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Stimulus-responsive nanomaterials for ocular antimicrobial therapy

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Nanomaterials exhibit a promising new avenue for treating infectious keratitis, having garnered considerable interest in the ophthalmic medical community due to their unique properties including higher target specificity, enhanced bioactivity of loaded agents, reduced drug dosage, and stimulus-responsive drug release. These stimulus-responsive nanomaterial-mediated therapeutic strategies offer innovative approaches for managing ocular antimicrobial diseases. In this review, we aim to summarize current applications of stimulus-responsive nanotherapeutics for ocular antimicrobial therapy. We briefly introduce the basic ocular structure, ocular barrier, infectious keratitis classification, and its microenvironment. Following this, we summarize the nanotherapeutic antimicrobial strategies employed in treating ocular infections including endogenous stimulus-responsive ocular nanodrugs, sonodynamic therapy, and wearable device-based therapy, focusing on their design principles, developmental progress, and advantages and limitations. Finally, we critically evaluate the biosafety profiles of responsive nanomaterials, specifically addressing cytotoxicity and immune interactions. To conclude, we discuss key challenges in this research field and future opportunities with explicit emphasis on clinical translation and practical medical applications.

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1. Introduction

The Eye of Horus is an emblem deeply woven into the fabric of ancient Egyptian culture. It embodies reverence for deities and symbolizes the pursuit of longevity, well-being, and renewal of life.[1] The human eye is a remarkable organ with a complex physiological structure that enables us to perceive the world. Such structural sophistication also renders it susceptible to pathological threats. Unfortunately, infectious keratitis is increasing globally, affecting approximately 800 people per 100 000. Eye infections and inflammation are now the fifth leading cause of blindness worldwide, highlighting the urgent need for prevention, diagnosis, and therapeutic strategies to protect this vital sense organ.[2]

Bacterial and fungal infections are the most common causes of infectious keratitis. Broad-spectrum topical antibiotics are often used as the first line of treatment for these infections. However, this practice usually leads to failure caused by antibiotic-resistant strains.[3,4] These dual challenges of pathogen resistance and suboptimal drug delivery collectively undermine conventional therapeutic efficacy. Despite advances in ocular drug delivery, several challenges remain. For example, topically administered drugs often struggle with low bioavailability due to their lower penetration. Fortunately, the recent surge in nanomedicine presents a promising path forward, potentially paving the way for both early diagnosis and effective treatment of infectious keratitis.[5,6] The versatility of nanotechnology allows tailored designs to overcome ocular barriers while countering microbial resistance. Thus, many nanomedicine platforms which are compatible with the pathological environment of ocular infections have been developed, such as liposomes,[7] nanoenzymes,[8,9] polymer micelles,[10] microneedles, hydrogels and so on.[11]

Among these platforms, stimulus-responsive delivery systems have emerged as a promising type of drug delivery platform due to their outstanding abilities, achieving precise drug release and regulating reactive oxygen species (ROS) scavenging/generation in response to endogenous signaling molecules present in ocular infectious microenvironments.[12,13] Incorporating stimulus-responsive properties into ocular drug delivery systems improves drug targeting and reduces biotoxicity. Ocular nanoplatforms show the potential to halt disease progression and mitigate vision loss in infectious keratitis.[14,15] These nanomedicines offer unique physicochemical properties due to their ultra-small dimensions, providing an effective alternative to clinical therapies.

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Unlike macroscopic materials, nanomaterials have better photothermal and electro-mechanical conversion capabilities, providing a rich choice for stimulus-responsive ocular drug delivery systems.[16,17] Furthermore, compared to conventional antimicrobial agents, this concept can also be applied in the design of nanodrugs for treating infectious keratitis. The loaded drugs are designed to release at specific sites which can be triggered by external stimuli, including light, ultrasound, magnetism, X-rays, and endogenous stimuli such as anterior segment pathology markers, pH, and endogenous ROS.[18,19] Such innovative nanomedicines show immense potential for clinical applications such as treatment of infectious keratitis with minimal side effects.

While most existing reviews on stimulus-responsive nanomaterials for ocular diseases predominantly focus on singular material categories (*e.g.*, polymers or hydrogels) or specific infection types (bacterial or fungal), the field has recently witnessed exponential growth in publications exploring various stimulus-responsive nano-systems for ocular anti-infective applications.[20,21] Thus, our review specifically examines infectious keratitis through systematic analysis of emerging responsive nanomaterial platforms. The discussion is structured through three critical dimensions: (1) classification of functional nanomaterials with therapeutic potential, (2) mechanisms of endogenous/exogenous activation, and (3) structure–function relationships in material design. By consolidating recent advances in stimulus-responsive drug delivery systems (SPR-DDS), we particularly emphasize their therapeutic implementations for ocular infections. Through rigorous analysis of design principles and performance benchmarks, this work establishes a foundational framework connecting structural parameters to antimicrobial efficacy. The proposed structure–performance correlation model ultimately advances the development of nanomedicines for improved clinical outcomes in keratitis treatment (Fig. 1).

2. Overview of eye infections

2.1 Ocular structure and the ocular barrier

Eye drops account for around 90% of clinical drug delivery. This route of administration can avoid hepatic toxicity, a concern with oral drug delivery.[22,23] Yet, precise drug targeting across the ocular barrier is a challenge in clinics. Human eyes have natural barriers to prevent external bacteria and viruses, but these also impede traditional drug delivery. These barriers consist of eyeball walls and contents. In addition, the cornea's monolayer of fibers and posterior wall create a sealed outer wall to protect eyes and ensure their optimal function.

When eyes are infected, drugs must overcome various barriers to reach the infection site. The physiological barriers include the tear and mucus barriers. The tear film (~3 μm

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Zichao Luo obtained his M.Sc. in Cellular Biology from Sichuan University (2011) under Prof. Yuquan Wei, subsequently advancing to a Research Assistant position at the Chinese Academy of Sciences (2011–2016) where he pioneered smart nanomaterials for cancer immunotherapy. He earned his Ph.D. in Chemistry from the National University of Singapore (2021) under Prof. Xiaogang Liu, focusing on the rational design of lanthanide-based nanomaterials for bioimaging and targeted drug delivery systems. Building upon this expertise, he conducted postdoctoral research (2021–2023) to develop photo-activatable nano-systems for cancer theranostics. Currently, Dr Luo serves as an Associate Professor at Fudan University (2023–present), leading an independent research group that bridges materials chemistry with translational medicine. His program systematically addresses three interconnected challenges: (1) engineering ocular drug delivery systems to penetrate ocular barriers, (2) developing precision-engineered nanoprobes for multimodal imaging diagnostics, and (3) designing light-responsive nanotherapeutics that synergistically integrate photodynamic therapy with immunomodulation strategies.

