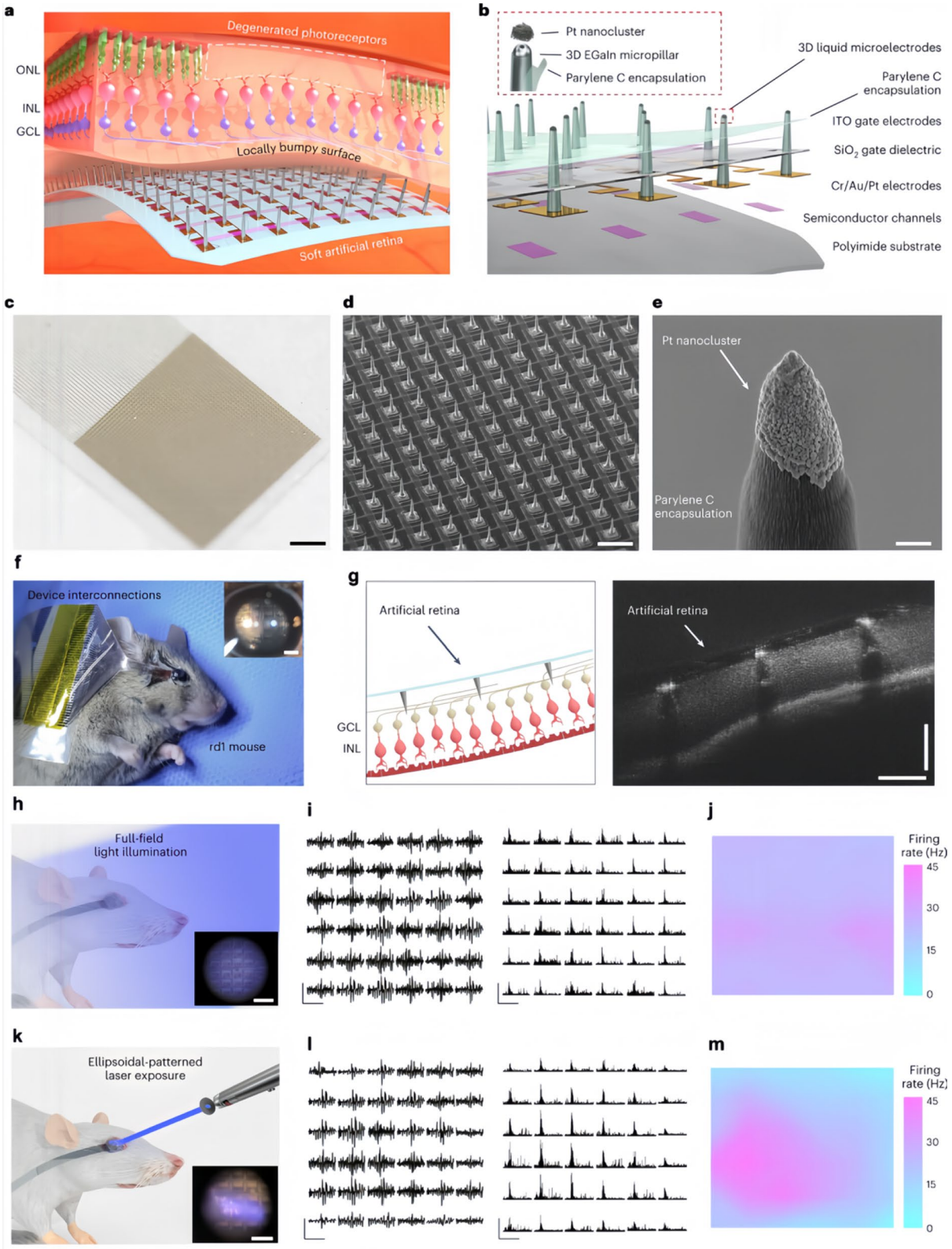

Fig. 12 (See legend on previous page.)

