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REVIEW

Where and when to strike: Spatiotemporally controlled smart nanomedicines for precision antibacterial therapy

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Abstract The global rise of antimicrobial resistance calls for new therapeutic approaches that move beyond conventional broad-spectrum antibiotics toward precision-guided nanotherapeutics. This review examines how smart antibacterial nanomedicines achieve better therapeutic outcomes through two key control dimensions: Spatial precision (where) and temporal activation (when). We first discuss active targeting strategies that direct therapeutic payloads to infection sites while sparing healthy tissues. We then analyze microenvironment-responsive mechanisms that keep therapeutic agents inactive until they encounter specific pathological signals. Moving beyond a simple catalog of material properties, we propose a "Hierarchical Intelligence Framework" that organizes nanoparticles along a spectrum of increasing complexity—from basic ligand-guided systems to integrated, logic-responsive nanodevices operating through "Target−Trigger−Treat" protocols. By examining design principles and practical challenges in pharmaceutical development, this work outlines a path toward resistance-overcoming nanomedicines that may reshape infection management in the coming decades.

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1. Introduction

Bacterial infections cause devastating diseases ranging from sepsis and pneumonia to meningitis, and continue to rank among the leading causes of death and disability worldwide[1,2]. The discovery of penicillin once marked a turning point in medical history, yet decades of widespread—often careless—antibiotic use have fueled rapid bacterial evolution, driving the spread of resistance mechanisms largely through horizontal gene transfer[3,4]. Current trends paint a grim picture: multidrug-resistant (MDR) pathogens currently claim approximately 700,000 lives each year, with models predicting this toll could reach 10 million annually by 2050 without intervention[5]. Making matters worse, bacteria adapt far faster than we can develop new treatments. Resistance may emerge within just 1−2 years, whereas bringing a novel antibiotic to market requires a decade of rigorous research and development[6,7]. This disparity highlights the pressing need for therapeutic strategies that circumvent the limitations of traditional antibiotics.

Nanomedicine has emerged as a compelling alternative, harnessing materials that kill bacteria effectively while sidestepping the resistance problems plaguing conventional drugs[8]. These nanomaterials exploit distinct physical and chemical properties to attack pathogens through multiple simultaneous routes—whether by rupturing cell membranes, generating reactive oxygen species (ROS), or inducing photothermal damage[8,9]. Because these approaches strike at essential bacterial architectures rather than specific metabolic pathways, bacteria struggle to evolve countermeasures, making resistance unlikely[10−13].

However, there is another side to this powerful pharmacological coin. Although the pathways underlying broad-spectrum antimicrobial action are highly effective, they often fail to distinguish between pathogenic microbes and host cells. This lack of selectivity poses serious risks of collateral tissue damage and narrows the therapeutic index for clinical application[14−17]. Consequently, the primary challenge to clinical translation is not enhancing potency, but rather improving the capacity to specifically recognize and target only pathogenic invaders. Thus, the field has shifted from developing advanced nanomedicines capable of delivering their full therapeutic payload to infected sites toward precision-targeted strategies[18].

To overcome these challenges, scientists have pursued smart antibacterial agents whose activity can be precisely controlled in both space and time[13]. Such therapeutic nanomaterials employ two complementary pharmacological strategies to transform bulk therapeutics into precision medicines. The first strategy enables spatial control: it involves conjugating specific molecular recognition elements—such as antibodies or aptamers—to the nanoparticle (NP) surface. These ligands bind selectively to bacterial surface antigens, acting as molecular beacons that direct drug accumulation exclusively to the infection site—not systemically throughout the body[19]. This serves as a guidance system, concentrating the therapeutic payload at the infection site and minimizing systemic exposure. The second strategy relies on stimuli-responsive release: the nanodrug remains inert until triggered by infection-specific cues—such as acidic pH, bacterial enzymes, or altered redox states (Fig. 1)[20]. This functions analogously to a proximity sensor. The functionalization of the nanomaterial for treatment can be triggered on demand, thus protecting healthy tissue from its effects.

While several reviews have discussed active targeting and stimuli-responsive strategies separately[21,22], and even focusing only on one specific technique (*e.g.*, photothermal therapy driven *via* the body's own signaling)[23], little work has been done to unify these aspects in an integrated framework. Here, we do more than just list methods; we propose a new framework for organizing the different approaches by how "smart" they are and how well-targeted they are.

Building on top of such complementaritity, here we propose a "Hierarchical Intelligence Framework" to design next-generation smart and effective antibacterial nanomedicines, which divides the evolution path of an antibacterial nanoplatform into three increasing levels:

The first step (Material Properties) considers the intrinsic antimicrobial activity of relevant nanomaterials (Section 2), which also serve as structural supports and constitute a core component of the "elimination mechanism". Next, we analyze the precision dimensions of place and time: "Where" (Section 3) addresses spatially targeted intervention strategies to achieve localized therapeutic impact; "When" (Section 4) covers stimuli-responsive activation mechanisms that enable temporally controlled functionality. The final section—"system integration" (Section 5)—discusses the assembly of these elements into complex, adaptive systems capable of rudimentary decision-making—laying the groundwork for sophisticated "smart" devices that execute integrated "Target-Trigger-Treat" cycles.

This systematic analysis proceeds from fundamental material properties to increasingly complex and integrated functionalities, providing a rational foundation for designing next-generation antibiotic therapies.

2. Foundational platforms for smart antibacterial systems

The genesis of smart antibacterial nanomedicines lies in resolving a fundamental therapeutic paradox: the intrinsic bactericidal mechanisms of core materials are often indistinguishable from their cytotoxicity toward host cells. Essential platforms—based on metals, carbon, or polymers—can inflict catastrophic damage on microbial cells; however, without pharmaceutical engineering, this unregulated potency limits their clinical utility. Here, we use "nanomedicine" to refer to therapeutic agents whose core nanostructures serve dual roles: as delivery vehicles and as bioactive molecules whose activity can be precisely controlled in both space and time[18,24]. A key design principle is the transformation of conventional small-molecule drugs into "smart" therapeutics capable of distinguishing host cells from pathogens[25]. To clarify the pharmacological diversity of such agents, this review classifies nanomedicine architectures into five structural-functional categories: metal-based, metal-composite, carbon-based, polymer-based, and hybrid systems (Fig. 2A−E)[26-32]. This categorization is essential, as the intrinsic physicochemical properties of each class govern their *in vivo* behavior, safety profiles, and potential clinical applications.

In this work, we define metal-containing nanomaterials as specifically ordered inorganic compounds with definite chemical composition, wherein metal atoms are covalently bonded to nonmetallic elements—such as oxygen or sulfur. The most common examples include metal oxides (*e.g.*, ZnO, TiO_2, CuO) and metal chalcogenides (*e.g.*, Ag_2S and CuS), alongside emerging two-dimensional inorganic materials—including MXenes and layered double hydroxides (LDHs)—which exhibit antimicrobial activity through intrinsic semiconducting properties or controlled metallic ion leaching[33]. Hybrid nanomaterials, by contrast, are rationally engineered composites integrating both organic and

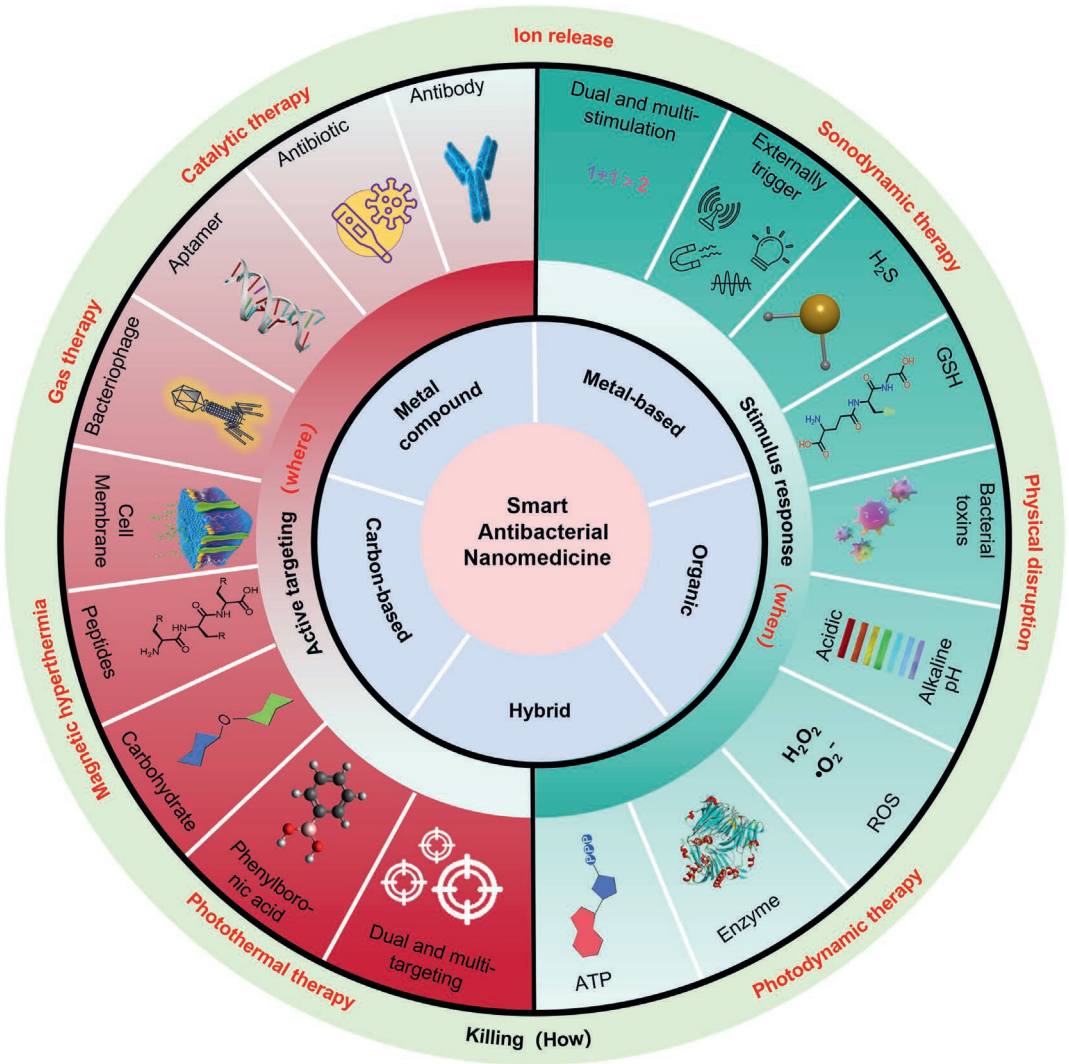

Figure 1 Schematic overview of smart antibacterial nanomedicine. These systems integrate a core therapeutic nano-platform with either active targeting functionalities (*e.g.*, antibodies, aptamers) for site-specific delivery or stimulus-responsive mechanisms that are triggered by specific cues in the bacterial infection microenvironment (*e.g.*, low pH, enzymes, ROS) for on-demand activation. This dual approach aims to enhance therapeutic precision and minimize off-target effects.

inorganic components to achieve synergistic functionalities unattainable by either constituent alone[34]. These hybrids fall into two primary categories: (1) coordination polymers—particularly metal-organic frameworks (MOFs)—in which metal nodes are bridged by multitopic organic ligands to form crystalline, porous architectures[28]; and (2) heterogeneous nanostructures—such as those encapsulated within biomimetic cell membranes or coated with metal-phenolic networks (MPNs)[30,31]. Unlike simple metal compounds, such hybrid scaffolds integrate the mechanical robustness and catalytic activity of inorganic phases with the biocompatibility and multifunctional adaptability of organic moieties. This synergy enables an integrative strategy to combat multidrug-resistant pathogens[11,35].

Despite the advantages offered by each platform, practical implementation often involves a trade-off between efficacy and biocompatibility. To facilitate comparative assessment of these properties, we analyzed representative materials from each class (Fig. 2F) and assigned performance scores on a standardized 1−5 scale—where 5 denotes optimal drug-like attributes. The evaluated criteria were as follows: "antibacterial efficacy" reflects the intrinsic bactericidal potency (5 = high potency at low doses); "Biocompatibility" indicates the safety profile toward mammalian cells (5 = non-toxic/biodegradable); "Stability" measures resistance to physiological degradation or aggregation (5 = highly stable); "Functionalizability" assesses the ease of surface modification (5 = distinct chemically reactive sites); and "resistance propensity" evaluates the likelihood of bacteria developing resistance (5 = low risk/resistance-refractory).