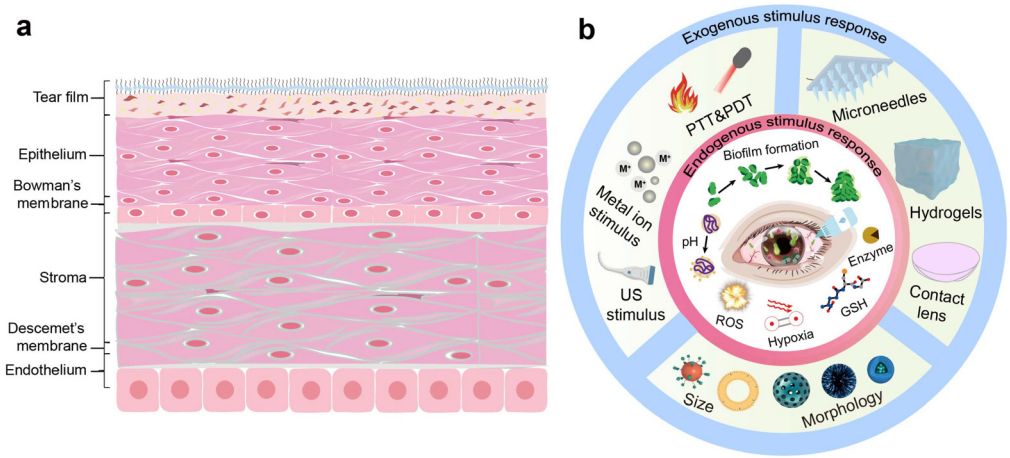

Fig. 1 Diverse applications of stimulus-responsive drug delivery systems for ocular infectious keratitis. (a) Schematic diagram of corneal anatomy. (b) Schematic diagram of the stimulus-response strategy used to treat corneal infections.

thick) has a lipid layer to prevent water loss and an aqueous layer for lubrication (Fig. 1a). Eye drops are quickly excreted *via* nasolacrimal drainage, and the tear barrier's mucin binds with foreign substances, further hindering drug access.[24,25]

2.2 Infectious keratitis classification and microenvironment

Infection keratitis can be categorized into bacterial keratitis (caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa*),[26] fungal keratitis (due to *Candida albicans*, *Fusarium*, *Aspergillus*, and *Cryptococcus*),[27] and viral keratitis (induced by *Herpesvirus*).[28] The pathological microenvironment of bacterial keratitis is a complex and delicate system. When foreign pathogenic microorganisms attack and damage corneas, corneal limbal blood vessels dilate and constrict, forming greyish-white cloudy foci with indistinct borders. As inflammation progresses, inflammatory infiltration is further aggravated, resulting in dark-greyish or greyish-yellow opacified foci with darker edges. Corneal epithelial cells proliferate quickly to cover the ulcerated surface. At this point, the collagen I/III ratio increases, compromising the biomechanical properties of the repaired skin, leading to scarring and compromising vision recovery. Bacterial biofilm formation represents a further serious characteristic of bacterial and fungal keratitis.[29] Biofilms are typically constituted by extracellular polymers, which coalesce to facilitate settlement at the biotic/abiotic interface, particularly in applications of ocular implantable and non-implantable devices (*e.g.*, intraocular lenses, contact lenses, lacrimal duct cannulas, and orbital implants).[40] The formation of bacterial biofilms effectively shields bacteria within the biofilm from external interference. More importantly, the bacterial biofilm has characteristics of reduced internal O_2 levels,[30] low pH,[31,32] and high GSH/H_2O_2 expression.[33,34] Besides, bacteria and fungi often exhibit elevated levels of MMP-9,[35,36] HAase, lipase, and gelatinase. Other specific enzymes are essential for the successful invasion, expansion, and colonization of bacteria against the host.[37–39]

2.3 Bacterial biofilm formation and infection in ocular implants

It is estimated that two-thirds of human infections are biofilm-associated. The formation of bacterial biofilms plays a vital role in ocular diseases, particularly on the ocular surface, where microbial abundance is relatively low compared to other body parts. This apparent paradox—biofilm predominance in a low-biomass niche—may arise from the ocular surface's unique immunological tolerance, which inadvertently creates permissive conditions for biofilm initiation. The limited number of bacteria also contributes to maintaining ocular health by competing with potential pathogens in the external environment and modulating immune response.[40,41] Moreover, when the ocular surface is stimulated by other high-risk factors, such as surgery, trauma, and other ocular devices, such as contact lenses, bacteria breach ocular surface defenses and increase rapidly in clusters. Such environmental perturbations destabilize the ocular surface microbiota equilibrium, triggering quorum sensing pathways that accelerate biofilm developmental phases. This process is characterized by highly dynamic regulation of adherence, colony formation, extracellular matrix production, maturation, and dispersal.[41,42] The formation of bacterial biofilms is regulated by external factors (mechanical vibration, temperature, ionic concentration, and nutrients) and internal factors (genetic factors and signaling molecules). Synergistic interactions between these regulatory factors promote preferential colonization of abiotic surfaces, as exemplified by the accelerated biofilm formation on contact lenses—a process initiated by pathogen adhesion to surface irregularities in ocular implants.[42]

Since the Second World War, the successful introduction of poly(methyl methacrylate) intraocular lenses (PMMA IOLs) has revolutionized conventional treatments.[43] Since then, ophthalmic implants have undergone significant advancements, offering patients benefits through innovative ocular implants, including contact lenses, drainage valves, corneal stromal

rings, and intraocular lenses. Furthermore, bacteria at the biotic/non-biotic interface have constrained the application and design of ocular implants. The prevailing view on biofilm formation is that surface properties of solid objects provide conditions for colonization by specific microorganisms. For example, *Pseudomonas aeruginosa* has a highly hydrophobic surface, while *Staphylococcus aureus* has a highly hydrophilic surface. The surface hydrophilicity of a solid implant influences its adsorption of specific proteins. For instance, lysozyme in tear film is preferentially adsorbed by contact lenses with hydrophilic interfaces, while contact lenses with hydrophobic interfaces accumulate more lipoproteins and lactoferrin.

In addition, bacterial biofilms play a significant role in ocular infections. These biofilms have been confirmed in various ocular implants, including IOLs, vitreous globules, corneal stromal rings, and prosthetic lenses. In the U.S., around 56% of corneal ulcers are linked to contact lens wear.[44] Bacterial adhesion and biofilm formation can be divided into two main stages. Initially, an abiotic/abiotic interface is established, which enables bacteria to bind to each other through bacterial adhesion. This process is mediated by bacterial surfaces, such as autolysin protein. Secondly, biofilm formation is partially controlled by colony sensing. This process involves bacteria interacting with each other and utilizing a range of intercellular communication and colony sensing systems to facilitate collective behavior *in vivo*, such as biofilm formation and colony escape.[45,46]

3. Stimulus-responsive ocular nanodrug

3.1 Endogenous stimulus-responsive ocular nanodrugs

3.1.1 Enzyme/pH-based nanodrug therapy. As is known, the level of matrix metalloprotein (MMP), nitroreductase (NTR), and ROS is increased at bacterial keratitis sites.[34] Thus, MMP-9 responsive nanocarriers can be exploited as a novel nanoplatform for ocular infection treatment. In 2020, Han *et al.*[47] developed a photosensitive supramolecular nanocomposite (MMP-S NPs) responding to MMP-9 for keratitis treatments (Fig. 2a). Triggered by the high expression of MMP-9 in the keratitis microenvironment, the protective polypeptide shell of MMP-S NPs was removed. The internal cationic peptide was exposed, thus achieving efficient penetration into the bacterial biofilm and efficient binding of bacteria. This MMP-S NP exhibited excellent antibacterial activity through a time-dependent antibacterial behavior test (Fig. 2b).