Table 1 Summary of representative retinal nanomedicine for frontier applications

Applications	Composition of nanomaterials	Cargos	Route	Functions	Authors and the year of publication	Current stage of application
Natural organic nanomaterial-based eye drops	Fluorocarbon-modified chitosan-based nanocomplexes	Anti-VEGFA proteins or anti-PDL1 drugs	Eye drops	Via conjunctiva-sclera/blood-choroid-retina pathways, inhibited vascular proliferation and tumor growth	Zhuang Liu et al., 2023 [42]	In vitro and animal studies
	Chitosan and crosslinked with polyacrylic acid	Dexamethasone	Eye drops	Suppressed pain and inflammation post-ocular surgery	Investigators not provided; last update posted at 2021	Phase III clinical trial (NCT03192137)
	Chitosan-HA nanoparticles	Erythropoietin	Eye drops	Enabled erythropoietin delivery to the retina of glaucomatous rats and promoted an earlier retinal recovery	Esmeralda Delgado et al., 2023 [55]	In vitro and animal studies
	Smart supramolecular peptides	/	Eye drops	Specifically identified and captured pro-angiogenesis to alleviate pathological retinal angiogenesis in DR mice	Bo Hu et al., 2023 [58]	In vitro and animal studies
	Cell penetrating-peptide-based nanoparticles	Melphalan	Eye drops	Penetrated dense blood vessels of sclera to treat RB	Gang Wei et al., 2022[64]	In vitro and animal studies
	Cyclodextrin nanoparticle	Dexamethasone	Eye drops	Significantly improved visual acuity and decreased macular thickness in patients with DME	Einar Stefánsson et al., 2015 [36]	Clinical trial (number not provided)
	Cyclodextrin nanoparticle	Dexamethasone	Eye drops	Showed high biosafety and efficiency in patients with DME	Investigators, not provided, last update posted at 2022	Phase II clinical trial (NCT05343156)

Table 1 (continued)

Applications	Composition of nanomaterials	Cargos	Route	Functions	Authors and the year of publication	Current stage of application
Synthetic organic nanomaterial-based eye drops	Thermosensitive triblock copolymer	Hydrophilic and hydrophobic drugs	Gelling drops	Prolonged ocular surface contact and drug absorption	Laura M Ensign et al., 2020 [69]	In animal studies
	Nanomicelles	Aflibercept	Eye drops	Penetrated via corneal-scleral routes, remarkably inhibited anti-angiogenic activity in CNV	Xian Jun Loh et al., 2022 [84]	In vitro and animal studies
	Nanoemulsion	Latanoprost and α-tocopherol	Eye drops	Prolonged ocular retention and enhanced retinal permeability for glaucoma treatment	Jian You et al., 2023 [90]	In vitro and animal studies
	Liposomes	Conbercept	Eye drops	Inhibited CNV with high biosafety and achieved an equivalent effect to a single intravitreal injection	Xueying Ding et al., 2024 [100]	In vitro and animal studies
	Solid lipid nanoparticles	Clarithromycin	Eye drops	Improved ocular permeation and drug therapeutic effect in endophthalmitis model	Pottathil Shinu et al., 2021 [102]	In animal studies
	Liposomes	Triamcinolone acetonide	Eye drops	Improved visual acuity and diminished central foveal thickness in patients with DME	Arturo Santos et al., 2021 [107]	Phase I clinical trial (number not provided)

Table 1 (continued)

Applications	Composition of nanomaterials	Cargos	Route	Functions	Authors and the year of publication	Current stage of application
Inorganic nanomaterial-based eye drops	Carbon dots	Aflibercept	Eye drops	Enabled noninvasive intraocular concentration monitoring by the inherent fluorescence of carbon dots and inhibited angiogenesis	Yossi Mandel et al., 2019 [111]	In vitro and animal studies
	Magnetic nanoparticles	Guanabenz and valproic acid	Eye drops	Enabled noninvasive retinal drug imaging and targeted photoreceptors to protect retinal function	Vincent Marion et al., 2021 [113]	In animal studies
	Hollow ceria nanoparticle	Pilocarpine	Eye drops	Improved intraocular drug delivery and intrinsic therapeutic activity of drug	Jui-Yang Lai et al., 2020 [114]	In vitro and animal studies
	Gold nanoparticles	Large macromolecules	Eye drops	Effectively reach the retina layers with high biosafety	Nathan Ravi et al., 2021 [116]	In vitro and animal studies
Nanomaterial-based retinal contrast agents	Ultraminiature chain-like gold nanoparticle clusters	/	Intravenous injection	Achieved photoacoustic and optical coherence tomography imaging to visualize CNV	Yannis M Paulus et al., 2023 [127]	In animal studies
	Silicone elastomer contact lens	/	Repeated wearing	Emitted by far near-infrared light, and reduced retinal vascular hyperpermeability in DR rabbit model	Sei Kwang Hahn et al., 2022 [137]	In animal studies
	MnO_2 nanosponge	RB-targeted DNA aptamers		Targeted two different mRNAs, and realized fluorescence/magnetic resonance bimodal imaging and dual-gene therapy	Shanni Hong et al., 2024 [138]	In vitro and animal studies
	AuNCs-conjugated with Fe_3O_4 nanoparticles	Muramyl dipeptide and perfluoropentane	Intravenous injection	Enhanced photoacoustic, ultrasound, and magnetic resonance imaging-guided low-intensity focused ultrasound / immunosynergistic therapy of RB	Xiyuan Zhou et al., 2020 [145]	In vitro and animal studies