Studies have demonstrated that metal- and metal compound-based inorganic nanomaterials exhibit superior antibacterial activity—primarily through ionic dissolution and ROS generation. Photocatalytic materials (*e.g.*, TiO_2 and ZnO) and layered inorganic nanomaterials (*e.g.*, MXenes and LDHs) provide large interfacial surface areas for microbial contact, enabling membrane disruption or photothermal killing—though often at the expense of biocompatibility[36−41]. In contrast, soft-matter nanosystems—including polymers, covalent organic frameworks (COFs), and biomole cules—offer high biocompatibility and multifunctionality, making

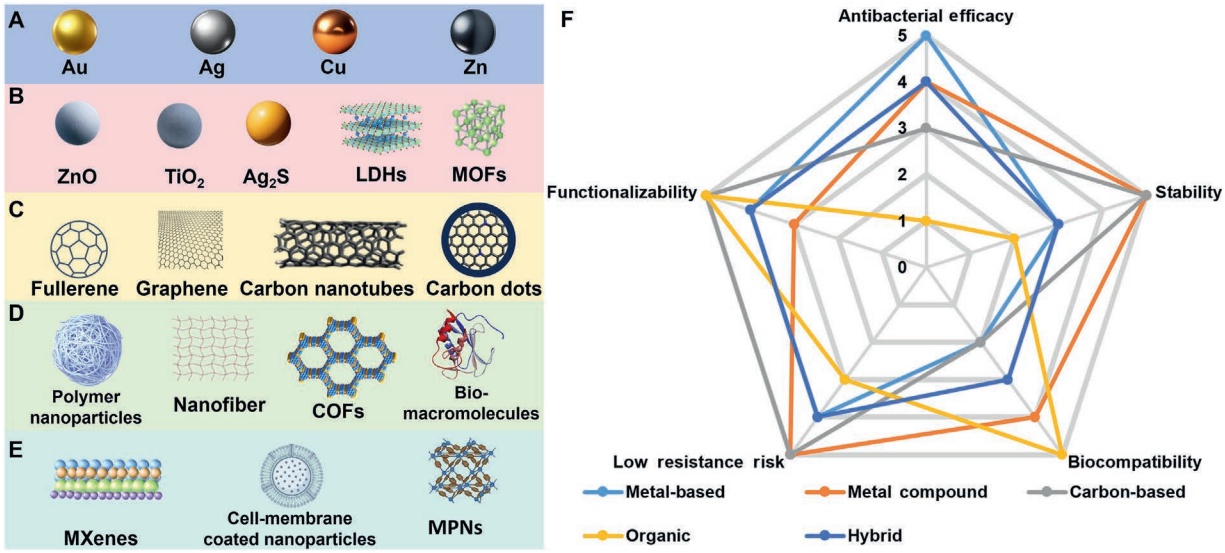

Figure 2 Foundational platforms for smart antibacterial systems and their comparative performance. (A−E) Schematic representation of five categories: metal-based, metal compound, carbon-based, organic, and hybrid nanomaterials. Representative structural characteristics are adapted with permission from Refs. 29−32. (F) A radar chart provides a semi-quantitative comparison across five key performance dimensions (scored from 1 to 5). Data for scoring are derived from a meta-analysis of literature benchmarks cited in Section 2.

them promising drug carriers; however, they frequently suffer from limited intrinsic stability or modest antibacterial potency[31]. Graphene- and carbon nanofiber-based materials strike a favorable balance between structural stability and bioactivity, capable of physically disrupting bacterial membranes *via* nanoscale mechanical action[15,42]. Critically, hybrid nanomaterials represent especially attractive candidates for overcoming these trade-offs, as they synergistically integrate complementary properties from distinct material classes. By incorporating unique advantages—such as the programmable porosity of MOFs, the charge-separation efficiency of organic-inorganic heterojunctions, and the immune-evasive functionality of bioinspired surface camouflaging—these composites achieve enhanced performance across multiple parameters. Such multifunctional platforms hold significant promise for developing next-generation antimicrobials that suppress biofilm formation more effectively than conventional antibiotic therapy[43].

The antimicrobial activity of the platform is based on several nonspecific effects, which are difficult for microbes to overcome (see Fig. 3)[44-48].

a. **Physical disruption**: Direct damage to bacterial membranes by materials with sharp edges, such as graphene oxide and nanofibers[49];
b. **Electrostatic interaction**: Direct damage to bacterial membranes through electrostatic attraction to positively charged materials, such as cationic polymers[50];
c. **Oxidative stress:** Generation of cytotoxic ROS through photodynamic therapy (PDT), sonodynamic therapy (SDT), or nanozyme-catalyzed reactions[35,44,45];
d. **Hyperthermia**: Localized heat generation *via* photothermal therapy (PTT) or magnetic hyperthermia (MHT), induced by external stimuli like near-infrared (NIR) irradiation or an alternating magnetic field (AMF), respectively[46,47];
e. **Ion release**: The release of toxic metal ions (*e.g.*, Ag^{+}, Cu^{2+}) that disrupt essential metabolic processes[26];
f. **Gas therapy:** Controlled release of therapeutic gases like nitric oxide (NO) or carbon monoxide (CO)[48].

These strategies are highly effective but inherently nonselective; without precise spatiotemporal control, they risk damaging host cells. A central objective is therefore to transform conventional antimicrobial agents into "smart" nanotherapeutics capable of site-specific and stimulus-responsive action. This functional upgrade is achieved by engineering nanomaterials that activate exclusively under pathologically relevant conditions—primarily through two complementary mechanisms: (1) spatially targeted delivery, which localizes therapeutics precisely at the infection site; and (2) stimuli-triggered actuation, which releases payloads only upon exposure to infection-specific cues. The practical implementation of these strategies is detailed below, alongside discussion of how rational design enables focused therapeutic action while minimizing off-target effects—thereby maximizing the clinical utility of antimicrobial nanomaterial-based therapies.

3. Active targeting antibacterial nanomaterials: The intelligence of recognition

Active targeting has been established as a cornerstone strategy for engineering smart antimicrobial nanomaterials[51]. It confers foundational "intelligence" to nanomaterials—specifically, molecular recognition capability—thereby converting passive nanocarriers into responsive platforms that selectively bind pathogenic microorganisms[18]. The ability to discriminate pathogens from host cells *in vivo* is achieved by surface functionalization with target-specific receptors—such as monoclonal antibodies or nucleic acid aptamers—that bind exclusively to pathogen-associated molecular patterns, without cross-reacting with human cells[52]. This approach directly addresses the spatial ("where") dimension of spatiotemporal control in smart drug delivery systems, enabling targeted antibiotic delivery to infection sites[53]. Such precision minimizes systemic exposure, thereby reducing off-target toxicity and significantly enhancing therapeutic efficacy[54].

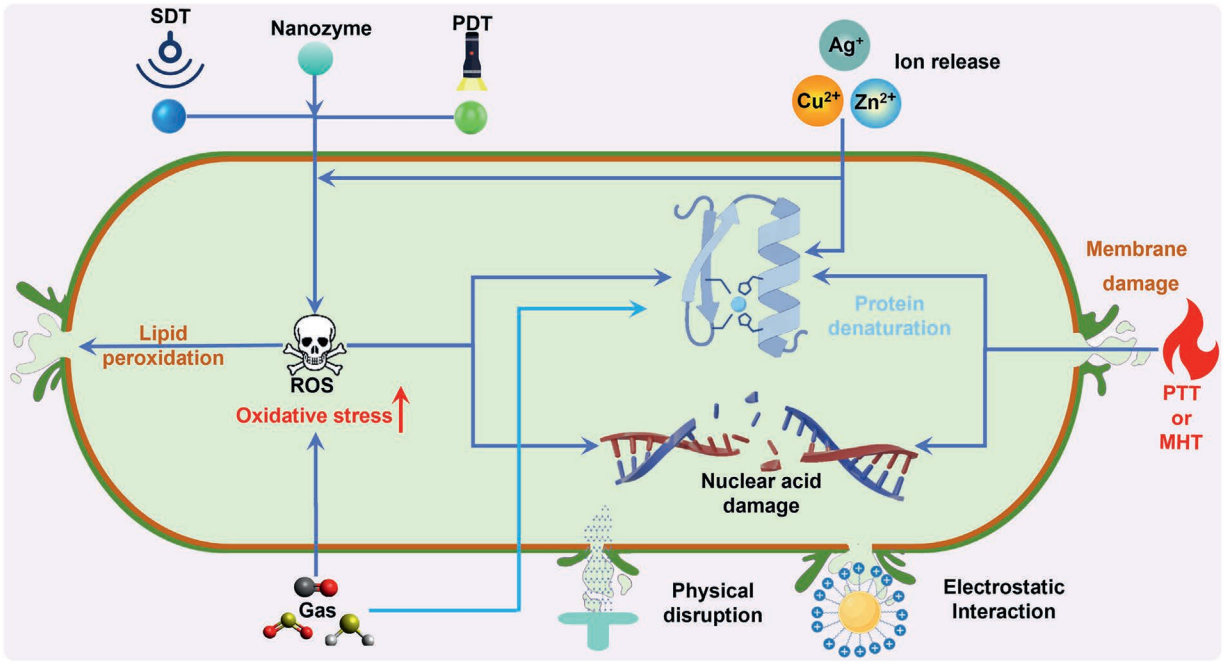

Figure 3 Primary antibacterial mechanisms of nanomaterials. These mechanisms are often non-specific for bacteria to develop resistance against, including physical disruption, oxidative stress (*e.g.*, ROS generation), hyperthermia (*e.g.*, PTT, MHT), and ion release, based on design principles detailed in Refs. 159−166. The goal of smart design is to control and localize these potent but indiscriminate effects.

The principle of molecular recognition relies on exploiting distinct chemical features displayed on microbial cell surfaces. Unlike eukaryotic cells, microorganisms possess unique structural elements—such as the thick peptidoglycan layer and teichoic acids in Gram-positive bacteria, and the lipopolysaccharide (LPS)-containing outer membrane in Gram-negative bacteria—that serve as pathogen-specific epitopes[55,56]. Additionally, surface appendages—including fimbriae, flagella, and other motility structures—provide additional molecular contact points that enhance both the avidity and specificity of ligand-microbe binding[57,58]. By conjugating nanomaterials with diverse targeting ligands—such as monoclonal antibodies, nucleic acid aptamers, and glycosyl moieties (Fig. 4)—researchers can engineer drug delivery nanocarriers capable of navigating the physiological environment to deliver therapeutics precisely to pathogens[59-68]. In this section, we systematically review the key aspects of receptor-targeted antimicrobial strategies, including their design principles, performance metrics, and translational challenges for clinical implementation. An organized view on the current targeting platforms with their respective binding molecules, target microbe, and their realizations in biological systems is presented in Table 1[69−93].

3.1. Antibody-conjugated nanomaterials: From potency enhancement to ecological precision

Exploiting highly selective antigen-antibody recognition is a foundational principle in designing antibody-based antimicrobial nanomedicines, aiming to overcome the limitations of conventional broad-spectrum therapeutics through precise pathogen targeting at infection sites—thereby enhancing therapeutic potency while minimizing collateral damage to commensal microbiota and systemic toxicity[94]. Efforts in this domain fall into two complementary strategies: (1) augmenting the intrinsic antimicrobial efficacy of nanosystems; and (2) enabling selective eradication of target pathogens within heterogeneous bacterial populations[70,95].

A more recent trend involves designing multifunctional theranostic platforms that integrate antibody-mediated targeting with advanced therapeutic modalities. For example, Zhong et al.[69] developed an antibody-conjugated nanozyme capable of combining PTT and catalytic antimicrobial activity. By leveraging antibody-directed accumulation of the nanomaterial at the infection site, the required bactericidal concentration against *Staphylococcus aureus* was reduced fourfold compared with the non-targeted counterpart—demonstrating the substantial efficacy enhancement afforded by precision targeting. This principle extends to diagnostics: the same group[70] reported an Ag@Pt-based nanoimmunosensor that exploits antibody targeting for simultaneous rapid colorimetric detection and localized PTT-mediated ablation of *Helicobacter pylori*. Similarly, researchers have conjugated pathogen-specific antibodies onto PEGylated graphene; gold NP-decorated graphene oxide (GO) serves as a dual-function probe enabling concurrent bacterial detection and enhanced photothermal eradication of target pathogens—thereby achieving selective antimicrobial action without disrupting commensal microbiota[71].

Beyond mere potency amplification, a more nuanced and clinically vital application of antibody conjugation is the pursuit of "ecological precision": the ability to selectively eliminate pathogens while preserving the commensal microbiota[25]. This is particularly critical in environments like the gastrointestinal tract[96]. A compelling demonstration was provided by Ma et al.[72], who conjugated hen-derived IgY antibodies to chitosan NPs. This strategic modification transformed the inherently broad-spectrum antibacterial activity of chitosan NPs into a highly selective bactericidal system against pathogenic Shiga toxin-producing *E. coli* (STEC). This transition from indiscriminate to targeted killing is pivotal for maintaining microbiome integrity, a paramount consideration for clinical translation. The work by Prinz Setter

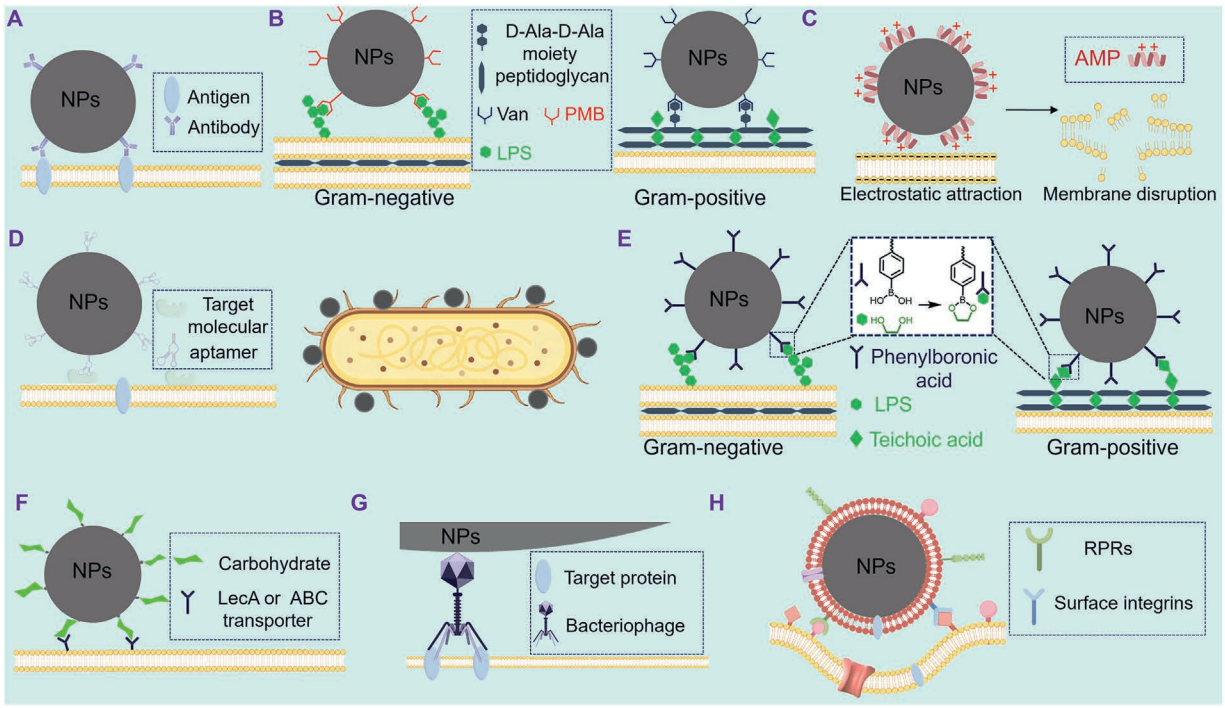

Figure 4 Schematic illustration of various active targeting strategies for antibacterial NPs. (A) Antibodies[59], (B) Antibiotics[60], (C) Antimicrobial peptides (AMPs)[61], (D) Aptamers[62], (E) Phenylboronic acid (PBA)[63], (F) Carbohydrates[64–66], (G) Bacteriophages[67], and (H) Cell membranes[68]. These ligands enable precise binding to specific bacterial markers such as LPS and peptidoglycan.

et al.[73], who functionalized halloysite nanotubes with anti-*E. coli* antibodies further reinforces this concept of selective lethality, achieving enhanced elimination of the target pathogen with minimal collateral damage to non-target bacteria.