Nitroreductase is a predominantly bacterial enzyme also found in some eukaryotes. Thus, it can also be employed in designing novel delivery systems. In 2024, Xiang *et al.*[48] designed a novel nanoplatform, named $Cu_{2-x}Se$@BSA@NTRP, for combinational diagnostic and therapeutic applications, exhibiting effective antibacterial activity (Fig. 2c and d). This nanoplatform facilitated corneal wound epithelization *in vivo* by leveraging bacterial endogenous nitroreductase probes (NTRP) to generate responsive signals within bacterial cells. This endogenous enzyme response nanoplatform effectively reduced potential biological toxicity and was expected to achieve clinical applications. However, the main pathogenic microorganisms of keratitis infection are very different; screening more endogenous enzyme response platforms with high targeting and low toxicity has become more challenging.

The environment of infectious corneal trauma exhibits acidic pH, which has been widely applied to design smart nanotherapeutics. Low pH plays a key role in corneal epithelium regeneration, inflammation progression, neovascularization, and scarring during wound healing.[37] For example, in 2022, He *et al.* proposed an integrated nanoplatform (MSNs@lyticase-PDA-Ga, MLPGa) based on lyticase and Ga^{3+} for eradication of both planktonic *Candida albicans* and mature biofilms (Fig. 2e and f).[49] After degrading the dense extracellular polysaccharide produced by fungi, Ga^{3+} is released in the acidic biofilm microenvironment of fungi (pH 6.5). This nanoplatform achieved excellent antibacterial performance *in vivo* and real-time monitoring of Ga^{3+} release, demonstrating promising potential in clinical practice. In another study, under an endogenous stimulus of pH 5.5, Wang *et al.* developed a novel low-temperature photothermal antibacterial agent for *E. coli*-induced mouse keratitis treatment, confirming that pH could trigger nanoreactors for keratitis biofilm disruption and deep biofilm penetration.[50]

3.1.2 ROS-based nanodrug therapy. ROS can effectively eliminate pathogens through various mechanisms involving oxidative and non-oxidative stress pathways. Oxidative stress damage occurs upon direct interaction with bacteria, whereas non-oxidative stress damage is associated with ROS-mediated signaling *via* pattern recognition receptors, autophagy processes, neutrophil extracellular traps, and T cell infiltration.[51–53] However, certain pathogenic microorganisms have developed adaptive strategies in response to the host's immune-mediated production of ROS. This persistent adaptation demands precise control of ROS levels. Consequently, focusing on the regulation of ROS is considered a novel antibiotic alternative therapy.[54–56] Current antimicrobial therapies *via* ROS can be categorized into two types: those triggered endogenously and those activated exogenously. Endogenous ROS-based antimicrobial strategies involve chemical reactions facilitated by ROS within the disease microenvironment or through intrinsic chemical processes inherent to materials.

Thus, triggering a dramatic increase in endogenous ROS in keratitis therapy is considered to be a more promising antibiotic replacement therapy.[57] For example, in 2024, Huang *et al.* constructed a collagen nanosheet loaded with the antibacterial peptide Tet213 in the treatment of keratitis by up-regulating intracellular ROS generation.[58] In another study, Zhang *et al.* also harnessed the up-regulated ROS at infection sites to effectively address bacterial keratitis.[59] By employing poly(phenylboronic acid-(3,4-dihydropyrimidin-2(1*H*)-one))-*co*-(2-lactobionamidoethyl methacrylate) glycopolymeric micelles, the PBA-DHPM moiety serves as a targeting ligand, which facilitates penetration through the corneal epithelium while

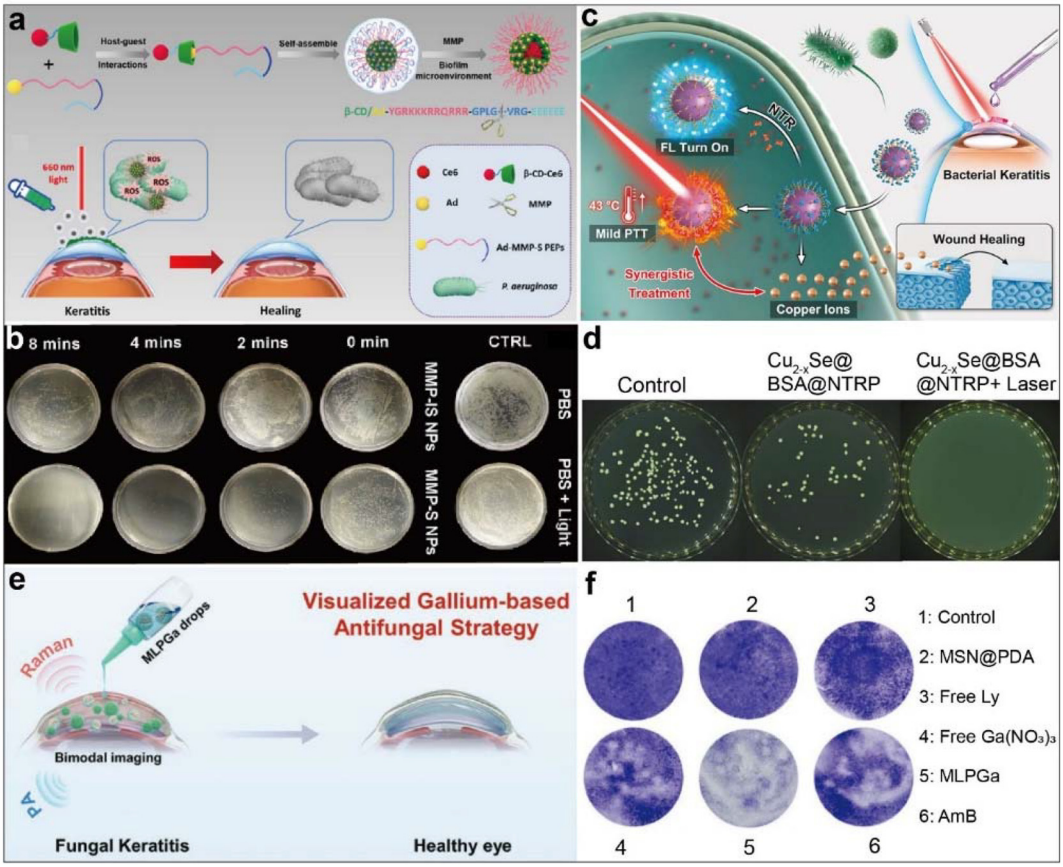

Fig. 2 Representative enzyme/pH-responsive nanoplatform for keratitis infection treatment. (a and b) Schematic diagram of MMP-9 sensitive nanoparticle and corresponding anti-bacterial assay. Reproduced with permission from ref. 47. Copyright© 2020 Elsevier. (c and d) Nitroreductase-sensitive nanoparticle and corresponding anti-bacterial test. Reproduced with permission from ref. 48. Copyright© 2024 Elsevier. (e) Schematic diagram of visualized gallium-based antifungal strategy. (f) Corresponding antifungal biofilm assay of MSNs@lyticase-PDA-Ga. Reproduced with permission from ref. 49. Copyright© 2022 Willy.

simultaneously eliminating local ROS at infected areas. This approach not only promoted bacterial eradication but also aided in ROS removal, enhancing wound healing processes.