Table 1 (continued)

Applications	Composition of nanomaterials	Cargos	Route	Functions	Authors and the year of publication	Current stage of application
Inorganic nanomaterial-based retinal therapeutic agents	Platinum nanozyme	/	Intravitreal injection	Suppressed hypoxia-induced abnormal neovascularization and facilitated retinal avascular normalization	Zhenglin Yang et al., 2022 [154]	In vitro and animal studies
	Cerium oxide nanoparticles	/	Eye drops	Penetrated via conjunctiva transscleral-retina pathway, inhibited inflammation and oxidative stress in AMD mouse model	Josep García-Arumí et al., 2023 [265]	In vitro and animal studies
	Prussian blue analogue KCa[FeIII (CN)6] nanoparticles	/	Intravitreal injection	Rescued retinal structures and visual function by ferroptosis inhibition in AMD mouse model	Ping Gu et al., 2021 [162]	In vitro and animal studies
	Fe-N4-based single-atom nanozymes	/	Intravitreal injection	Performing catalase-like catalysis and eliminating pathological angiogenesis in retinal vasculopathies	Kelong Fan et al., 2022 [166]	In vitro and animal studies
Organic nanomaterial-based retinal therapeutic agents	MSC-EVs	/	Intravitreal injection	Improved retinal function and alleviated retinal apoptosis, inflammation, and angiogenesis in rats with DR	Hui Qian et al., 2024 [178]	In vitro and animal studies
	MSC-EVs	/	Intravitreal injection	Promoted healing of macular holes	Xiaomin Zhang et al., Last update posted at 2021	Phase I clinical trial (NCT03437759)
	MSC-EVs	/	Subtenon injection	Rescued visual functions for 6 months in patients with RP	Kuddusi Erkılıç, et al., Last update posted at 2022	Phase II/III clinical trial (NCT05413148)
	Synthetic melanin-like nanoparticles	/	Intravenous injection	Accumulated in the RPE for 3 months upon a single-dose application, and alleviated oxidative stress	Zongchao Han et al., 2022 [185]	In vitro and animal studies
	Hybrid cell-membrane-cloaked nanoparticles	/	Intravenous injection	Decreased VEGF, protected from phagocytosis by macrophages, and enhanced accumulation in CNV region	Yuanyuan Su et al., 2021 [188]	In vitro and animal studies

Table 1 (continued)

Applications	Composition of nanomaterials	Cargos	Route	Functions	Authors and the year of publication	Current stage of application
Retinal nanomedicine-based gene therapy at early RD	HA nanospheres	Plasmid DNA carrying a GFP reporter gene	Intravitreal injection	Showed widespread gene expression in RPE	Muayyad R Al-Ubaidi et al., 2024 [193]	In animal studies
	Peptide-guided lipid nanoparticles	mRNA	Intravitreal injection	Observed robust protein expression in neural retina	Gaurav Sahay et al., 2023 [197]	In animal studies
	Supramolecular nanoparticle vectors	CRISPR-Cas9 genome and Retinoschisin 1 DNA plasmid	Intravitreal or subretinal injection	Enabled CRISPR/Cas9-mediated gene knockin for treating X-linked juvenile retinoschisis	Shih-Hwa Chiou et al., 2020 [200]	In animal studies
	Glutathione-responsive silica nanoparticles	Biomacromolecules (e.g., mRNA or ribonucleoprotein)	Intravenous or subretinal injection	Effectively delivered mRNA and ribonucleoprotein to RPE for gene therapy and genome editing	Shaoqin Gong et al., 2021 [204]	In vitro and animal studies
Retinal nanomedicine-assisted stem cell-based therapy at RD progression	HA-methylcellulose-based hydrogel	RPE and photoreceptors	Subretinal injection	Promoted vision respire in blind mice with advanced RD	Molly S Shoichet et al., 2020 [210]	In vitro and animal studies
	Gellan gum/silk sericin hydrogels	RPE	/	Supported RPE growth, enhanced cell proliferation and differentiation	Gilson Khang, et al., 2022 [215]	In vitro studies
	Electrospun poly(glycerol sebacate)/poly(ε-caprolactone) biopolymer	Ciliary neurotrophic factor	/	Mimicked natural extracellular matrix and increased neurite extensions of RGC	Maksym Rybachuk et al., 2024 [219]	In vitro studies
	Niobium carbide nanosheets	RPCs	Subretinal injection	Improved retinal neuronal differentiation of RPCs and protected RPCs by scavenging free radicals	Gu Ping et al., 2023 [222]	In vitro and animal studies
Retinal nanomedicine-based retinal optogenetics at late RD	Gold nanorods	/	Subretinal injection	Near-infrared stimulation increased activity in retinal neurons, and enabled mice to perform a learned light-driven behavior	Botond Roska et al., 2020 [230]	In animal studies
	UCNPs- graphene channelrhodopsin-2 biohybrid sensor	/	/	UCNP and optogenetically engineered cells on a graphene transistor for infrared sensing and imaging	Lianqing Liu et al., 2023 [231]	In animal studies