While all these studies highlight the incredible potential of antibody engineering strategies for targeted therapy, they also encounter significant obstacles in moving toward clinical translation because of inherent limitations associated with traditional antibodies: high production costs, complex chemical modification needs, and potential immunogenicity of intact mAbs are major drawbacks to their use in practice. Furthermore, the sensitivity of antibodies to enzymatic degradation influences their structural stability *in vivo* and under storage conditions, which can degrade target accuracy and provoke unwanted immune responses. These problems motivate research into smaller, robust, and cost-effective targeters[97]. Some other interesting alternatives that have been explored are different forms of antibodies such as single-chain Fv or nanobodies derived from camelids, which have improved stability and/or biodistribution profiles. Other studies are exploring new chemical modifications that may improve the intrinsic stability as well as biocompatibility of the covalently bound system. These are important factors to be considered in themselves[98]. It will be necessary to overcome such molecular engineering challenges before the complete therapeutic potential of this highly specific antimicrobial strategy can be harnessed clinically.

3.2. *Bifunctional therapeutic ligands: Antibiotics and peptides*

A promising strategy that is both simple and feasible to achieve selective targeting is the modification of natural antibiotics or peptides, which can act both as a targeting moiety and a pharmacologically active agent. Unlike passive targeting strategies involving antibodies or aptamers, these modified agents can actively localize to the site of infection by recognizing and binding to the pathogen's cell wall, thereby exerting an antibacterial effect in addition to their targeting function.

Antimicrobials can retain their high affinity for specific bacterial surface receptors despite being conjugated with NPs[76,99]. Vancomycin, a glycopeptide antibiotic that recognizes the D-Ala-D-Ala carboxyl terminal residues present at the ends of the peptidoglycan precursor chains from Gram-positive bacteria *via* H-bonding, has been used by scientists to improve existing therapies[100]. An interesting case is provided by Jiang et al.[76], where it was demonstrated that coupling vancomycin to AgNPs supported by a PAMAM dendrimer significantly reduced minimum inhibitory concentration (MIC) values for drug-resistant enterococci by up to three quarters. The effectiveness improvement can be attributed to both blocking the synthesis of the cell wall (vancomycin) as well as disrupting the integrity of the cellular membranes (silver). Similar efforts have also been made with optical treatments, and the same type of targeting is promising in these cases as well. Zou et al.[77] synthesized CuS NPs coated by Vancomycin (CuS@Van) that selectively bind to Gram-positive bacterial cells, leading to efficient PTT/PDT destruction. For Gram-negative bacteria, the desired targeting molecule is polymyxin B (PMB), which has a strong affinity towards the LPS of the outer bacterial membrane[74]. It has been found that PMB-conjugated oligomer NPs could selectively identify *E. coli* resistant to kanamycin, significantly enhancing PDT efficacy and minimizing the nephrotoxicity of free PMB by altering its pharmacokinetic profile[75].

The use of peptides allows for a very flexible range of targets: between the broad charge-based recognition that is characteristic of AMPs and the narrow recognition domains of *de novo* designed peptides[101,102]. For example, one can pair the amphipathic nature

Table 1 An overview of active targeting nanomaterials for antibacterial application.

Classification	Nanomaterials	Targeting ligand	Target receptor/ component	Microorganism	*In vivo* application	Ref.
Antibody conjugated nanomaterials	AbAu/Ir@ Cu/Zn-MOF	Anti-*S. aureus* antibody	*S. aureus* surface antigens	*S. aureus*	N/A	69
	Ag@Pt	Anti-*H. pylori* antibody	*H. pylori* surface antigens	*H. pylori*	N/A	70
	(PEG)-GO-AuNPs	Anti-*S. typhimurium* antibody	*S. typhimurium* surface antigens	*Salmonella typhimurium*	N/A	71
	CN-IgY	Anti-STEC IgY antibody	STEC antigens	*E. coli*	Gastric diseases	72
	AuNR-Ab-HNT	Anti-*E. coli* antibody	*E. coli* surface antigens	*E. coli*	N/A	73
Antibiotic modified nanomaterials	PMB-CON	PMB	LPS on outer membrane	*E. coli*	Wound healing	74
	VMNPs	Vancomycin	D-Ala-D-Ala terminus of peptidoglycan precursors	MRSA	N/A	75
	Van-PAMAM-AgNP	Vancomycin	D-Ala-D-Ala terminus of peptidoglycan precursors	MRSA	Wound healing	76
	CuS@Van	Vancomycin	D-Ala-D-Ala terminus of peptidoglycan precursors	*Enterococcus faecium*, *Enterococcus faecalis*	Wound healing	77
Peptide modified nanomaterials	Se NP-ε-PL	ε-poly-L-lysine	Negatively charged LPS, teichoic acids	*E. coli*, *S. aureus*	Wound healing	78
	UiO-66-NH_2@TB@PEP&PEG	PEP (YVLWKRKRKFCFI-NH_2)	LPS in the cell walls of bacteria	*P. aeruginosa*, *Staphylococcus epidermidis*	Wound healing, keratitis	79
Aptamer modified nanomaterials	T-Ag@CIP	Specific aptamer	Specific molecules on bacterial surface	*E. coli*, *S. aureus*, *P. aeruginosa*	Wound healing	80
	DNA-AgNCs	*S. aureus* aptamer	Specific protein targets on *S. aureus* surface	*S. aureus*	N/A	81
PBA modified nanomaterials	Au_MBA NPs	Mercaptophenyl PBA	*cis*-Diol groups on bacterial cell wall	MRSA, *S. aureus*, *Staphylococcus epidermidis*	Wound healing	82
Carbohydrate-modified nanomaterials	GP-SiNPs-asPNA	Glucose polymers	ABC sugar transporters	*E. coli*, *S. aureus*, *P. aeruginosa*, *Bacillus subtilis*	Keratitis	83
	B@MPDA-Mal	Maltotriose	Maltodextrin transport systems	*E. coli*, *S. aureus*, MRSA	Myositis	84
Bacteriophage-modified nanomaterials	Phanorod-Zn	Bacteriophage tail proteins	LPS, teichoic acids, porins	*E. coli*, *P. aeruginosa*	Wound healing	85
Cell membrane-coated nanomaterials	Rif@MSN@OMV	OMV surface proteins	Homologous bacterial surface components	*E. coli*	Peritonitis	86
	AGS-NPs	Gastric epithelial cell membrane proteins.	Homologous bacterial surface components	*H. pylori*	Gastritis	87
	CeO_2-TCPP	Macrophage membrane receptors (TLR2, TLR4, TLR6)	Bacterial pathogen-associated molecular patterns	*E. coli*, *S. aureus*	Wound healing	88
	M-AMPNP	Macrophage membrane receptors (TLR2, TLR4)	Bacterial pathogen-associated molecular patterns	*E. coli*, *S. aureus*	Abscess	89

$CuFeSe_2$	Macrophage membrane receptors (TLR2, TLR4, TLR6)	PAMPs	*S. aureus,*	Abscess, osteomyelitis	90
NPs@M-P	Leukocyte membrane and PMB	Surface receptors of inflammatory cells and LPS	*E. coli*, *P. aeruginosa* *B. subtilis*, *S. aureus*	N/A	91
RPTR-701Ns	RBC membrane receptor	Bacterial toxin	MRSA	Wound healing	92
PNPs	Platelet membrane	Bacterial toxin	MRSA	Systemic infection	93

N/A, lack of *in-vivo* application; ABC, ATP-binding cassette; STEC, Shiga toxin-producing *E. coli*; LPS, lipopolysaccharide; OMV, outer membrane vesicles; PMB, polymyxin B; PAMPs, pathogen-associated molecular patterns; RBC, Red blood cell.

of most AMPs with another mode of action. Huang et al.[78] synthesized SeNPs functionalized by epsilon poly-L-lysine (SeNP-epsilon-PL), in which the lysine acts as a targeting agent directing ROS-generating NPs toward microorganisms, significantly reducing the MIC without inducing resistance. Apart from natural AMPs, synthetic peptides may be used to provide the specificity of an antibody for a particular antigen. Jin et al.[79] fabricated a MOF containing LPS-binding peptides that facilitated the targeted transport of PSs into the cell membranes of Gram-negative bacteria and thus effectively destroyed biofilms. In addition, the penetration capability of the peptide through biological membranes is excellent, as demonstrated by Gao et al.[61], who designed a new photosensitizer by co-assembly with polyethylene glycol-modified antimicrobial peptides (PEG-AMPs), revealing a novel functional shift. Rather than serving only as targeting agents, these peptides physically invade dense extracellular polymeric substances, effectively delivering drugs into viable but non-culturable bacteria within the biofilm matrix.

This dual-function strategy provides a promising "Find and Kill" approach to simplify NP design, as it eliminates the need for any irrelevant targeting moieties. However, this promising approach has the following unique challenge to overcome: repurposing clinically approved antibiotics (*e.g.*, vancomycin) as intrinsic targeting moieties risks selecting for antimicrobial resistance if pathogens are exposed to subtherapeutic concentrations[103]. Therefore, future studies need to use structurally similar but nonclinical agents or carefully controlled dosing regimens. In addition, although peptides offer a high degree of design freedom, the challenge lies in improving their resistance to protease degradation and reducing the cost of synthesis to bring these materials into the clinic[102,104].

3.3. Synthetic and chemical recognition elements: Aptamers and PBA

To overcome limitations of naturally occurring biological ligands—including high production costs, unreliable antibodies, variable batch-to-batch performance, and potential immunogenicity—researchers have begun to turn toward synthetic ligands. Of these options, nucleic acid aptamers and PBA serve as chemical counterparts to traditional antibodies, offering tunable properties, improved stability, and easily modifiable functionality. These artificial ligands exhibit strong binding capabilities while avoiding the drawbacks of their natural counterparts.

Aptamers (synthetic counterparts for antibodies) are small, single-stranded DNA or RNA sequences obtained using a process known as systematic evolution of ligands by exponential enrichment (SELEX). They have high affinity and selectivity toward ligands present on microbial surfaces. In addition to providing high affinity for targets, their ability to achieve molecular recognition through specific geometrical shapes allows them to be incorporated into various applications.

In the case of phototherapy, accurate targeting is necessary, as shown in a study where Pourhajibagher et al.[62] attached a Porphyromonas gingivalis-specific aptamer to nano-graphene oxide (NGO), which greatly increased PS accumulation on the bacteria and thus improved PDT efficiency. Moreover, the modularity of aptamers enables the construction of better delivery systems. For example, Wu and colleagues[80] constructed a DNA tetrahedron that self-assembles, including the incorporation of both aptamers and AMPs. Here, the aptamer acts like an address for delivering the DNA nanostructure towards the target microorganism. The ability to deliver AMPs directly into the bacteria can be exploited by

using nanostructures as vehicles that specifically target pathogenic bacteria and thus increase the effectiveness of AMPs, while decreasing their toxicity against non-target cells[80]. Moreover, an aptamer can also be used to combine diagnostics with therapy. Yang et al.[81] reported a DNA-protected Ag NCs-based sensing platform which was able to produce a colorimetric signal as well as to generate silver ions for antibacterial activity through *S. aureus*-specific aptamers.

Phenylboronic acid (PBA) employs a molecular recognition mechanism that mimics the interaction between bacteria and the cellular surface. This mechanism relies on the capability of phenylboronic acids to form reversible covalent bonds with *cis*-diols through boronate ester formation[63]. The bacterial cell wall is abundant in peptidoglycan and LPS, which bear diol groups. These offer multiple points of attachment that are rare on the eukaryotic cell membrane, providing PBA with exceptional pathogen specificity[63,105,106]. Another benefit is the use of PBA as a molecular booster. It was found in an experiment conducted by Wang et al.[82] that both free PBA and AuNP alone did not demonstrate antibacterial activity, but their hybridization (Au_MBA) showed significant broad-spectrum bactericidal properties. In this hybrid, PBA helps to achieve high loading of NPs onto bacteria, converting short-term contacts into long-term focused relationships. This localized positioning also enhances the bactericidal efficacy in a synergistic manner. Catalytic treatment techniques have also shown novel ideas; for example, in the work of Li et al.[107], phenylboronic acid-based nanozymes could be specifically anchored onto the microbe surface due to the good targetability of PBA, thereby greatly improving the killing effect of photothermal and photocatalytic reactions.

Synthetic recognition units represent an important step towards the development of standardized, reproducible nanomedicines. Nucleic acid aptamers offer flexible recognition capabilities *via* combinatorial selection, which fits the diagnostic criteria quite nicely. PBA, by contrast, is a robust chemical linker of general utility. However, the particular problem of stability is important in practice for real-life medical application. Aptamer oligonucleotides are susceptible to degradation by nucleases present *in vivo*, and thus chemical modification of the backbone (*e.g.*, phosphorothioates) or ribose groups (*e.g.*, 2′-*O*-methyl group) is often necessary for increased half-life. The transient state of binding between PBAs and saccharides can be affected by intracellular glucose or any other molecule, making advanced molecular design critical. This involves the introduction of electron-deficient moieties, or nitrogen-containing functionalities, in order to tune PBA's acid dissociation constant, thus optimizing the affinity properties and sensitivity to complex infection states.