3.2 Exogenous stimulus-responsive ocular nanodrugs

3.2.1 PDT & PTT-based therapy. Photodynamic therapy (PDT) effectively eliminates bacterial cells by generating highly toxic ROS species. Typically, PDT comprises three essential components: the photosensitizer, light, and oxygen. Based on the distinct mechanisms of ROS generation, photosensitizers can be categorized into Type I and Type II. Under light excitation, Type II photosensitizers generate singlet oxygen ($^1O_2$) through an energy transfer mechanism, whereas Type I photosensitizers produce $^{\bullet}OH$, $O_2^{\bullet-}$, and H_2O_2 *via* an electron transfer process. However, the therapeutic efficacy of PDT is constrained by the limited light penetration depth and suboptimal levels of tissue oxygenation.[60–62]

Photosensitizers are a key factor of PDT. Porphyrin derivatives, methylene blue, riboflavin, and rose red are most commonly applied in ophthalmology (Fig. 3a–c).[63,64] Under irradiation with light, typically small organic molecule photosensitizers can generate high-yield ROS that can rapidly and effectively eliminate bacteria and exhibit low toxicity to normal tissues. However, due to the inadequate regulation of ROS, the excessive cross-linking of corneal collagen fibers and the blocking of photosensitizers to bacterial membranes restrict the applications of photodynamic therapy (PDT) in eye infections.[65]

Therefore, combining photosensitizers with other targeted functional components is applied to achieve specific bacterial capture and enhance photodynamic therapy. For example, in 2002, Zhu *et al.* obtained a series of block-specific diblock copolymers PαGal$_{50}$-*b*-PGRB$_n$ *via* reversible addition-break chain transfer polymerization (RAFT) for killing internal bacteria through carbohydrate–protein interactions to disperse the biofilm (Fig. 3d).[66] In another study, Chen *et al.* developed an intelligent phage eye drop that combined the phage with a type I photosensitizer to overcome the oxygen-deficient dependence of the bacterial biofilm of the eye and subsequently penetrate and destroy the biofilm, effectively clearing the bacterial biofilm of the cornea (Fig. 3a and b).[63] Similarly, the difference in membrane structure between G^- and G^+ bacteria

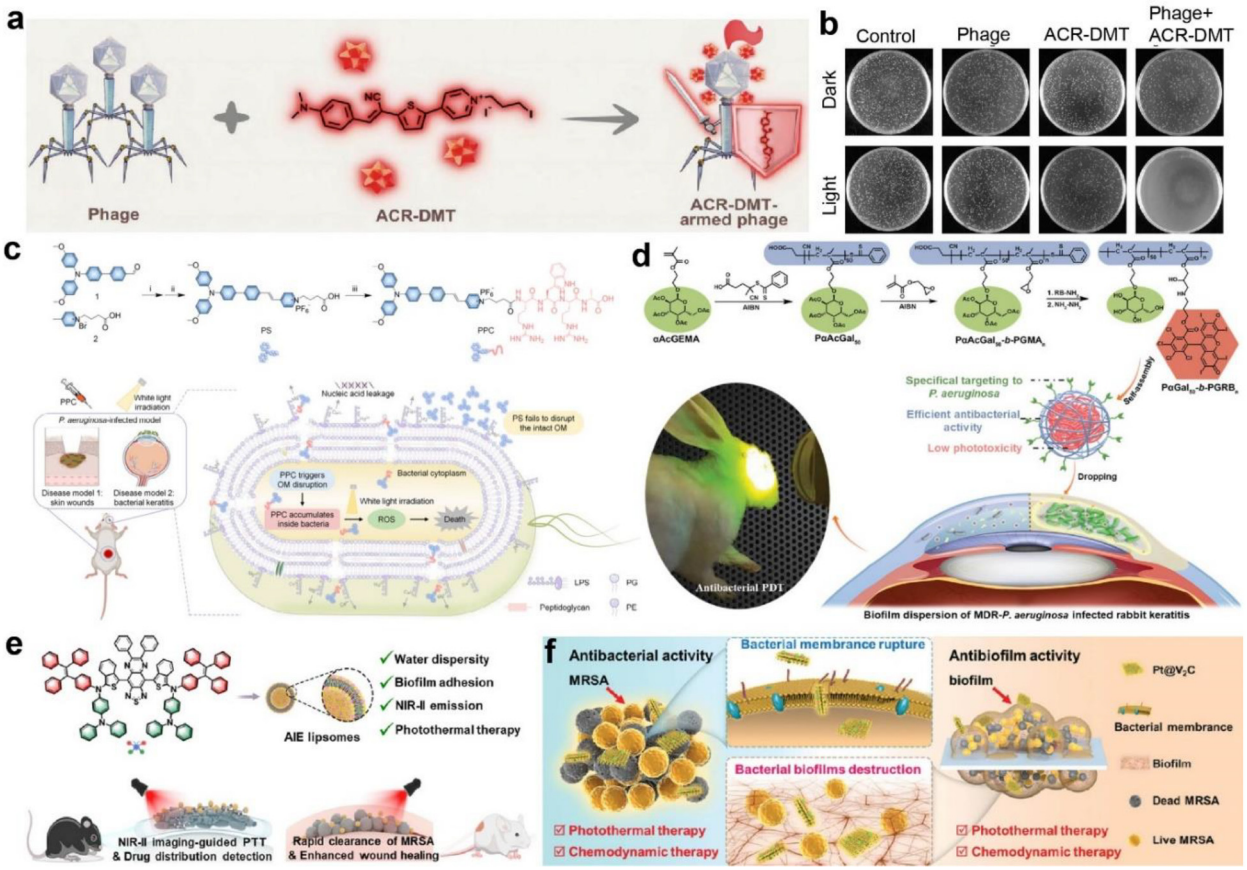

Fig. 3 Representative anti-keratitis PDT&PTT therapy. (a and b) Type I photosensitizer-armed phage to eliminate MDR-PA keratitis and corresponding antibacterial assay. Reproduced with permission from ref. 63. Copyright© 2024 from Willy. (c) Peptide-photosensitizer conjugate for the targeted killing of G^- bacteria. Reproduced with permission ref. 64. Copyright© 2024 American Chemical Society. (d) PαGal$_{50}$-*b*-PGRB$_n$ targeting bacterial extracellular polymers. Reproduced with permission from ref. 66. Copyright© 2022 Willy. (e) Butterfly-shaped aggregation-induced luminescent polymeric assemblies for the treatment of keratitis bacterial biofilms. Reproduced with permission from ref. 72. Copyright© 2023 American Chemical Society. (f) V_2C MXene nanoplatforms for PTT and CDT therapy. Reproduced with permission from ref. 77. Copyright© 2024 Willy.