Table 1 (continued)

Applications	Composition of nanomaterials	Cargos	Route	Functions	Authors and the year of publication	Current stage of application
Retinal nanomedicine-based retinal prostheses at late RD	Molybdenum disulfide-coated optical synapses	/	Subretinal implants	Improved image sensing and learning functions	PingAn Hu et al., 2021 [250]	In vitro studies
	P3HT NPs	/	Subretinal injection	NPs spread out over the entire subretinal space, promoted light-dependent activation and recovered visual responses in late RD	Fabio Benfenati et al., 2020 [240]	In animal studies
	P3HT NPs	/	Subretinal injection	Reinstated physiological signals at cortical level and visually driven activities in late RD rats bearing fully light-insensitive retinas	Fabio Benfenati et al., 2022 [241]	In animal studies
	Quantum dots	/	Intravitreal injection	Converted light to electrical stimulus and improved mean best corrected visual acuity in patients with RP	Jeffrey Olson et al.,2021 [239]	Phase I clinical trial (NCT04008771)

VEGF vascular endothelial growth factor, *HA* hyaluronic acid, *DME* diabetic macular edema, *RP* retinitis pigmentosa, *RB* retinoblastoma, *DR* diabetic retinopathy, *AMD* age-related macular degeneration, *RD* retinal degeneration, *RPE* retinal pigment epithelium, *RGC* retinal ganglion cells, *RPCs* retinal progenitor cells, *CNV* choroidal neovascularization, *MSC-EVs* mesenchymal stem cell-derived extracellular vesicles, MnO_2 manganese dioxide, *AuNCs* magnetic hollow mesoporous gold nanocages, *P3HT NPs* poly[3-hexylthiophene] nanoparticles

Table 2 The key advantages, challenges, and clinical status of different retinal nanomedicine applications

Nanomedicine applications	Advantages	Challenges	Clinical status
Retinal nanomaterial-based eye drops	Noninvasive route and decreasing side effects Ease of administration and promoting patient compliance Enhancing contact with ocular surface and drug penetration Improving sustained release of drugs and retinal drug bioavailability	The cost and difficulties of synthesis/preparation varying in different nanomaterials Relatively complex manufacturing techniques Discrepancy in drug-loading efficiency	Some eye drops from organic nanomaterial, e.g., chitosan, cyclodextrin, liposome, have entered clinical trials for treatment of diabetic macular edema
Nanomaterial-based retinal contrast agents	Good tissue permeability due to small nanosize High sensitivity and spatial resolution Real-time monitoring and multimodal retinal imaging	Difficulty in interactions with biomolecules and biological processes Surrounding ocular leakage and irritation Drug resistance and higher dosage for use Additional invasiveness of extraction process	Failed to progress through clinical trials
Nanomaterial-based retinal therapeutic agents	Facilitating retinal pathology-targeted treatments Modulating the retinal microenvironment Enabling precisely control over biophysical and biochemical properties	Accounting for low marketed ophthalmic formulations Commercial viability barriers and regulatory barriers Delays in therapeutic development and economic losses	Clinical trials of mesenchymal stem cell-derived extracellular vesicles have been conducted to treat macular holes, retinitis pigmentosa and diabetic retinopathy
Retinal nanomedicine-based gene therapy for early RD	Minimizing off-target editing Improving biosafety Increasing gene encapsulation efficiency	Limited penetration and specific targeting Difficult to large-scale production Lacking economic and solvent-free production techniques	No clinical trials
Retinal nanomedicine-assisted stem cell-based therapy for RD progression	Supporting cell survival Regulating stem cell proliferation and differentiation Enhancing cell transplantation, immigration and integration in vivo	Lacking animal model that are consistent with clinical reality A single product or biomaterial cannot meet the design standards Difficult to achieve personalized retinal regenerative medicine	Have not yet been applied clinically
Retinal nanomedicine-based retinal optogenetics for late RD	Enabling deep-tissue optogenetic manipulation High tissue penetration Wireless optogenetic technology and reducing tissue damage	Technical complexity and high cost of research Low light conversion efficiency	No clinical trials
Retinal nanomedicine-based retinal prostheses for late RD	Improving the sensitivity and conversion of light Making retinal implants more flexible, adaptable and compatible with biological organisms Avoiding complex surgical procedures Reducing patient recovery time	Unavailable long-term stability and effects Difficulties in reconstruction of visual system	Clinical trials associated with quantum dots and phosphenes have been performed to treat retinitis pigmentosa