3.4. Biomimetic and metabolic targeting strategies: Carbohydrates and phages

A more sophisticated approach involves the use of a "Trojan horse" (or biomimetic) targeting strategy that exploits either the microbe's intrinsic need to acquire certain nutrients from its environment or some other vulnerability in the microbe's biology, allowing this approach to achieve specific targeting. Examples include sugar-targets, which exploit the microbe's requirement to import sugars into cells, and phage-targets, which make use of the bacteria's own highly evolved recognition machinery.

The manipulation of carbohydrates is a powerful metabolic camouflage that allows therapeutics to masquerade as essential nutrients in order to improve cell entry or target-specific interactions *via* glycan-lectin recognition[83]. Bacteria have widespread presentation of lectins on their surfaces and nutrient importers (*e.g.*, the adenosine triphosphate (ATP) binding cassette transporters which take up nutrients from the environment) or exporters (*e.g.*, the multidrug efflux pumps)[108,109]. One of the best-established ways is to target a particular carbohydrate on pathogens, *e.g.*, LecA from *Pseudomonas aeruginosa*. NPs functionalized with galactose have demonstrated selectivity towards LecA, significantly enhancing PS adsorption to bacterial cell surfaces and leading to better PDT outcomes[66]. In addition to adhesion, new strategies based on the use of maltodextrin derivatives have been developed recently with a view to taking advantage of the maltodextrin uptake system that is widespread among Gram-negative species. In particular, maltodextrins have been conjugated to fluorophores and tested in biological systems[84]. It was also demonstrated, for instance, that certain molecules may be able to work like "metabolic Trojan horses", being brought into the body of a bacterium against its own gradient.

Bacteriophages (viruses which infect bacteria) demonstrate exquisite biological specificity as the result of billions of years of evolutionary pressure to recognize a specific target bacterial species. Unlike broad-spectrum antibiotics or antibodies, phage-guided delivery utilizes the tail fibers of a phage as receptors or receptor binding proteins (RBPs), which can recognize and specifically bind to certain target bacteria through their cell surface receptors. Such specificity allows these structures to be used as guiding elements for artificial vehicles. Peng et al.[85] conjugated *M13* bacteriophages with Au NRs (*M13*@AuNRs). The phage guides the conjugates through complex *P. aeruginosa* biofilms *via* recognition of bacterial cell surface epitopes, while the metal components enable selective destruction of biofilm structures through heating—a capability that cannot be achieved using phage treatment alone. Moreover, engineered phages can be tailored and used as flexible scaffolds. Genetically engineered *M13* phages can display specific peptides on the major coat proteins. Viral mimetics loaded with drug-loaded NPs constitute biomimetic delivery systems, which combine the advantages from both the inherent targeting capabilities and the designed functions for therapy; therefore, they are promising to solve many transportation problems by learning from biology.

Targeting by carbohydrates is especially useful to facilitate cell internalization *via* active transport, although phage technology can be more specific to target one bacterial strain over another and thus avoid harming the "good bacteria". However, the translation of these technologies towards their use in a clinical setting poses two main challenges: the carbohydrates must be well-characterized and engineered to avoid unwanted immunological responses against them by the human body (biocompatibility); while phage-based therapies need to address issues of immunity, scale-up manufacturing, and a narrow range of bacterial targets, which could necessitate cocktail preparations.

3.5. Cell membrane-coated nanomaterials: Biomimetic targeting

Coating NPs with cell membranes is a new biomimetic strategy that endows NPs with various biological functions of natural cells. This "bottom-up" editing strategy preserves the complex architecture of membrane-bound proteins and lipids, thus enabling functions such as immunological evasion and detoxification, and in particular correct molecular recognition[110,111]. In comparison with antibody- or aptamer-based single ligand attachments, this

approach of cellular membrane encapsulation offers polyvalent display of naturally configured receptors and cell adhesion molecules, which can lead to distinct, often synergistic targeting routes. Choosing an optimal donor cell is one of the most important design parameters which influences not only NP's biological route but also the targeting strategy itself.

3.5.1. Homotypic and host-cell targeting: Leveraging natural adhesion

Outer membrane vesicles (OMVs), which are secreted by many Gram-negative bacterial species, retain the native membrane topology and lipidome of the source organisms, thereby facilitating targeted recognition through interactions with homologous bacterial species[112]. Homotypic targeting was also exploited by Wu et al.[86], who produced rifampicin-loaded mesoporous silica NPs coated by *E. coli* OMVs (Rif@MSN@OMV). The bacterial membrane covering conferred these NPs with accurate targeting ability to its parental strain, significantly improving the efficiency of antimicrobial agent release against Gram-negative bacteria but not Gram-positive bacteria, as well as better biocompatibility and higher animal survival rate in a mouse model of peritonitis. On the other hand, specific pathogens can be targeted using cell membranes from host cells that they selectively infect. For instance, Angsantikul et al.[87] constructed an approach targeted toward *H. pylori* using the stomach lining. These NPs (AGS-NPs) are designed to mimic a cell membrane and its surface composition from the host cells, exploiting the bacterium's colonization machinery for precise delivery within the gastric environment.

3.5.2. Immune cell mimicry: Co-opting pathogen recognition and inflammation homing

Regarding immune cell mimicry, biologically inspired membranes extracted from immune cells can offer multiple targeting mechanisms due to their inherent immune properties. These mechanisms mainly include direct identification of microbes or indirect migration through inflamed tissues.

Direct Pathogen Recognition: Macrophage and dendritic cell-like innate immune cells have surface receptors, especially Toll-like receptors, which recognize specific ligands on pathogens[113,114]. Research has shown that NPs coated with such membranes are able to gain those recognition properties as well. Li et al.[88] and Meng et al.[89] have reported the use of macrophage membranes to direct M-AMPNP and CeO_2-TCPP towards *S. aureus* (Gram-positive) and *E. coli* (Gram-negative) bacteria, respectively, *via* Toll-like receptors. Continuing in a similar line, Hou's team improved the specificity using pre-*S. aureus*-activated dendritic cell membranes, generating TLR2-loaded NPs that have enhanced affinity toward their target microorganism[90]. In this way, we are using our first line of defense against pathogens as a targeting mechanism.

Inflammation Homing: Neutrophils, white blood cells, and macrophages migrate toward the site of infection or inflammation due to interactions with the intercellular adhesion molecule 1 (ICAM-1), a surface receptor found in inflamed endothelium, *via* their integrins (*e.g.*, CD11b)[115−117]. This natural process could be exploited to deliver drugs or other bioactive molecules to the location of the infection through the coating of NPs using one of those cellular membranes. Indeed, Duan et al.[115] and Liu et al.[118] used macrophage and T cell membranes as vehicles to transport their cargo inside tissue that was infected but did not target invading microbes. This will particularly benefit the treatment of difficult-to-treat infections like antibiotic-resistant pneumonia, where the major challenge is to achieve a high enough drug concentration within infected lung tissue. This targeting accuracy can be further enhanced with the addition of pathogen-specific ligands, designing a two-step targeting strategy where the nano construct is initially attracted by inflammation and then binds to bacteria, *e.g.*, using NPs@M-P described by Wei et al[91].

3.5.3. Bio-decoy and stealth strategies: Leveraging non-immune cell membranes

Membranes from various origins have other important biological features in addition to the immune camouflaging effect. Among these, red blood cell (RBC) coatings are the de facto benchmark for achieving prolonged vascular half-life and immune evasion[119]. Crucially, they also act as "nanosponges", as their surfaces can adsorb and neutralize bacterial exotoxins, thereby mitigating pathogen virulence[92]. This dual-functionality was effectively used by Wu et al.[92] to create a system that both delivered antibiotics and protected host cells from methicillin-resistant *S. aureus* (MRSA)-derived toxins. Similarly, platelet membranes offer a hybrid functionality, combining inflammation homing with toxin neutralization (platelet-derived NPs)[93]. The molecular basis of this "homing" capability lies in the preservation of key surface immunomodulatory proteins, such as P-selectin and CD40 ligand[120]. For example, the adhesion molecule ICAM-1, which is highly expressed on activated endothelial cells, allows specific NP accumulation at sites of injury-associated vasculopathy[121]. Such bio-inspired systems can also be used as efficient "toxicant sinks"[30]. *In vitro*, quantitatively assessed experiments show that NPs can specifically absorb significant amounts of cytotoxic molecules that damage cell membranes, such as α-hemolysin secreted by MRSA[122]. Sequestering such toxins significantly reduces red blood cell lysis in the presence of these toxic molecules compared to free NPs, efficiently shielding cells against toxins.

In summary, cell membrane coating is an extremely versatile and efficient strategy to construct desired functionalities in the bacterial killing of nanozymes. Depending on the source of membranes, these vesicles have different targeting mechanisms (Table 2), such as direct homotypic fusion (OMVs), pathogen detection by pattern recognition recepotrs (macrophages), recruitment to inflammation sites (neutrophils), and toxin neutralization (erythrocyte membrane). While there are still challenges with manufacturing scalability, reproducibility, and stability across multiple batches, such a bio-inspired method provides a platform to design complex NPs that can navigate through complicated biological environments and carry out precise treatment[123,124].

3.6. Beyond binding: Overcoming physiological barriers for deep tissue delivery

Precision targeting of pathogens is essential, but the efficacy of antimicrobial nanomaterials is usually compromised by biological barriers that prevent effective delivery to the site of infection. Therefore, advanced NP platforms need to be designed not only to promote microbial adhesion but also to incorporate strategies that overcome these complex physiological barriers.

3.6.1. Crossing the blood−brain barrier (BBB) for central nervous system infections

The restricted permeability of the blood-brain barrier (BBB) makes meningitis—a bacterial infection of brain tissue and cerebrospinal fluid—difficult to treat; consequently, approaches designed to deliver antibiotics directly to the pathogen typically

Table 2 Targeting characteristics of different cell membrane-coated nanomaterials.

Cell membrane source	Targeting strategy	Key recognition mechanism	Target	Main functionality/advantage	Limitation/challenge
Bacterial OMVs	Homotypic targeting.	Interactions *via* adhesion molecules with the homologous bacterial species from which the membrane originated.	Source bacterium	Confers high specific affinity for the source pathogen, enhancing drug uptake and therapeutic efficacy.	Endotoxin (LPS) presence poses significant immunogenicity and safety risks; narrow targeting spectrum limits use in polymicrobial infections.
Gastric epithelial cell	Host-cell mimicry	Mimicking the host cell surface to exploit the pathogen's natural colonization machinery.	Pathogens with specific cellular tropism	"Tricks" the pathogen into binding, enabling precise delivery to its specific colonization site.	Highly niche application; difficulty in source cell acquisition and large-scale, consistent membrane production.
Macrophage/dendritic cell	Direct pathogen recognition	Binding of PRRs like TLRs on the nano-surface to conserved motifs on bacteria.	Broad-spectrum bacteria (Gram-positive & Gram-negative)	Leverages the immune system's innate recognition instinct for universal pathogen recognition.	Risk of unintended immune modulation (*e.g.*, *via* major histocompatibility complex molecules); potential for rapid clearance by the reticuloendothelial system.
Neutrophil/leukocyte/ macrophage	Inflammation homing	Interaction between surface integrins (*e.g.*, CD11b) and adhesion molecules (*e.g.*, ICAM-1) on activated endothelium.	Inflamed tissues/site of infection	Directs therapy to the location of infection rather than the pathogen itself, ideal for deep-seated infections.	Lacks pathogen-specificity, leading to potential off-target accumulation at sites of sterile inflammation (*e.g.*, injury, autoimmune disease).
RBC	Bio-decoy and stealth	Mimics self-cells for immune evasion; its surface also adsorbs and neutralizes bacterial exotoxins.	Immune system (for evasion) & bacterial exotoxins	Provides dual functionality: Prolonged circulation (stealth) and mitigation of pathogen virulence (toxin sponge).	Lacks active targeting capability, relying on passive accumulation; toxin-neutralizing capacity can be saturated by high toxin loads.
Platelet	Hybrid functionality	Combines inflammation-homing capabilities with the ability to neutralize toxins.	Inflamed sites & bacterial toxins	Offers a multi-pronged attack by simultaneously targeting the infection site and neutralizing toxins.	Potential thrombotic risk due to the inherent pro-coagulant nature of platelet membranes; concerns over stability and premature activation.

PRRs, pattern recognition receptors; LPS, lipopolysaccharide; OMV, outer membrane vesicles; TLRs, toll-like receptors.

require disruption of the BBB prior to antibiotic delivery[125,126]. A number of recent strategies take advantage of receptors for facilitated transport across the BBB *via* transcytosis by mimicking the viral entry process[127]. In particular, NPs may be designed to carry molecular recognition elements (*e.g.*, RVG29 peptide derived from rabies virus, transferrin molecules), which allow them to bind particular receptors expressed on the surface of cerebral microvascular endothelial cells, thereby facilitating entry into the brain[128]. Once inside the brain, these carriers could use additional targeting ligands, such as pathogen-specific aptamers, for the specific delivery of their cargo to infection sites. This two-step targeting model is an important breakthrough in the treatment of central nervous system bacterial infection[129].

3.6.2. Penetrating the mucus barrier in gastrointestinal tract and pulmonary infections

In both the digestive tract and the respiratory system, an abundant mucus layer acts as a physical barrier to trap foreign matter prior to its arrival on epithelial surfaces[130]. In order to penetrate through that barrier, scientists have developed "mucus-resistant" methods. The best-known approach is the PEGylation of NPs, *i.e.*, their surface functionalization by poly(ethylene glycol) chains forming a hydrophilic layer that minimizes adsorption on mucus proteins, which allows for particles to move through this mucus network[131]. A second promising strategy involves the modification of the zeta potential of surfaces and consists in functionalizing the NPs with a neutral or negative charge that facilitates mucus translocation, and switching into a positive charge (activated through removal of a protective coat) in order to adhere well to the bacterial wall underneath the mucous membrane[132].