means that the membrane of G^- bacteria comprises LPS (lipopolysaccharide), which restricts the adhesion and deep penetration of photosensitizers. For instance, Zhou *et al.* developed a peptide–photosensitizer conjugate by conjugating a hydrophobic cationic short peptide and a hydrophobic AIE photosensitizer for anti-skin infection and anti-keratitis infection, demonstrating an effective degradation of the structural integrity of bacterial outer membranes *in vivo* by the nanoconjugate-mediated PDT effect (Fig. 3c).[64]

Photothermal therapy (PTT), by converting absorbed light energy into heat, produces a thermal effect in the disease area and destroys the integrity of bacterial membrane, disrupting the normal physiological function of bacteria.[67,68] Specifically, photothermal preparations do not require endocytosis, endowing them as a strong competitor to antibiotic replacement therapy. To improve small molecule-based photothermal conversion efficiency, there are two strategies: (I) increase the molar absorption coefficient[69,70] and (II) excited intramolecular motion.[71] For instance, in 2023, Yan *et al.* designed three butterfly-shaped aggregation-induced luminophores (AIEgens) with balanced non-radiative and radiative attenuation for imaging-assisted photothermal killing of bacterial biofilms (Fig. 3e).[72] In another study, Lochenie *et al.* designed a benzothiazole-paired material by combining non-photosensitive and photosensitive benzothiazoles and modularized this material into a pathogen-binding peptide, achieving broad-spectrum antimicrobial activity.[73]

On the other hand, hypoxia is a common state of bacterial infection, which limits the application of photosensitizing agents in an anoxic microenvironment at infectious sites. Hypoxia-triggered drug releasing systems also have been applied in bacterial infections. For example, in 2021, Bai *et al.* developed an oxygen-self-supplied nanoplatform based on a fluoridated BODIPY sugar simulator through RAFT polymerization.[74] This platform could alleviate the anoxic microenvironment in keratitis and interfere with bacterial biofilm colonization. In *in vivo* studies, target inactivation of nanodrugs was achieved under visible light irradiation, thus enhancing the photodynamic therapy effect on bacterial infections. For another example, in 2022, Wang *et al.* used the spontaneous

oxygen-producing capacity of cyanophytes as carriers for delivering photosensitizers Ce6 and ultra-small $Cu_{4.5}O$ nanoparticles with catalase activity for relieving hypoxia.[75] Under laser irradiation, this nano complex showed enhanced photodynamic therapy on refractory keratitis by reversing the inherent oxidative stress state of the keratitis microenvironment.

Among inorganic nanomaterials, MXene-based nanomaterials exhibit excellent photothermal conversion efficiency (PCE).[76] However, MXene has a limited response to laser irradiation in the NIR-II region. Thus, constructing an MXene-based heterojunction is an effective strategy to improve its therapeutic efficacy. For instance, in 2024, He *et al.* modified platinum nanoparticles onto V_2C nanosheets to obtain a novel artificial nanoplatform ($Pt@V_2C$) for eliminating methicillin-resistant *Staphylococcus aureus*. This nanocomposite showed enhanced photothermal conversion efficiency, NIR-II region light absorption, and NIR-II region enhanced POD-like and OXD-like activities (Fig. 3f).[77] In another study, they constructed monolayer high-entropy MXenes (HE MXenes) for anti-infection treatment by implementing transition metals with high entropy and low Gibbs free energy to fill the gap.[78] By exposing the active site of the high-entropy atomic layer, HE MXenes realized NIR-II enhanced intrinsic oxidase mimic activity for eliminating *Staphylococcus aureus* and quickly removing the biofilm *in vivo*.

Nanoenzyme or PDT, PTT-mediated antibacterial nanomaterials with high catalytic activity have advantages against skin and corneal infections.[79–81] Under the stimulation of an external light source and endogenous factors, the photocatalytic and enzymic catalytic nanomaterials exhibit an advantage in low cost and easy manipulation, which may provide a promising potential for clinical applications.[82,83]

3.2.2 SDT-based therapy. As a non-invasive and highly penetrating cancer treatment, sonodynamic therapy (SDT) can overcome the insufficient penetration depth of light-triggered therapy.[84–86] The main mechanisms of SDT include inertial cavitation triggering sonosensitizer-mediated generation of ROS species and pyrolysis bubble rupture generating ROS.[87,88] Some photosensitizers also can be activated by ultrasound, such as porphyrin monomethyl ether, indocyanine green, and phthalocyanine.[89–91] Inorganic sonosensitizers (piezoelectric materials, metal oxide nanomaterials, *etc.*) and organic sonosensitizers (porphyrin derivatives, phthalocyanine derivatives, *etc.*) are the primary sources. More importantly, sonodynamic antibacterial therapy could enhance the permeability of sonosensitizers into bacterial biofilms.

In the realm of ophthalmic ultrasound medicine, ultrasound-based imaging leverages unique properties of sound waves because they traverse ocular tissues to furnish ophthalmologists with critical diagnostic insights regarding eye morphology.[92,93] This technique is characterized by its rapid execution, non-invasive nature, and absence of radiation exposure. However, SDT is infrequently employed in ophthalmology, potentially due to hypoxic conditions prevalent in the ocular microenvironment. The intricate structure of ocular anatomy combined with high-intensity ultrasound can generate heat that leads to irreversible damage to ocular tissues, subsequently impairing patients' vision. Conversely, therapeutic ultrasound has significant advantages in high-intensity focused ultrasound (HIFU) treatment of glaucoma and ultrasound-mediated drug delivery.[94] On the other hand, due to the ocular barriers, local ultrasound-mediated drug delivery is a promising strategy for treating ocular infectious diseases.[95,96] As a nano-therapy platform, the ultrasound-responsive hydrogel patch is designed to fit seamlessly into the eye, offering an excellent choice for antibacterial treatment of keratitis. For instance, in 2024, Kong *et al.* developed a composite antibacterial patch that integrated near-field electrospinning microfibers with gold nanoparticle-modified barium piezoelectric titanate nanoparticles (Au@BTO) and human collagen (RHC) hydrogel (Fig. 4a).[97] This platform simulated the natural structure of corneal tissue, enhancing adhesion and delivering effective ocular antibacterial therapy. After being treated with an ultrasound patch, the corneal defect of mice was significantly relieved, and the wound was recovered (Fig. 4b). Thus, sonodynamic therapy combined with new drug delivery vehicles could achieve multifunctional and full-cycle treatments of anti-keratitis.

3.2.3 Wearable device-based therapy. Wearable devices provide a new therapeutic paradigm for treating ocular infectious diseases.[98–100] Three wearable devices (microneedles, hydrogels, and contact lenses) are considered closely related to ophthalmology for treating keratitis. While these innovations offer targeted delivery advantages, conventional ocular therapies confront fundamental limitations. Local administration of eye drops requires multiple administrations due to their low bioavailability. Thus, microneedles have gained continuous attention and significant progress as an innovative ocular drug delivery method in the past decades.