material-based eye drops have entered clinical trials, thereby laying a better clinical foundation.

2) Multifunctional nanoparticle-derived contrast agents are widely used for multimodal retinal imaging and synergistic theranostics. Real-time tracking and imaging probes with deep tissue penetration, excellent sensitivity, high spatial resolution, and analyte quantification are required to accurately localize retinal lesions in clinical settings. However, most nanomaterials can only achieve one aspect of these demands, compromising other functions [262]. Thus, more systematic investigation of imaging and therapeutic performance, as well as pharmacodynamics and pharmacokinetics may facilitate select the most suitable nanostructure configuration and nanomaterials. Additionally, novel technologies and approaches are crucial for promoting the capability of nanomaterials as contrast agents and improving imaging quality. Machine learning techniques allow the rapid processing and analysis of large amounts of data produced via the operation of imaging probes. The combination of cutting-edge imaging probes and advanced medical technologies to establish a medically superior platform may accelerate the clinical application of retinal nano-scale probes.
3) Innovative nanoformulations with inherent therapeutic features have facilitated the development of pathology-targeted treatments for various retinal diseases. However, inorganic nanomaterial-based drugs have failed to progress through clinical trials mainly due to potential in vivo toxicity, resulting in delays in therapeutic development and economic losses. Thus, their preparation should be focused on an environmentally friendly approach by simplifying and optimizing their physicochemical properties, including biostability, morphology, surface charge, particle size, hydrophilic/lipophilic properties, and permeability. Fortunately, several clinical trials of MSC-EVs have been conducted to treat a serial of retinal diseases, including macular holes, RP and DR. However, some challenges of EVs remain, especially poor recovery and purity, low extraction yields, low encapsulation efficiencies, and lack of standardized storage and preservation protocols. These problems should be considered prior to introduction into clinical practice. It is anticipated that more clinical trials will focus on the therapeutic potential of nanomaterial-based therapeutic agents, rather than on their monotonous role as drug delivery systems.
4) The application of nanomaterials in gene therapy holds great promise and deserves further attention. In contrast to traditional viral vectors, nanomaterial-based gene nanocarriers, combined with user-friendly nanotechnologies, minimize off-target editing, improve biosafety, and increase gene encapsulation efficiency, making them promising substitutes for viral vectors. However, it is necessary to further study the penetration and specific targeting of nanoparticles to explore more suitable gene delivery routes and to enhance gene expression and life expectancy by modifying DNA or vectors. Additionally, nanomaterials as gene nanocarriers have achieved remarkable results in preclinical research, but they have rarely achieved clinical transformation. Over the past few years, viral vector gene therapy has crossed the research and development gap since Luxturna was first approved in 2017, and an increasing number of gene therapies have entered the clinic in the past 4 years, giving scientists confidence that promising nanomaterial-derived gene vectors may benefit patients with retinal diseases more quickly after being more fully studied and tested.
5) In stem cell-based therapies for retinal regeneration, nanomaterial-derived nanoformulations or scaffolds can effectively regulate stem cell proliferation and differentiation, and improve cell transplantation. Although biomaterials play a crucial role in supporting and guiding strong plasticity, animal model experiments that are consistent with clinical reality are lacking. Therefore, the vast majority of nanomaterial scaffolds have not yet been applied clinically; however, the results of the present review suggest that stem cell-based therapy combined with nanomaterial scaffolds may be a promising strategy for ocular tissue regeneration. Currently, a single product or biomaterial cannot meet the design standards and patient requirements for each clinical application. With the development of regenerative medicine, the arrival of the era of precision medicine and more in-depth research on materials and tissue engineering, the application of nanomaterials in retinal regenerative medicine may achieve personalized clinical transformation.
6) The application of nanomaterials in retinal optogenetics offers new possibilities for deep-tissue optogenetic manipulation, but also presents some challenges needed to be further research and optimization. Their advantages include high tissue penetration and wireless optogenetic technology. Nanomaterials, especially UCNPs, can absorb NIR light and convert it to visible light, a property that allows light to penetrate deeper tissues, which is particularly important for retinal applications because the retina is located deep in the eye. Additionally, the use of nanomaterials can avoid optical fiber implantation required in traditional optogenetics, thus reducing