3.6.3. Penetrating the skin and biofilm barrier with microneedle patches

In order to overcome biological barriers, it is not enough for smart delivery platforms to pass through cell membranes; they need to be able to pass through skin or the complex extracellular matrix that surrounds microbes in biofilms[133]. One example is microneedle (MN) arrays, which are emerging as a useful mechanical modality by creating microchannels for local delivery of nanosized therapeutics into the site of infection[134]. One such study was performed by Jiang et al.[135], who demonstrated that this mechanical invasion technique could be combined with an on-demand nanocarrier delivery system. In particular, Jiang et al.[135] fabricated biodegradable MN patches with surfaces containing bismuth sulfide nanocrystals conjugated to a Ga^{3+}-catecholate complex. The MNs physically penetrate through the skin as well as the MRSA biofilms first. After implantation, this triggered an integrated treatment regimen comprising NIR light-mediated O_2-independent type I PDT; while the acidic pH typical for biofilms promoted the controlled release of both active moieties.

The above-mentioned active targeting methods represent an important step towards improvement of the specificity of antimicrobial NP actions at the desired location, by conjugating with ligands (antigen−antibody pairs, peptides, oligonucleotide aptamers, and/or small molecule ligands attached to a nanomaterial surface) in order to allow the NP to specifically accumulate at an area of infection. This allows for higher levels of treatment at the site of illness with less overall exposure to the body.

However, simply having accumulation of therapeutics at a location is insufficient for controlled drug release. A different strategy addresses this problem using the unique pathological features of the diseased tissue niche itself as an intrinsic switch. Such a strategy led to the development of stimuli-responsive nanocarriers that are programmed for quiescence until they receive infection-specific biochemical or physical cues. These systems enable the targeted drug release only at the site of infection and provide necessary temporal control which enhances the therapeutic efficiency with reduced side effects. These intelligent delivery systems are discussed below, sorted according to the particular cue they respond to.

4. Stimulus-responsive antibacterial nanomaterials

The recent progress in understanding the microenvironment of bacterial infection, as well as developments in material science, has motivated the development of smart antimicrobial nanostructures with a stimulus-responsive function, which aim to remain relatively inert until they sense specific trigger stimuli, upon which they initiate preprogrammed treatment interventions[136,137]. This strategy provides needed spatiotemporal control to maximize the efficacy of therapy while minimizing side effects. The triggering systems of such nanomaterials can be classified into three main categories: (1) endogenous triggers based on specific biological and chemical parameters occurring at the site of infection, *e.g.*, pH variations; (2) internal stimuli requiring a triggering event such as an enzyme's action or a reduction in oxidation potential; and (3) exogenous stimuli that necessitate the targeted introduction of extrinsic energy sources, *e.g.*, light or oscillations in the AMF. By functionalizing the nanomaterial with a receptor that responds to one of these stimuli, researchers can achieve on-demand tunable antibacterial activity (Table 3[138−158]; Fig. 5[159-166]). In this section, we first examine models based on critical endogenous signals and secondly discuss various possible initiating strategies that are allowed through an external supply of energy.

4.1. ATP-responsive nanomaterials: Exploiting a universal metabolic signal for targeted activation

Extracellular ATP (eATP) concentrations at the site of bacterial infection can be as high as a few hundred μmol/L and are also a key stress-response metabolite. As such, it is a very good candidate to be targeted by specific antibiotics[167]. In recent years, the development of stimulus-responsive smart materials has evolved to encompass two general categories: (1) triggering degradation as an on-demand method to deliver a cargo or (2) activating enzymatic activity that can be used both diagnostically and therapeutically "on demand".

A simple strategy is based on using eATP, an endogenous nucleotide that can serve as fuel for driving nanosystems and triggering drug release from NP carriers[139]. For example, the cascade reaction of a DNAzyme triggered by ATP was developed by the Chen group[139], wherein ATP is recognized to trigger on-demand disassembly of the ZIF-8 NP. This effect is due to metal competition, as the three phosphates in ATP can bind more Zn^{2+} than the two imidazoles in an imidazole linker, which finally disassembles the metal-organic framework structure, releasing the catalytic G-quadruplex/hemin DNAzyme to generate ROS with antibacterial activity. Interestingly, in such cases they have an autocatalytic loop of microbe degradation leading to cell lysis, releasing more eATP, and thus enhancing the beneficial cascade that leads to faster elimination of pathogens. Such a concept transforms a classic drug carrier into an autonomous amplifying system for therapy.

Table 3 An overview of stimulus-responsive nanomaterials for antibacterial application.

Classification	Nanomaterials	Mechanisms	Microorganism	*In vivo* application	Ref.
ATP-responsive nanomaterials	CeO_2	ATP-triggered oxidase-like activity	*E. coli*, *S. aureus*	N/A	138
	G4@ZIF-8	ATP-triggered framework disintegration, agent release	*E. coli*, *S. aureus*	Wound healing	139
Enzyme-responsive nanomaterials	BLAP	β-Lactamase-triggered self-assembly, bacterial capture	MRSA	Myositis, abscess	140
	Nap-FYp-Ada	ALP-triggered self-assembly, membrane disruption	*S. aureus*	Wound healing	141
	CuO NPs/AAP	ALP-activated prodrug, ROS generation	*E. coli*	Wound healing	142
	SGQDs-CORM@HA	HAase-triggered "nanoknife", PDT, CO release	*E. coli*, MRSA	Wound healing	143
	MoS_2 NSs	HAase-triggered release, PTT, PDT	MRSA	Abscess	144
	AuNR@PDMA/ PCM-b-PEG	Lipase-triggered charge reversal, electrostatic binding	MRSA, *Enterococcus faecalis*	N/A	145
	MMP-S NPs	MMP-triggered peptide removal, enhanced PDT	*P. aeruginosa*	Keratitis	146
	MFP@AgNPs	MMP-triggered peptide cleavage and exposure	*S. aureus*, MRSA, *E. coli*, *Acinetobacter baumannii*	Pneumonia	147
ROS-responsive nanomaterials	Van-mPEG-TK-MSNs	ROS-triggered gate opening, drug release	*S. aureus*	Wound healing	148
	α-CD-Ce6-NO-DA	pH-triggered charge reversal, NO release, enhanced PDT	MRSA	Wound healing	149
	FePOs-CeO_2-ZnO_2-ICG	pH-activated nanozyme cascade, PTT, PDT	*S. aureus*, *Candida. albicans*	Wound healing	150
Toxin-responsive nanomaterials	GOX-MPO-DS	Toxin-triggered nanoreactor activation, HOCl generation	*S. aureus*, *P. aeruginosa*	N/A	151
GSH-responsive nanomaterials	IO@PMB-SNO	GSH-activated NO release, nanomotor propulsion	*P. aeruginosa*	Wound healing	152
H_2S-responsive nanomaterial	PRGP	H_2S-triggered bond cleavage, drug release	*Salmonella typhimurium*	Digestive tract disease	153
	Cu_2O NPs	H_2S-triggered conversion to Cu_9S_8, PTT/PDT & chemodynamic therapy	MRSA	Abscess	154
External stimulus	Ti_3C_2 MXenes	PTT	*Streptococcus mutans*, *Streptococcus sanguinis*, *Streptococcus sobrinus*	Caries	155
	PB@MnPPc	PDT	*S. aureus*	Wound healing	156
	PCMX	Ultrasound-driven ROS generation	*S. aureus*	N/A	157
	Fe_3O_4 NPs	Magnetic targeting & hyperthermia and PDT	*S. aureus*	Wound healing	158

N/A, lack of *in-vivo* application; CO, carbon monoxide; HOCl, hypochlorous acid; NO, nitric oxide; HAase, hyaluronidase; ROS, reactive oxygen species; PDT, photodynamic therapy; PTT, photothermal therapy.

In contrast to these mechanical disintegration processes, a more sophisticated approach is based on ATP acting directly as a cofactor for activating catalytic activity in nanocatalysts. Mehta et al.[138] showed that CeO_2 NPs, which are usually biologically quiescent, exhibit substantial oxidase-like activity in the presence of ATP. The reaction generates free radicals which kill bacteria. This research is the first to show, transcending the traditional role of ATP acting only as a destabilizing agent for structure stabilization, an innovative role as a toggle device which can modulate the targeted nanozyme therapy at the disease location in a controlled manner, with an efficacy that depends on the ATP content of the local environment.

Despite their sophistication, challenges remain for deploying ATP-sensitive devices clinically due primarily to issues with

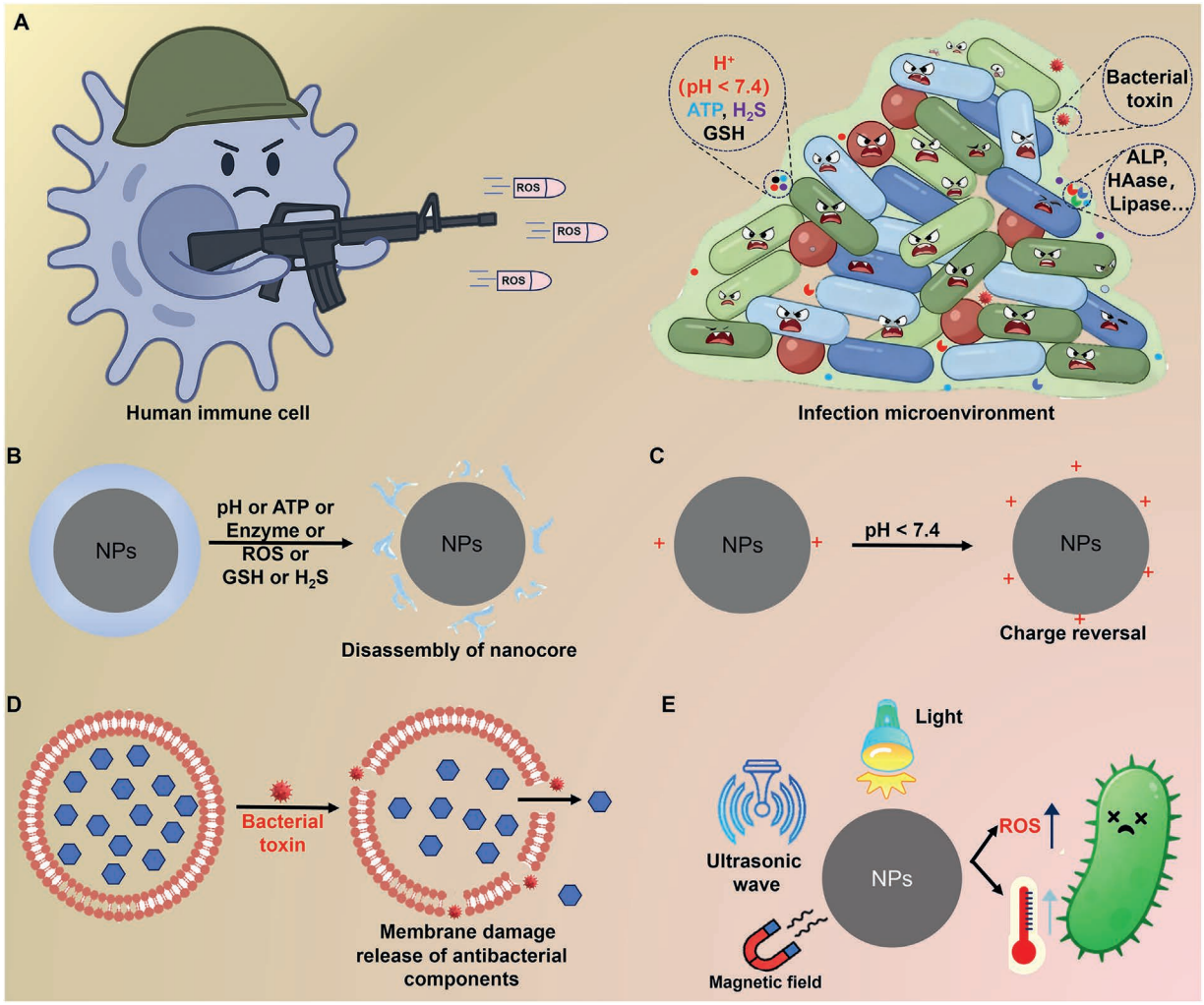

Figure 5 Characteristics of the bacterial microenvironment and stimulus-responsive mechanisms. (A) Overview of endogenous stimuli: pH (<6.5), specific enzymes (*e.g.*, hyaluronidase (HAase), lipase), and redox potential (GSH). (B−E) Mechanistic illustrations of cargo release and activation, based on design principles detailed in Refs. 159−166.

selectivity and stability. For example, there is difficulty in discriminating increased amounts of extracellular ATP from diseased tissue from physiological intracellular ATP within healthy tissue. Accidental triggering can lead to adverse consequences for off-target tissue[168]. ZIF-8 is a promising system to sense exogenous signals; however, the inherent poor stability of many ATP-responsive nanocarriers limits their ability to achieve uniform drug loading capacity and storage period in industrial manufacturing processes[169]. Future research could explore multifunctional stimulus-responsive platforms based on ATP sensing coupled to other noncorrelated stimuli such as acidity, bacterial enzymes, and higher levels of oxidative stress. The multiplexed signaling strategy will greatly enhance the targeting specificity to ensure drug release only occurs in conditions where all of these disease-specific signals exist concurrently.

4.2. Enzyme-responsive nanomaterials: Leveraging the pathogen's biochemical machinery

In addition to using general metabolites like ATP for the detection of microbes, scientists also engineered special types of nanosensors, which are sensitive to the presence of specific enzymes associated with microbes and thus can detect them. Enzyme-based nanosensors function in the following way: being kept in dormancy in healthy tissues but activated specifically at the location of infection upon exposure to microbial metabolites and/or pathogen-associated proteases[170,171]. Catalytic proteins produced by microorganisms include alkaline phosphatase (ALP), HAase, lipases, and β-lactamase, which are used for nutrient acquisition, host tissue degradation, and antibiotic resistance[140]. These unique enzymatic signatures present at the site of infection offer a biochemical cue that may be exploited to trigger therapeutic action. Researchers build into the NP an enzyme-dependent linkage or a shell that can be degraded, so that release of drugs and/or switching from one function to another is possible, thus targeting treatment effects exactly where they are needed and minimizing the systemic effects.