To date, due to the pain caused by microneedles in the eye's cornea, miniaturization and degradable microneedles have been developed as a promising approach for the treatment of ocular infections. For instance, in 2022, Park *et al.* designed a novel ocular drug delivery platform integrating silicon nanoneedles with a tear-soluble contact lens.[101] The silicon nanoneedles penetrated the cornea in a minimally invasive manner and achieved long-term sustained anti-inflammatory ocular drug delivery. This platform showed a new way to deliver drugs to the eye and played a role in eye tumors or infections (Fig. 5a–c). Another representative example is the topical delivery of predatory bacteria to fight eye bacterial infections. In 2021, Cui *et al.* developed frozen microneedles filled with bacterial suspension of glycerin, PBS, and predatory bacterium *B. bacteriovorus* for treatments of ocular surface disorders.[102] These frozen MNs can release *B. bacteriovorus* to remove Gram-negative bacteria and achieve an excellent antibacterial effect in a rodent eye infection model (Fig. 5d–f).

Loading nano-enzymes with antibacterial activity into wearable devices is a promising antimicrobial strategy. In 2023, Kong *et al.* designed frozen reinforced microneedles loaded

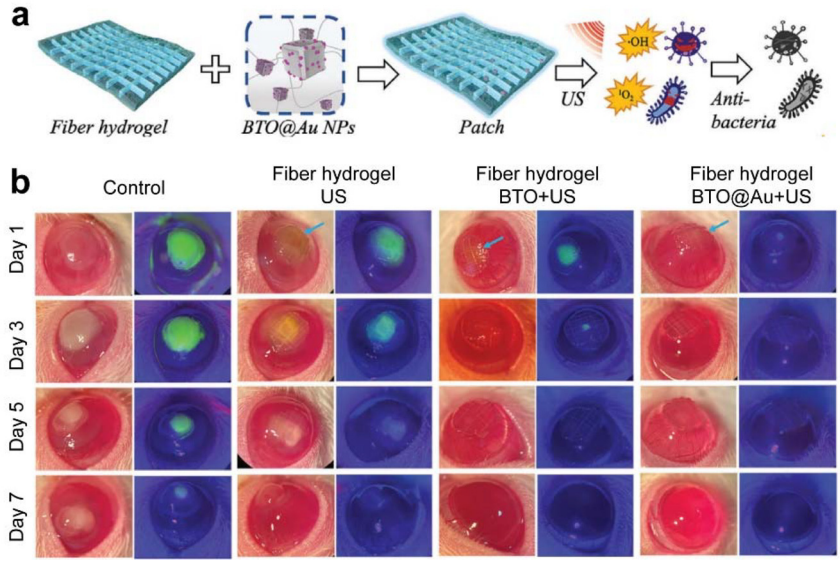

Fig. 4 Representative SDT-based therapy. (a and b) Schema of representative SDT anti-keratitis therapy and related antibacterial effect in the bacterial keratitis model. Reproduced with permission from ref. 97. Copyright© 2024 Willy.

with an iron ion-based nano-enzyme, tannic acid (TA), and polyethylpyrrolidone (PVP) for keratitis treatments (Fig. 5g).[103] This microneedle showed a superior therapeutic effect in rat eye infections compared with conventional eye drops, owing to the photothermal effect and peroxidase-mimetic activities. However, the preparation progress of this microneedle treatment is complicated, limiting its further clinical applications. In another example, Liu *et al.* developed Mn oxide nanocluster-modified graphene nanosheets (MnOx/GDY) as multi-enzyme-like nanoenzymes.[11] These nanosheets were then loaded into hyaluronic acid (HA) and polymethyl methacrylate ocular microneedles (MGMN) to treat bacterial and fungal keratitis (Fig. 5h). This MGMN platform potently eliminated pathogens, prevented biofilm formation, reduced inflammation, and alleviated ocular hypoxia *in vitro and in vivo*.

Hydrogel, a promising drug carrier and sustained drug release system, has received extensive attention in treating corneal infection and promoting corneal wound repair. Recently, hydrogels have mainly been applied to combat severe infectious keratitis. For example, in 2023, Meng *et al.* introduced a hybrid hydrogel composed of silk fibroin protein and chitosan for treating infectious keratitis.[106] The hybrid hydrogel showed excellent capabilities of anti-inflammatory, anti-bacterial, and proliferative stimulation due to the double network formed from silk fibroin and polydeoxyribonucleotide quaternary chitosan (Fig. 6). This dual network-based hydrogel showed mechanical strength and transparency like a natural cornea, thus effectively eliminating residual bacteria *in vitro* and *in vivo*, alleviating inflammation, promoting regeneration of corneal epithelium, and finally promoting wound healing.

Stimulus-responsive hydrogels with tailored material designs are emerging as transformative platforms for ocular infection therapy by integrating precise immunomodulation and antibacterial functions through advanced chemical engineering. For instance, Lin *et al.* engineered a pHEMA CL-based hydrogel *via* synergistic integration of quaternized chitosan (QCS) and epigallocatechin gallate (EGCG), creating a ROS-responsive dual-functional system that combines cationic antimicrobial action with antioxidant polyphenol activity.[107] This design achieved high bacterial eradication and significantly reduced inflammatory TNF-α levels through sustained ROS scavenging and controlled drug release. In addition, Fan *et al.* developed a cGelMA/CGA-CL hydrogel using UV-initiated photopolymerization to conjugate chlorogenic acid (CGA) into a moisture-retentive porous network, enabling pH-dependent CGA release.[108] The system demonstrated potent antibacterial efficiency against *Pseudomonas aeruginosa* and suppressed IL-6 production *via* simultaneous pathogen elimination and macrophage polarization modulation. These advances highlight the potential of chemically engineered hydrogels to address ocular infections through multifunctional therapeutic mechanisms.

Stimulus-responsive nanoplatforms combining endogenous triggers (*e.g.*, pathological pH/enzymes) with exogenous actuation (*e.g.*, near-infrared/ultrasound) represent a paradigm-shifting approach for precision management of bacterial keratitis through spatiotemporally resolved therapeutic actions. Endogenously activated systems leverage infection-specific biomarkers to enhance biofilm penetration and trigger localized drug release, addressing antibiotic resistance by minimizing off-target effects. Externally guided modalities enable on-demand pathogen eradication *via* physical energy conversion while preserving ocular tissue integrity through controlled energy deposition. Critical advancements require (1) development of adaptive smart nanocarriers capable of sequential responses to dynamic infection microenvironments, (2) systematic optimization of stimulus parameters to maximize antimicrobial efficacy while maintaining corneal transparency,