tissue damage and allowing experimental animals to be in a free state, which is advantageous for the study of long-term or complex behaviors. However, they encounter two major challenges: technical complexity and low light conversion efficiency. Precise control of the preparation and surface modification of nanomaterials is required to ensure that they functionalize effectively and safely in living organisms. However, this process increases the complexity and cost of research. Although nanomaterials can enhance the applications of optogenetics, their light conversion efficiency may not be as good as that of direct light activation, which can affect the efficiency and effectiveness of the experiments.

7) Existing retinal prostheses that use electrical pulses to trigger retinal neuronal activity have paved the way for visual restoration. Owing to their unique optical properties, nanomaterials can significantly improve the sensitivity and conversion of light. For example, nanowire arrays and quantum-dot materials can be designed as supersensitive photoreceptors that mimic or even exceed the functions of the natural retina. Nanotechnology also makes retinal implants more flexible and adaptable, making them more compatible with biological organisms, avoiding complex surgical procedures, and reducing patient recovery time. In addition, nanotechnology has significantly improved the resolution of retinal prostheses and compensated for the constraints of traditional methods. However, the subretinal injection of semiconductor polymer nanoparticles demonstrated in animal models is effective in the short term, and its long-term stability and effects are still needed to be verified. Reconstruction of the on- and off-pathways of the visual system remains a challenge that requires greater complexity and time investment.

In conclusion, the regulatory hurdles, toxicity, and long-term stability of retinal nanomedicines pose major challenges in clinical practice. For example, silicon dioxide nanoparticles initiate size-dependent retinal toxicity and subsequently induce ROS generation and glial cell activation [263]. Additionally, a vast spectrum of inorganic nanomaterials presents relatively poor pharmacokinetics and biodegradability; thus, there is a significant room for improvement in subsequent studies [264]. In terms of regulatory approval, regulatory scientists have established protocols with most agencies to facilitate early participation. These early interactions present an opportunity to assist ophthalmologists at regulatory agencies in setting expectations and requirements regarding new nanomaterials and nanotechnologies, and helping shape the appropriate path for proposed nanomaterials (pharmaceutical products versus medical devices). However, this mainly focuses on the preclinical development phase, and there is no specific path. Currently, mutual enhancement and communication among different fields is important, the unprecedented augmentation of bio-nanotechnology launched by private entities and academic institutions may provide a unique opportunity and possible solution. Connecting ophthalmologists with manufacturers, regulatory science experts, patent attorneys, and venture capitalists, may support ophthalmologists to familiarize themselves with different communities. Moreover, more thorough research on potential nanomaterials in suitable fields will facilitate the establishment of standardized procedures to accelerate the approval of nanomaterial applications. We believe that the collaborative efforts of ophthalmologists with various communities that are stakeholders will facilitate the successful translation of retinal nanomedicine into clinical practice in the near future.

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Author contributions
Zhimin Tang: Writing – original draft, Methodology, Investigation, Formal analysis. Fuxiang Ye: Writing – original draft, Methodology, Investigation, Formal analysis. Ni Ni: Writing – original draft, Methodology, Investigation, Formal analysis. Xianqun Fan: Supervision, Project administration. Linna Lu: Supervision, Project administration, Conceptualization. Ping Gu: Supervision, Project administration, Funding acquisition, Conceptualization.

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Availiability of data materials
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Declarations

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Not applicable.

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