4.2.1. ALP as a trigger for in situ activation

When nutrients are scarce, certain bacteria like *S. aureus* and *P. aeruginosa* upregulate the production of ALP; this enzyme therefore serves as a reliable biomarker for targeted therapy[172,173]. The nanomaterials designed to target ALP are generally based on a prodrug strategy or self-assembly strategy. Another example is

the study from Zhan and coworkers, who designed an ALP-responsive peptidic sequence able to form antimicrobial nanofibers after its own dephosphorylation catalyzed by the enzyme[141]. Herein, the enzyme drives a conformational switch, converting dissolved single entities to potent, penetrating through-membrane nanomaterials directly at the microbe surface. Another approach is to trigger an ordered cascade of enzymatic reactions, as was demonstrated, for example, by the group of Zhuang[142] with a CuO nanozyme-prodrug system, where ALP converts a precursor of AA to activate ROS generation through CuO nanozyme. The two-step mechanism makes sure that the toxic action is limited to regions where there are high levels of ALP activity, thus leading to very specific targeting towards bacteria expressing a high level of this enzyme, including *E. coli*.

4.2.2. *HAase-mediated de-shielding for payload exposure*

HAase, an enzyme secreted by virulent bacteria (*e.g.*, *Streptococcus pyogenes* and *S. aureus*), is important for degrading extracellular matrices from host organisms. This enzyme activity is thus an excellent biomolecular trigger to initiate NP "unmasking" strategies, where NPs that first are masked by a hyaluronic acid (HA) shell block their therapeutic activity[174−176]. Once the NP reaches infected tissue containing HAase, the enzyme degrades HA, releasing the active payload. The idea that HA degradation *via* HAase can be used as a switch was cleverly employed: Liu et al.[143] used this approach to reveal the active areas and reaction sites on nanostructures intended for combined photodynamic and gas-therapy applications. The same basic principle has also been used for the controlled release of therapeutics such as sonosensitisers from carbon-based nanomaterials in order to increase penetration into biofilms and improve SDT[42]; as well as photosensitizing agents derived from molybdenum disulfide nanosheets to achieve a multimodal phototherapeutic treatment, which can be triggered remotely in an on-demand manner with the aim of minimizing side effects and premature release[144].

4.2.3. *Lipase-triggered charge reversal for enhanced targeting*

Some pathogenic organisms such as *P. aeruginosa* and *S. aureus* release some enzymes like lipase, which can be used to perform a switch from negative to positive charges on NP surfaces[177]. One example of such an application was described by Ma et al[145]. In their work, they functionalized AuNRs with molecules keeping them electrically neutral, thereby minimizing nonspecific binding to host cells. When these nanocarriers were exposed to lipolytic enzyme from MRSA, enzyme-mediated hydrolysis of an anionic polymer causes the surface charge on the NP to shift from neutral to positive. This enzyme-mediated charge switch greatly enhances the NP's ability to electrostatically interact with the bacterial cell wall, which normally carries a negative charge. This improved binding led to local photothermal killing of the infectious targets. The novel strategy eliminates the paradox between retaining a net-zero charge in the bloodstream to avoid nonspecific targeting, but also being positively charged when it reaches the infected site to adhere to pathogens and kill them.

4.2.4. *β-Lactamase: Turning antibiotic resistance into a therapeutic trigger*

Alternatively, researchers have repurposed the mechanism of antibiotic resistance itself as a therapeutic trigger. β-lactamases, the enzymes responsible for inactivating penicillin and cephalosporin antibiotics, can be repurposed as highly specific triggers. In this strategy, an enzyme associated with resistance is converted into a catalyst for therapeutic action[170,171]. One example is the system developed by Wu et al.[178], in which β-lactamases hydrolyze cephalosporins, which leads to the spontaneous self-assembly of the released peptides into fibrillar nanostructures. Its main strength lies in its intrinsic accuracy: as long as no resistance marker is present, the protein remains inactive. This selective triggering offers the potential to target especially virulent and/or antibiotic-resistant bacteria while leaving other organisms unharmed.

4.2.5. *Matrix metalloproteinases (MMPs) as infection microenvironment sensor*

However, despite their origin in the host, the upregulation of MMPs is an important marker of inflammation due to bacterial infection and thus can be considered a reliable biomarker of the microbial niche[179,180]. Similar to the hyaluronidase-based systems, many of the MMP-sensitive linkers are used for masking removal. Han et al.[146] created MNPs that respond to MMPs, an enzyme found in some biofilms; when a protein shell was cleaved by MMPs, it exposed cationic cores inside the MNPs, which facilitated transport through the biofilm matrices and enhanced adhesion to *P. aeruginosa*, thus increasing the efficacy of PDT. This study demonstrates that the use of endogenous chemical cues from the host may enable navigation around physical barriers such as biofilms. Other studies have coupled MMP-responsive motifs to multifunctional peptides. As an example, Li et al.[147] engineered a release system where a potent AMP is liberated from AgNPs *via* proteolytic degradation; this ensures that only at sites of inflammation with high concentrations of MMPs will the therapeutic AMP be released, thereby maximizing treatment efficacy and minimizing toxicity to normal tissue.

In summary, enzyme-responsive nanomaterials exploit unique biochemical features at an infected site for on-demand drug release. While challenges including inter- and intra-patient variability in enzymes and complex synthesis remain, these devices allow for unparalleled control over where and when drugs are released[181,182]. Future work will need to focus on determining what activates the bacterial enzymes in a broad range of species, as well as optimizing the expression process, which will all be important to translate such dynamic treatment tools into the clinic.

4.3. *ROS-responsive nanomaterials: Hijacking host defense signals for synergistic therapy*

A more sophisticated therapeutic strategy aims not only to detect pathogen-specific signals but also trigger treatment by exploiting the innate immune response of an organism. For example, if macrophages produce ROS at the location of an infection, that creates an exclusive oxidative milieu which serves as an extremely selective activation trigger of nanomaterials intended to react with ROS[183,184]. In fact, this strategy evolved starting from simple drug carriers towards more sophisticated multifunctional nanosystems with enhanced targeting capacity and/or combinatory therapy effect.

The main idea behind such an approach relies on the accurate control over the drug release process, in terms of space-time distribution. An outstanding example is represented by thioketal-protected mesoporous silica NPs that are normally closed and do not release any material in the body but open up when H_2O_2 is present in high amounts during an infection. These NPs rapidly release the drug cargo, *e.g.*, antibiotics such as vancomycin[148]. The principle is oxidation—that is, ROS oxidize the sulfur atoms of the thioketal linkages, forming labile sulfoxides and sulfones,

which are water-soluble, leading to the breakdown of the polymer backbone. Such localized stimulation guarantees an optimum level of drugs in the affected area and minimizes systemic side effects, which constitutes a basic building block for ROS-responsive systems.

The biggest advantage that the ROS-responsive system has is its ability to produce a combinatorial effect. These nanocarriers have an inherent response towards ROS, which can be used for drug delivery but also function as therapeutics themselves. The scavenging of excess ROS would alleviate some of the oxidative damage caused by chronic inflammation on adjacent tissue. These ROS-scavenging capabilities facilitate a healing environment and thus make these scaffolds ideal candidates in treating complex clinical scenarios like chronic wound infections. However, this duality poses an important control problem, namely that it must be carefully balanced so as to avoid excessive levels of ROS without sacrificing the necessary, baseline ROS signaling required to perform normal cell activities. Addressing the complex balance issue above, as well as developing flexible, repeatable manufacturing processes for current fabrication, is essential.

4.4. pH-responsive nanomaterials: Weaponizing the acidic microenvironment for targeted action

The acidic microenvironment (pH < 6.8) characteristic of bacterial infections and biofilms presents a reliable pathological signature for engineering environment-responsive nanomaterials[185−188]. This distinctive characteristic has been harnessed to develop sophisticated stimuli-responsive designs, shifting from simple pH-triggered drug release to advanced NP surface functionalization strategies. These features enable the systems to overcome major biological barriers, such as the anionic extracellular polymeric substance (EPS) matrix of biofilms.

One of the major challenges when treating diseases involving biofilms is what we call "the problem of penetrating the biofilm": on one hand, NPs need to be nontoxic and stable (*i.e.*, they need a neutral or negative charge) to circulate long enough *in vivo*; on the other hand, they need substantial positive charge to attach well and penetrate into the negative EPS. To overcome such a challenge, new types of charge-switching nano-platforms were designed and introduced, which are smart materials capable of changing their net zeta potential according to changes in the surrounding pH at the infection location; this was made possible by different types of stimuli-responsive functionalities. For instance, by employing boronate ester bonds, it is possible to design reversible negative charges which are degraded under acidic conditions, revealing positively charged cores that target improved biofilm penetration[189]. A similar approach uses 2,3-dimethylmaleic anhydride; a temporary charge mask that is cleaved by acid and therefore removes the masking of cationic residues, promoting electrostatic interaction with the biofilm and enabling on-demand delivery of drugs[149]. Such methods provide an overview of a general principle that could be exploited in clinical applications; namely, to maintain camouflaging during circulation but enable targeted, high drug concentrations only in the target area.

Beyond enhancing physical penetration, pH sensitivity can serve as the initial domino in a multi-stage therapeutic cascade, transforming the acidic environment into a factory for generating cytotoxic agents. A compelling example is the nanocomposite developed by Jiang and colleagues, where the acidic pH first triggers the decomposition of ZnO_2 to produce H_2O_2 *in situ*[150]. This locally generated H_2O_2 subsequently fuels an iron-based Fenton-like reaction, creating a high concentration of bactericidal ROS directly within the biofilm. This strategy elevates the role of pH from a simple trigger for physical change to an initiator of a potent, site-specific therapeutic cascade, showcasing a higher order of therapeutic design.

However, translating these elegant pH-responsive strategies to clinical settings hinges on overcoming formidable challenges in selectivity and stability. A primary concern is the limited pH differential between infection sites and certain physiological niches (*e.g.*, endosomes, tumor microenvironments), which can lead to premature activation and off-target effects[151]. The long-term stability of acid-labile chemistries, such as boronate esters, in complex biological fluids also requires rigorous validation. Consequently, the vanguard of the field is shifting towards multi-stimulus "AND-gate" systems, which require the simultaneous presence of both acidic pH and another infection-specific biomarker (*e.g.*, a bacterial enzyme) for activation. Such combinatorial-logic designs promise to deliver unparalleled targeting fidelity, ensuring these smart nanomaterials unleash their therapeutic potential with maximum precision and minimal collateral damage.

4.5. Bacterial component-responsive nanomaterials: Turning virulence factors and signaling molecules into triggers

To achieve high selectivity for target microorganisms, functionalized materials capable of specifically binding to biomolecules displayed on the surface of certain bacteria have been proposed and experimentally validated[190]. In this approach, treatment is triggered not by generic environmental parameters such as pH, but by pathogen-specific biomolecules—including bacterial toxins or cell-cell communication signals—thereby enabling highly selective activation[191]. Such smart nanoplatforms exploit the pathogen's own virulence factors and signaling molecules as precise molecular triggers, ensuring activation only in the presence of the target pathogen or biofilm-forming bacteria[192].

A prominent class of bacterial components exploited as triggers comprises secreted toxins—particularly pore-forming toxins (PFTs). These toxins can be harnessed to physically disrupt the protective shielding layer of NP carriers. One illustrative example is bioinspired nano-vehicles, such as erythrocyte membrane-camouflaged NPs. Zhuge et al.[162] demonstrated that PFTs penetrate the biomimetic shell, inducing localized cargo release from the system. This concept has been further advanced to develop dual-function platforms wherein the NP carrier both delivers therapeutics and actively scavenges toxins. Consequently, these platforms simultaneously administer therapy and neutralize virulent PFTs, thereby inhibiting pathogenicity through toxin sequestration—a paradigm termed "bioinspired toxin removal". Beyond direct sequestration, bacterial toxins can also serve as stimuli to initiate engineered biological cascade reactions; for instance, activating orthogonal nanoscale enzymes or powering *in situ* synthesis of antimicrobial agents within nanoreactors[193].

Apart from toxins, bacterial autoinducers and other cell-cell communication molecules have emerged as highly specific stimuli for engineering responsive nanosystems, as they constitute key components of quorum sensing (QS)[194]. QS signal molecules—such as acyl-homoserine lactones (AHLs)—accumulate in a cell-density-dependent manner to regulate collective behaviors, including biofilm formation and virulence factor production. NPs engineered to sense and respond to these signals can effectively disrupt QS pathways[195]. For example, a series of stimuli-responsive hydrogels have been developed that undergo state

transition or degradation upon exposure to specific QS signal compounds, enabling on-demand, targeted antibiotic delivery once pathogenic bacterial populations reach a critical threshold. This strategy is especially valuable for treating biofilm-associated infections, as therapy is initiated precisely in response to the molecular cues governing biofilm development[196]. Detection of these cues confirms active infection and enables pathogen-specific intervention[195].

4.6. Glutathione (GSH)-responsive nanomaterials: Turning a bacterial defense mechanism into an Achilles' heel

Shifting focus from the extracellular microenvironment to intracellular bacterial physiology, one strategy leverages the strongly reduced intracellular environment unique to many pathogens. The ability of numerous pathogens to upregulate glutathione (GSH) synthesis in response to host-derived ROS confers a potent antioxidant shield[197−200]. Elevated intracellular GSH concentrations thus provide a distinctive biomarker signature exploitable by synthetic nanomaterials—triggering their activation either upon cellular internalization or in response to the reductive microbiome niche. This type of targeted therapy is commonly based on nanostructures incorporating disulfide bonds, which undergo selective cleavage by intracellular GSH. The underlying mechanism is the thiol-disulfide exchange reaction: intracellular GSH acts as a nucleophile that attacks and cleaves disulfide (−S−S−) bonds. Cleavage of these covalent bonds releases free thiols, triggering NP disassembly and subsequent release of encapsulated therapeutic agents. Thus, this strategy enables site-specific drug delivery with enhanced payload retention at disease sites.