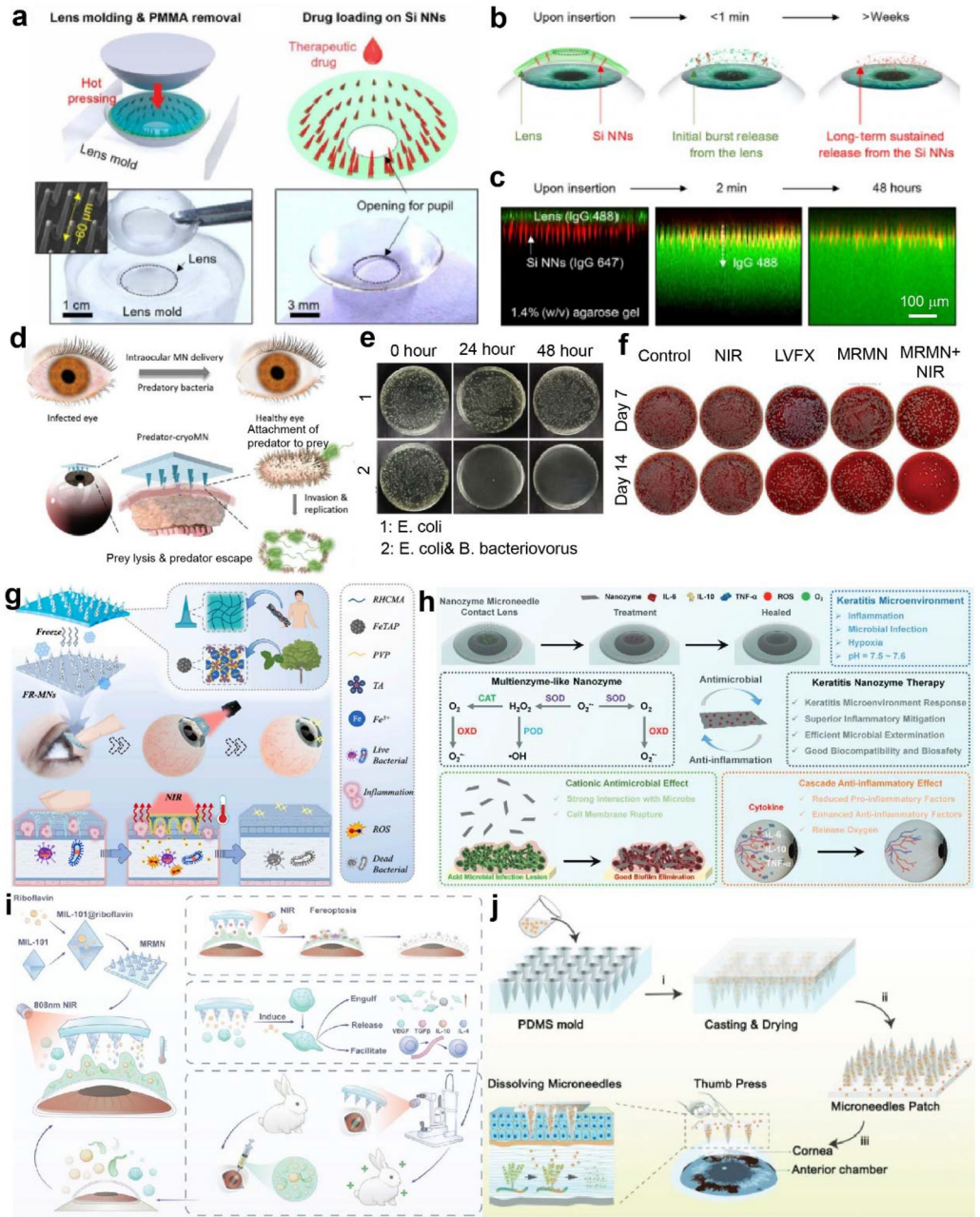

Fig. 5 Microneedle-based anti-bacterial keratitis platform. (a and b) Process for fabricating biodegradable silicon nanoneedles. (c) Fluorescence imaging of silicon nanoneedles penetrating the rabbit cornea. Reproduced with permission from ref. 101, Copyright© 2022 American Association for the Advancement of Science. (d–f) Cryo-microneedle filled with predatory bacteria against eye infection. Reproduced with permission from ref. 102. Copyright© 2021 Willy. (g) Schema of frozen reinforced microneedles loaded in nano-enzyme. Reproduced with permission from ref. 103. Copyright© 2023 Elsevier. (h) Scheme of microneedles loaded with nano-enzyme produced by manganese oxide nanocluster-decorated graphdiyne nanosheets for keratitis treatment. Reproduced with permission from ref. 11, Copyright© 2024 Willy. (i) Scheme of microneedles loaded with MIL-101@riboflavin for bacterial keratitis. Reproduced with permission from ref. 104. Copyright© 2024 Wiley. (j) Scheme of microneedles loaded with fluconazole against fungal infection of keratitis. Reproduced with permission from ref. 105. Copyright© 2022 Willy.

and (3) rational design of biodegradable nanocomposites with tunable ocular residence times to balance therapeutic persistence and metabolic clearance. This multimodal integration strategy establishes a foundation for next-generation personalized nanomedicine against sight-threatening corneal infections.

4 Biosafety: cytotoxicity and immune interactions

4.1 Cytotoxicity of nanomaterials

Stimulus-responsive nanomaterial platforms, including metallic, carbon-based, and polymeric nanomaterials, have demon-

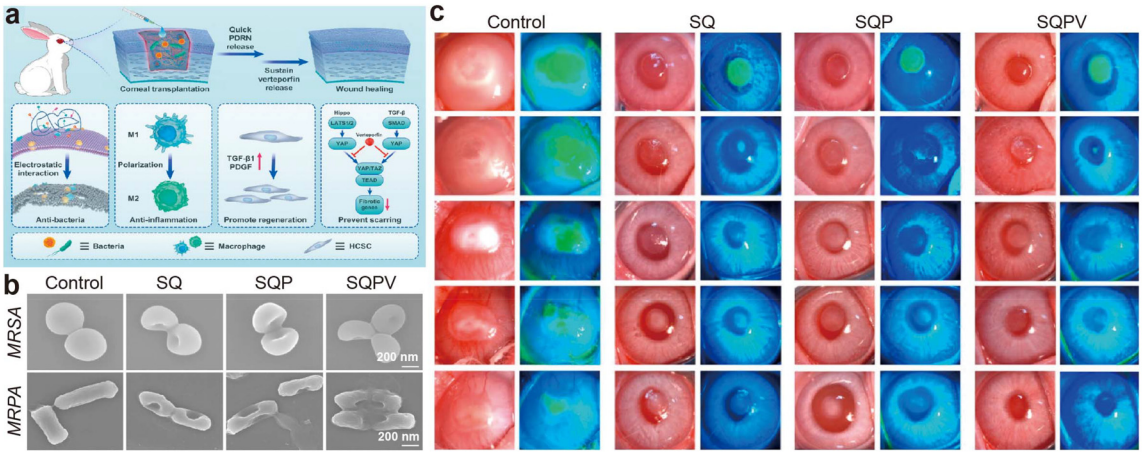

Fig. 6 Representative antibacterial hydrogels for treatment of infectious keratitis. (a) Scheme of versatile SF/CF-based hybrid hydrogel (SQPV) for antibacterial, anti-inflammatory, promotion proliferation, and prevention scare. (b and c) The anti-bacterial effect of SQPV *in vitro* and *in vivo*. Reproduced with permission from ref. 106, Copyright© 2023 Elsevier.

strated considerable potential in the treatment of ocular infections through the controlled generation of reactive oxygen species (ROS).[109,110] Preclinical studies have shown that silver nanoparticles (AgNPs), gold nanoparticles (AuNPs), carbon nanotubes, and graphene derivatives exhibit significant antimicrobial activity, primarily mediated by rapid ROS production.[111–113] However, the inherent ocular toxicity of these nanomaterials, driven by mechanisms such as oxidative stress, inflammatory cascades, mechanical damage, and apoptosis, necessitates rigorous evaluation. This is particularly critical given the eye's heightened sensitivity and the inevitable interactions between nanomaterials and ocular tissues.