The concept of GSH-triggered activation can be extended to multifunctional platforms that combine drug release with active transport. For example, Peng and colleagues developed a self-propelled nanomotor designed to target *P. aeruginosa* biofilms[152]. In this system, elevated GSH concentrations simultaneously trigger NO release, generation of a biofilm-disrupting molecule, and *in situ* formation of gaseous microbubbles that provide propulsive force. This GSH-fueled propulsion enables the nanomotors to actively penetrate dense biofilm matrices—achieving transport efficiency up to one order of magnitude greater than that of passive NPs. This work elegantly demonstrates how a single endogenous biological stimulus (GSH) can serve dual therapeutic functions: as a molecular trigger for site-specific activation and as an energy source to overcome physical barriers—including the complex rheology of biofilm networks that typically impede conventional antimicrobial delivery.

Despite all this sophistication, the GSH-responsive strategy faces an inherent selectivity challenge[152]. Both bacterial pathogens and eukaryotic cells maintain high intracellular GSH concentrations; thus, in the absence of substantial differences in their relative GSH levels, no significant differential triggering response occurs. Consequently, drugs may be prematurely released inside host cells following passive uptake, potentially causing unwanted off-target effects. Therefore, this mechanism is unlikely to be deployed clinically as a standalone trigger—but rather as a critical component within multistimuli-responsive "AND-gate" systems. Designing delivery platforms that require an extracellular foreign trigger—such as acidic pH or bacterial proteases—to first mediate cell-surface targeting and internalization, followed by intracellular GSH-triggered drug release, enables precise spatiotemporal control over therapeutic action. This dual-requirement logic is precisely what makes such strategies a powerful approach to harnessing the bacterial antioxidant defense system as a therapeutic target.

4.7. H_2S-responsive nanomaterials: Leveraging a gaseous virulence signal for theranostic activation

Besides common metabolic byproducts, some disease-causing microbes generate unique gaseous molecules that serve as highly specific biomarkers[201]. For example, H_2S is overproduced by clinically relevant pathogens such as *Salmonella* and *H. pylori*[202−204]. This gaseous mediator actively modulates the infection microenvironment, making it an ideal endogenous trigger for localized therapeutic activation. This field has evolved from simple drug delivery vehicles to sophisticated stimuli-responsive theranostics capable of simultaneous diagnosis and treatment.

This concept—though abstract—holds practical promise; for instance, H_2S can cleave specific chemical bonds (*e.g.*, disulfide bonds), triggering nano-carrier disassembly and subsequent release of encapsulated therapeutics. Disulfide-stabilized nanostructures, for example, rapidly decompose upon exposure to pathologically elevated H_2S concentrations at infection sites, enabling spatially controlled drug release[153]. Such targeting minimizes systemic drug distribution and thereby reduces off-target toxicity.

However, the most significant innovation in this field may lie in moving beyond simple drug delivery to chemically transforming the nanomaterial itself within a biological system—realizing an innovative "pro-nanodrug" platform. In this paradigm, initially inert NPs—such as copper(I) oxide (Cu_2O)—undergo *in situ* chemical modification upon reaction with endogenous hydrogen sulfide (H_2S), converting into theranostic copper sulfide NPs (Cu_9S_8)[154]. This represents a critical conceptual advance: the nanoplatform remains inert until it detects disease-specific molecular signatures, at which point it autonomously generates its diagnostic and therapeutic functionalities. Furthermore, these copper sulfide NPs enable infection site imaging in the second NIR window (NIR-II; 1000−1700 nm) for precise lesion localization, while simultaneously catalyzing PTT and chemodynamic therapy (CDT). This constitutes a new theranostic paradigm—one integrated step of diagnosis and multimodal therapy, triggered exclusively by disease biomarkers and enabling precision delivery with minimized off-target effects.

This is an elegant strategy; however, clinical translation requires tailoring such responses to function reliably within the highly complex chemical milieu of infected tissues. The first challenge is selectivity: endogenous reducing agents such as GSH may trigger premature activation or unintended degradation[205]. Moreover, H_2S consumption during NP conversion could confer additional therapeutic benefits by suppressing bacterial virulence factors—a mechanism warranting further investigation[201]. Future intelligent delivery systems should incorporate dual-stimuli responsiveness—combining H_2S sensing with complementary cues such as acidic pH. Such multi-responsive platforms would enhance targeting specificity and embed built-in safety features, enabling more precise, diagnostics-guided antibiotic deployment.

4.8. Externally-triggered nanomaterials: On-demand activation with spatiotemporal precision

In contrast to the use of naturally fluctuating endogenous signals, exogenously triggered nanostructures enable far more precise control over drug delivery from the clinician's perspective. Exogenous triggering sources—including light, ultrasound,

electrical fields, and ionizing radiation—allow clinicians to precisely determine the timing, spatial localization, and dosing parameters of antimicrobial therapies[159–161]. This type of controlled triggering is especially advantageous when treating infected areas while sparing surrounding healthy tissue.

4.8.1. Light-responsive nanomaterials (PTT/PDT)

Light is the most widely utilized external stimulus, enabling two primary therapeutic modalities: PTT and PDT[160].

PTT employs photothermal conversion materials—including Au-based nanomaterials, copper sulfides, two-dimensional MXenes, and the NIR-absorbing dye indocyanine green (ICG)—which efficiently convert NIR light into localized heat[160]. This induces a rapid, localized temperature increase above 50 °C, causing irreversible denaturation of microbial cell structures and membranes. Consequently, PTT achieves fast and broad-spectrum antimicrobial activity while minimizing the risk of resistance development; it is also effective against antibiotic-resistant persister cells, which are typically refractory to conventional antibiotics. To combat such pathogens in the context of early childhood caries (ECC), Zhang et al.[155] engineered a "nano-thermal knife" using Ti_3C_2 MXenes. Beyond their direct bactericidal effects (*via* thermal damage), these agents trigger heat-shock responses in mammalian cells—effectively disrupting the metabolic quiescence associated with persister cell formation. This dual-action strategy demonstrated significant efficacy against both planktonic and biofilm-embedded cariogenic persisters, offering a potent new approach for caries prevention.

PDT involves photosensitizers (PSs) such as porphyrins, chlorin e6 (Ce6), and phthalocyanines, which—upon irradiation at specific wavelengths in the presence of molecular oxygen (O_2)—generate ROS toxic to bacteria[206]. These ROS mediate broad-spectrum oxidative damage to cellular targets, including membrane phospholipids, structural proteins, and DNA. In recent work, Zhang et al.[156] developed a state-of-the-art hybrid nanomaterial comprising Prussian blue and manganese polyphthalocyanines (PB@MnPPc), demonstrating potent antibacterial and anti-inflammatory effects. NIR irradiation induced the nanocomposite to produce elevated levels of singlet oxygen ($^1O_2$) and localized heat, resulting in effective pathogen reduction. Notably, the system exhibited dual functionality: in the absence of light, the nanosystem acted as a ROS-scavenging enzyme mimic—reducing inflammation and promoting tissue repair. Such controlled, spatiotemporally regulated generation and scavenging of ROS represents a novel therapeutic strategy with promising applications in infected wound management.

4.8.2. Ultrasound-responsive nanomaterials

To overcome the limitation on the penetration depth of light into tissues, ultrasound is emerging as a suitable alternative modality for deep-tissue therapeutic triggering. Ultrasound can be used to trigger SDT through sonosensitizers like TiO_2, PpIX, etc., generating reactive ROS in an action similar to PDT but deeper into the tissues[207]. This feature makes SDT a promising treatment modality for deeper infections such as bone infection. One successful example is provided by Zhang et al.[157], who fabricated a novel Schottky heterojunction catalyst (PCMX) by combining two-dimensional MXene ($Ti_3C_2T_x$) and a porous porphyrin-based metal-organic framework (PCN-224). The formation of the interfacial heterojunction facilitated the effective separation of the charge carriers produced by ultrasound, greatly decreasing the rate of their recombination, thus significantly enhancing ROS generation. The resulting biohybrid showed high antibacterial activity, with 99.36% inactivation of *S. aureus* at the highest bacteria concentration tested, after only 15 min sonication, showing that smart nanomaterials can significantly improve SDT efficiency.

4.8.3. Magnetic field-responsive nanomaterials

Magnetic fields offer a nearly non-invasive method for delivering heat to deeply embedded tissues. In MHT, superparamagnetic iron oxide NPs exposed to an AMF undergo rapid reversal of their magnetic moments, inducing localized heating and resulting in a focal temperature increase[161]. This approach enables controlled thermal treatment of internal infected sites—potentially avoiding the need for surgical intervention. Li et al.[158] developed an adaptable platform based on mesoporous FeO_x nanocarriers functionalized with the NIR dye IR-820 to achieve synergistic effects from both MHT and PDT. The magnetism of the magnetic NPs (MNPs) was leveraged to achieve targeted accumulation at infection sites, while the AMF triggered two concurrent actions: (1) localized hyperthermia *via* the iron oxide component, and (2) stimulus-responsive release of the encapsulated photosensitizer (IR-820). Upon subsequent NIR irradiation, the released IR-820 generated ROS. Thus, a synergistic therapeutic process—comprising heat-induced disruption of the biofilm matrix, localized hyperthermia, and oxidative damage by ROS—has been demonstrated to effectively eradicate biofilms *in vitro* and successfully treat biofilm-infected tissues *in vivo*, showing promise for clinical translation. *In vivo* wound and abscess model experiments confirmed the efficacy of this stimuli-responsive platform, highlighting the advantages of a multi-stimuli-responsive system.

4.8.4. Microwave-responsive systems

Microwaves can serve as another useful external stimulus to achieve on-demand antibacterial therapy, offering advantages including deeper tissue penetration than light-based modalities and precise, non-contact operation[208]. The most common mechanism is microwave-induced hyperthermia: materials exhibiting high dielectric and/or magnetic losses—such as carbon-based nanostructures or certain metal oxides—efficiently convert incident electromagnetic (EM) radiation into localized heat[209,210]. Beyond thermal effects, microwave dynamic therapy (MDT) exploits microwave irradiation to trigger catalytic reactions that generate ROS with cytotoxic activity[211].

A compelling example of this novel strategy is the recent work by Cheng et al.[212], who addressed the clinically challenging case of MRSA osteomyelitis using a microwave-activated nanomedicine ($Mn_{0.1}$PCC). This system comprises Mn-doped macroporous MOFs loaded with calcium peroxide (CaO_2). Upon microwave irradiation, it initiates a surface-mediated, multistep healing process. The MOF acts as an efficient converter of EM energy into localized heating, while CaO_2 simultaneously decomposes *in situ* to release H_2O_2—the substrate for a Mn(II)-catalyzed Fenton-like reaction, which is accelerated under microwave irradiation to produce a burst of antimicrobial hydroxyl radicals (•OH). Critically, this reaction proceeds efficiently in both oxic and anoxic environments and generates O_2 as a beneficial byproduct, thereby enhancing overall treatment efficacy. In addition to direct pathogen killing *via* localized hyperthermia, robust ROS generation in anaerobic conditions effectively eradicates antibiotic-resistant bacteria and disrupts bacterial communication pathways, including quorum sensing. The development of integrated sensing and responsive systems represents a critical

advance in treating deep-seated infections, as these materials enable spatiotemporal control over antibiotic activity—a significant step toward overcoming inherent limitations of conventional deep-tissue therapies.

In summary, external stimulation affords exquisite spatiotemporal control over antimicrobial effectors. Although it requires specialized equipment and faces challenges—including limited penetration depth (for optical systems) and difficulties in achieving homogeneous field distribution—its capacity to deliver on-demand, localized therapy renders external stimuli ideal foundational elements for smart nanomaterials designed to combat infections.

4.9. Higher-order precision: Logical gating and hierarchical activation in multi-stimulus systems

Although single-stimulus-based approaches have advanced the field toward personalized medicine, they are often impractical in clinical settings because each individual biomarker is typically an unreliable signal on its own. To address this limitation, researchers have developed advanced nanomaterials capable of responding to multiple stimuli through logical operations—termed Boolean logic. One such design implements an AND gate that triggers a therapeutic response only when two distinct pathological conditions are simultaneously satisfied. This strategy significantly enhances selectivity, as the probability of two uncorrelated biomarkers being co-expressed by chance in healthy tissue is substantially lower than that of a single biomarker. A representative implementation combines a general physiological cue—such as the acidic pH associated with infection—with a pathogen-specific enzymatic biomarker (*e.g.*, HAase), ensuring drug release occurs exclusively when both conditions are met at the disease site[213].

Building upon this concept, more sophisticated systems employing hierarchical (or cascaded) triggering mechanisms have been proposed to tackle complex, spatially heterogeneous challenges—including bacterial biofilms. Such approaches represent a theoretical advance beyond simple spatial "AND logic gate" strategies, enabling spatiotemporally controlled interventions. For example, Wang et al.[214] developed a stimuli-responsive NP that first undergoes protonation reversal in response to the low pH of the biofilm surface layer to enable penetration; subsequently, it responds to elevated ATP concentrations in the biofilm core to trigger localized drug release (Fig. 6). These highly choreographed, spatiotemporally precise activation sequences can be intelligently deployed to traverse and dismantle such intricate biological barriers—a capability unattainable with conventional single-stimulus strategies.

To move beyond simple reflexes and toward more complex, logic-based control systems, we must understand the trade-offs associated with using any particular type of cue available in the biological environment. Using the internal sensing mechanisms described in Sections 4.1−4.7, we summarize the key properties of each in Table 4. This review focuses on various activation systems—such as pH shifts, proteolytic activity, and redox-driven processes—evaluating them through critical translational parameters including kinetics, selectivity, and challenges in *in silico* modeling and clinical translation. This comprehensive performance map can guide researchers in selecting an appropriate actuation strategy for specific infectious diseases; it also establishes the theoretical foundation for designing more sophisticated stimuli-responsive devices and "Target−Trigger−Treat" therapeutic strategies.