As summarized in Table 1, the toxicity profiles of nanomaterials vary significantly depending on their composition, including metals, metal oxides, carbon-based materials, polymers, and quantum dots. For instance, AgNPs have been associated with Ag^+-induced corneal ulceration, while TiO_2 nanoparticles can cause UV-activated ROS-mediated corneal epithelial damage. The route of exposure, whether topical, intravitreal, or systemic, also plays a critical role in determining the manifestation of toxicity, which may include conjunctival congestion,[114] corneal edema,[115] and retinal injury.[116,117] Furthermore, factors such as particle size, surface charge, surface modifications, and exposure duration significantly influence the ocular toxicity of nanomaterials.[118,119] For example, smaller nanoparticles are more likely to penetrate ocular tissues, while positively charged nanoparticles tend to exhibit stronger interactions with cell membranes.[120,121] These

Table 1 Ocular toxicity of stimulus-responsive nanomaterials

Category	Materials	Ocular toxicity manifestations	Toxicity mechanisms	Exposure routes	Symptoms/damage
Metal NPs	Au NPs[129]	Corneal deposition	Oxidative stress	Eye drops, *i.v.* injection	Corneal edema; blurred vision retinal vascular leakage
	Ag NPs[130]	Conjunctival hyperemia; lens damage	Ag^+ ion release ROS overproduction	Topical, environmental	corneal ulcers
Metal oxides	TiO_2 NPs[131]	Photo-induced retinal damage corneal scarring	Photocatalytic ROS inflammatory responses	UV exposure, topical	Photophobia macular degeneration; corneal opacity
	ZnO NPs[132]	Ocular surface inflammation	Zn^{2+} release, lysosomal membrane disruption	Topical, aerosol inhalation	Dry eye syndrome conjunctival hyperemia
Carbon-based	Carbon nanotubes,[133] GO[134]	Corneal injury, chronic fibrosis Retinal pigment epithelium (RPE) apoptosis, blood-retinal barrier disruption	Physical abrasion, NLRP3 inflammasome activation	Dust contact, surgical implants Intravitreal injection, systemic	Corneal scarring, vision loss, elevated glaucoma Retinal edema, visual field defects
Polymeric NPs	PLGA[135]	Transient intraocular pressure (IOP) elevation,	Particle blockage of trabecular meshwork,	Intravitreal injection, implants	IOP fluctuation; iris adhesion
Quantum dots	CdSe/ZnS QDs[136]	Retinal phototoxicity, optic nerve degeneration	Cd^{2+} leakage, ROS generation	*i.v.* injection, light exposure	Nyctalopia; optic nerve atrophy
Others	Black phosphorus[137]	Conjunctival goblet cell loss, tear film instability	Physical adsorption of tear components	Photothermal ocular application	Acute retinal detachment vitreous opacity

considerations highlight the need for a comprehensive understanding of nanomaterial properties and their biological interactions to ensure safe and effective therapeutic applications.

4.2 Immune response and biocompatibility

Immune compatibility and controlled biological interactions are pivotal for advancing nanomaterial-based drug delivery systems toward clinical translation. Nanomaterials exhibit material-dependent immunomodulatory effects, ranging from innate immune cell phagocytosis to inflammasome activation and pro-inflammatory cytokine upregulation. These divergent behaviors underscore the necessity of tailoring nanomaterial design to minimize unintended immune activation while preserving therapeutic efficacy.

The ocular immune response to nanoparticles is governed by distinct mechanisms across material categories. Metallic nanoparticles (AgNPs, AuNPs) activate NLRP3 inflammasomes in macrophages, promoting IL-1β, IL-6, and TNF-α secretion that exacerbates corneal inflammation and blood–ocular barrier disruption.[122] Metal oxides (TiO_2, ZnO), conversely, induce cellular stress through ROS-mediated complement activation and CXCL8 chemokine release, with PEGylation and size optimization (<50 nm) offering partial mitigation of immunogenicity.[123,124] Carbon-based materials, while prone to TGF-β-mediated fibrosis and corneal scarring due to physical damage, can be rendered safer by modulating oxidation states (C : O > 2) and applying biocompatible coatings (*e.g.*, polyethylene glycol, hyaluronic acid).[125,126] A notable exception lies in black phosphorus nanosheets (BPNS), which exhibit dual photothermal utility and immune risks: near-infrared irradiation triggers HSP70 release and TLR4/NF-κB pathway activation, while their oxidative degradation into phosphate derivatives stimulates APC-driven $CD4^+$ T cell activation.[127,128]

Collectively, these findings highlight three translational imperatives. First, rigorous evaluation of long-term biosafety, including cumulative retention and degradation kinetics, is essential for clinical adoption. Second, toxicity mitigation strategies (surface functionalization, size control, oxidation modulation) must be optimized to delay harmful byproduct release and attenuate immune recognition. Finally, engineering immunotolerant "stealth" systems through biomimetic coatings or microenvironment-specific property tailoring (*e.g.*, charge, stimuli-responsiveness) could enable precision targeting of ocular pathologies such as infectious keratitis or glaucoma, bridging the gap between nanomaterial innovation and clinical viability.

5 Conclusion

Stimulus-responsive nanomaterials have emerged as a transformative strategy for ocular antimicrobial therapy, particularly in managing infectious keratitis. While endogenous triggers (pH, enzymes, H_2O_2, hypoxia) enable localized drug activation, current mono-stimulus approaches inadequately address the multifactorial pathology of corneal infections. Externally activated systems utilizing light (PTT/PDT) or ultrasound (SDT) demonstrate superior clinical potential due to their spatiotemporal precision and dual-targeting capabilities against pathogens and inflammation. Combinatorial regimens integrating these modalities are poised to become first-line interventions, offering synergistic efficacy while circumventing antimicrobial resistance mechanisms. Future designs must prioritize multi-stimuli-responsive platforms to mimic dynamic ocular microenvironments.

The integration of ocular imaging technologies (PA, MRI, PET-CT) with smart nanocarriers represents a paradigm shift toward theranostic platforms. Real-time visualization of drug release kinetics and lesion progression through multimodal imaging enables personalized dose adjustment and therapeutic monitoring. For instance, PA imaging excels in mapping anterior segment vasculature, while MRI provides deep-tissue resolution for posterior segment infections. These advancements address critical challenges in assessing therapeutic responses within optically complex ocular tissues, bridging the gap between preclinical models and clinical translation.

In practical medical scenarios, stimulus-responsive systems demonstrate unique advantages: photoactivated nano-therapies enable precise treatment of perioperative infections during cataract surgery, while enzyme-sensitive carriers improve drug bioavailability in diabetic keratopathy with altered tear protease profiles. Fluorescence-guided nanosystems prove invaluable for intraoperative margin delineation in fungal keratitis debridement. Emerging technologies like OCT-coupled nano-thermometry allow non-invasive monitoring of treatment efficacy in acanthamoeba infections. However, clinical implementation requires rigorous optimization of nanomaterial biosafety profiles and imaging compatibility to meet ophthalmic standards, particularly regarding corneal transparency maintenance and intraocular pressure stability.

Data availability

This is a review paper; there are no data issues.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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