Another strategy for fine-tuning activation is to integrate internal disease signals with external stimulation sources. This approach grants clinicians greater flexibility in determining "when" and "where" therapy is applied. In such a scenario, the nanomaterial exploits endogenous biomarkers—such as local pH and ATP concentration—to achieve spontaneous *vs* active accumulation at infection sites. Once accumulated at the target location, the device remains inert until it receives an externally applied signal (*e.g.*, NIR light) delivered at a precise time and location. This signal triggers localized therapeutic action—including photothermal heating or ROS generation—with high spatial and temporal accuracy. The "internal guidance, external triggering" design decouples target recognition from drug release, a promising paradigm for stimuli-responsive antibiotics.

These complex systems pose significant coordination challenges for practical implementation. A major translational barrier lies not only in designing highly complex architectures, but also in ensuring that activation levels are both quantitatively precise and biologically appropriate within a dynamic living system. Scientists must understand the consequences of under- or over-stimulation in animal models—particularly when some signals are constitutively present while others fluctuate dynamically. Future work must therefore focus on developing tunable devices whose response parameters (*e.g.*, threshold, magnitude, duration) can be precisely controlled, alongside predictive mathematical models capable of accurately simulating device behavior under *in vivo* conditions. Only then can we achieve reproducible synchronization between such sophisticated smart devices and living organisms—a critical step toward clinical translation.

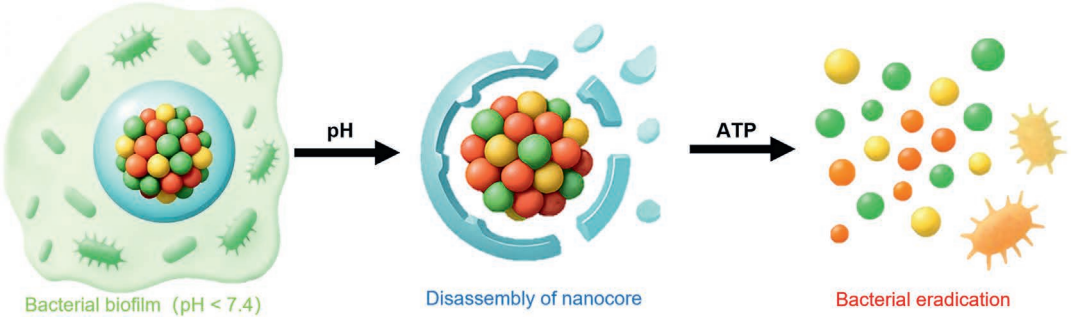

Figure 6 Antibacterial NPs based on dual stimulation response of pH and ATP[214].

Table 4 Comparative analysis of major endogenous stimuli-responsive mechanisms for smart antibacterial nanosystems.

Stimulus mechanism	Principle	Triggering conditions	Response rate	Selectivity	Key challenges	Clinical feasibility
pH	Protonation/deprotonation of polymers or cleavage of acid-labile bonds (*e.g.*, hydrazones).	Low pH (5.0−6.5) in infection microenvironments, abscesses, or intracellular compartments (endosomes/lysosomes).	Fast (minutes to <1).	Moderate. Other pathological sites like tumors also exhibit acidic pH. Susceptible to off-target activation in non-infected inflammatory. Tissues.	Insufficient pH differential for a sharp on/off switch; potential for premature release.	High. A well-established and widely used mechanism, valued for its simplicity and reliability, despite moderate selectivity.
Enzymes	Specific enzymatic cleavage of a peptide or ester linker within the nanostructure.	Overexpressed pathogenic enzymes (*e.g.*, proteases, lipases, hyaluronidases) specific to certain bacteria (*S. aureus*, *P. aeruginosa*).	Variable (minutes to hours). Dependent on enzyme concentration and substrate kinetics.	High to very high. Can be tailored to be highly specific to a target pathogen, offering precision targeting.	Heterogeneity of enzyme expression across strains and infection stages; potential substrate competition.	High. Highly promising due to its superior selectivity. A leading strategy for pathogen-specific theranostics.
ROS	Oxidation of ROS-sensitive moieties (*e.g.*, thioethers, boronic esters), leading to NP disassembly or drug release.	High levels of ROS (H_2O_2, OH) generated by host immune cells or bacteria during infection.	Fast. Oxidation reactions are typically rapid.	Moderate. ROS levels are elevated in general inflammation, not exclusively in bacterial infections.	NP stability during storage and circulation (avoiding premature oxidation); balancing sensitivity and stability.	Good. Useful for targeting inflammation-rich infection sites, but selectivity concerns remain a hurdle for systemic use.
GSH (redox)	Reduction of disulfide bonds by high intracellular GSH concentrations.	High GSH levels inside bacteria or phagocytes (∼1 −10 mmol/L) *vs* low levels in extracellular fluid (∼μmol/L).	Moderate too fast. Disulfide bond cleavage is generally efficient.	High (for intracellular targeting). Excellent for distinguishing between intracellular and extracellular environments.	Primarily effective for intracellular drug delivery; limited utility for targeting extracellular bacteria or biofilms.	Very high. A robust and reliable mechanism for intracellular delivery, widely validated in both cancer and infection models.
ATP	Conformational change or displacement in ATP-aptamer-based systems.	High concentrations of eATP from damaged cells at infection sites.	Moderate. Dependent on binding affinity and kinetics of the aptamer-ATP interaction.	Moderate to high. eATP is a strong indicator of tissue damage and acute inflammation, providing good site-specificity.	*In vivo* stability of aptamers against nuclease degradation; cost of aptamer synthesis.	Emerging & promising. Represents a novel and highly relevant trigger, but requires further in-depth validation and optimization.

eATP: extracellular ATP; ROS: reactive oxygen species.

5. Integrated smart systems: The fusion of spatial and temporal control

As shown in the preceding sections, active targeting enables spatiotemporal control over where nanomaterials accumulate, whereas stimuli-responsive approaches enable on-demand control over "when" therapeutic action occurs. Although each approach is powerful in its own right, the most advanced developments in smart nanomaterials engineering arise from their combined use. Researchers are now developing hybrid systems incorporating both target-specific ligands and stimuli-responsive moieties, laying the foundation for so-called "dual-lock" treatment strategies—in which NP delivery and accumulation at the target tissue site *in vivo* depend on active targeting and subsequent release of the loaded therapeutics is triggered by specific disease-associated signals or stimuli. This spatiotemporal control enhances treatment accuracy, reduces toxicity to healthy tissues, and enables the application of complex, multifactorial therapeutic strategies in complicated diseases.

5.1. The "AND" logic: Dual-locking for maximum specificity

The "AND" logic gate is an important application in clinical therapy, enabling drug release only when all specific disease markers are detected—thereby ensuring targeted treatment. It functions as a safety-check mechanism so that drug-loaded NPs respond exclusively to the simultaneous presence of pathogens and associated inflamed tissue, greatly enhancing treatment precision. One notable example is the study by Wang et al.[215] on ocular bacterial infection. The dual-targeting HPBH@GLA/AMP nanocomposite incorporates a phenylboronic acid group that binds to pathogen cell wall epitopes and HA, which targets overexpressed HA receptors on the patient's cells. This design delivers both antibacterial and anti-inflammatory agents specifically to infection sites where pathogens and inflammation coexist.

5.2. The sequential cascade: Penetrate-then-kill strategy

To overcome the difficulty of treating bacterial biofilms, complex systems have emerged that apply a "penetration-then-destruction" strategy: they decouple arrival at the treatment site from the therapy itself, enabling a carefully orchestrated, multiphase attack. An example of such an approach is the development of an NIR-activated nanodevice to combat entrenched MRSA biofilms[216]. Their novel yolk-shell structure incorporates photoresponsive ICG and the MRSA-destroying protein lysostaphin. The treatment begins with the infiltration phase: under NIR irradiation, the asymmetric structure of the nanodevice generates a thermal gradient capable of producing a propulsive force that drives the device into the thick EPS matrix. This mechanical disruption is then complemented by enzymatic degradation of biofilm extracellular matrix performed by lysostaphin, which can exert its antimicrobial effect only after penetrating the biofilm. Upon exposure to NIR light, the system initiates "elimination". The same light also triggers ICG, inducing combined photodynamic and photothermal reactions that destroy the bacterial population previously exposed to the nanodevice. This new "propel-then-eradicate" strategy enables the NPs to overcome diffusion limitations faced by static NPs, ensuring high treatment efficacy at hard-to-reach infectious sites.

5.3. Target, trigger, and treat: Integrating external command

Maximum spatial and temporal control can be achieved when the autonomous guidance system is decoupled from a remote-controlled trigger administered by clinicians. In the "Target—Trigger—Treat" strategy, the NP first uses its intrinsic targeting ability to deliver itself accurately to the target pathology and remains there in a dormant state until receiving an external trigger signal to initiate treatment. A good example of such an integrated strategy is the CBPV NP platform designed by Chen and coworkers to treat infected diabetic wounds[217]. This platform achieves primary spatial resolution *via* vancomycin moieties conjugated to its surface, which specifically bind MRSA at the infected site.

This localized "targeting" is followed by the application of a deep-penetrating NIR-II laser, which serves as the external "trigger" required to initiate a sophisticated multimodal therapeutic cascade for infection treatment. This activation unleashes a photothermally enhanced chemodynamic therapy to generate ROS, coupled with the controlled release of NO. This "Target—Trigger—Treat" approach not only results in potent MRSA eradication but also leverages the therapeutic NO to promote angiogenesis, simultaneously addressing both infection control and tissue regeneration. These studies demonstrate that coupling targeted molecular recognition with an external spatiotemporal trigger enables truly spatiotemporally controlled therapies, a paradigm especially well-suited for managing difficult chronic infections. It represents a significant advance over conventional multimodal treatment strategies for complex chronic diseases.

The case studies presented here illustrate how therapeutics—once monofunctional—have evolved into multifunctional tools programmed for complex, predefined workflows. The workflow progresses from simple "AND-gate" strategies that enhance passive targeting, through successive biologically guided steps that overcome physiological barriers, to externally regulated "Target—Trigger—Treat" systems. These advances hold clear potential to enhance treatment precision (in both space and time) and improve clinical controllability: integrating "where" with "when" lies at the core of smart antibiotic design. Despite the high therapeutic potential of such hybrid constructs, translation across development stages—from animal models to human clinical application—requires substantial advances in biocompatibility, scalable manufacturing, and environmental regulatory compliance. Implementation challenges are discussed in detail below.

6. Conclusions and perspectives

Owing to increasing AMR, there is an urgent need for new paradigms in antibiotic therapy featuring more precise and adaptable platforms. In this review, we summarize the progressive evolution of smart antimicrobial materials, demonstrating their progression toward complex systems capable of delivering therapy at high spatiotemporal resolution. Such devices typically integrate location information to enable spatially targeted delivery and time-dependent activation mechanisms to trigger drug release at a desired moment, showing great promise. The main conclusion of this analysis is that identifying new and more potent antibiotics alone will be insufficient for future generations to treat infections; instead of merely attempting to cure them, researchers must focus on creating "smart" tools that autonomously detect signs of illness and selectively kill pathogens—while, above all, remaining in

harmony with the physiological processes of the human body. Their future application in healthcare remains a key objective, presenting both significant benefits and challenges that require careful consideration.

6.1. The merits: A paradigm shift in anti-infective therapy

The rational design and synthesis of smart nanomaterials—as replacements or supplements to traditional antibiotic drugs—represent a feasible strategy to circumvent the shortcomings of currently available antibiotics. Smart nanomaterials have demonstrated effective eradication of drug-resistant pathogens through various antimicrobial mechanisms, including photothermal effects induced by irradiation with visible or NIR light, mechanical rupture of bacterial cell walls, and ROS generation *via* nanozyme activity. These mechanisms target essential bacterial structures and are unlikely to elicit resistance through conventional pathways such as genetic mutation or enzyme-mediated inactivation[40,44,218]. One of the main advantages offered by these nanostructures lies in their smart targeting capability, which successfully addresses the issue of off-target toxicity: they act exclusively at the site of infection and only upon intentional activation. This also minimizes collateral damage to the normal microbiota—a critical advantage compared with nonspecific antibiotics[13]. These developments open new perspectives for challenging clinical scenarios, from recalcitrant biofilms on medical implants to life-threatening systemic infections.

6.2. The translational gap: Pharmacokinetics, manufacturing, and biological safety

6.2.1. Biological identity and pharmacokinetic unpredictability

A key obstacle to translating such rational designs into effective clinical nanomedicine is the substantial disconnect between the well-designed synthetic structures of smart nanomaterials and how they behave *in vivo*. Upon introduction to the circulatory system, such engineered particles are quickly coated with a protein corona, which may mask even carefully added targeting moieties, such as antibody fragments or aptamer strands, thereby preventing them from detecting their target molecule[219]. This natural biofilm, coupled with potential immunological reactions—which might also take place for the bioinspired surface-modified systems—often results in surprising distribution profiles that are not predicted by animal models, and therefore NP-based therapies frequently get sequestered by endogenous immune systems, indicating long-term persistence in the liver and spleen[220]. Unlike traditional antibiotics, for which the absorption and elimination profile is known, intelligent nanotherapeutics show significant patient-to-patient variability in their biological processing, and their eventual removal from the body is poorly understood.

6.2.2. The complexity-feasibility paradox and Chemistry, manufacturing, and control standards

However, despite their obvious efficacy *in vitro* and in preclinical animal models, translational challenges must be addressed before smart antibacterial nanostructures can reach the clinic. This is due not only to potential toxicity but also to other drug-related issues.

The current state of medicine and biomedical research is characterized by a "feasibility-complexity paradox": whereas the most complex multilogic-controlled nanodevices are extremely effective as laboratory tools, their applicability is often hindered by manufacturing limitations. In particular, the major challenge lies in meeting the Chemistry, Manufacturing, and Control requirements for large-scale commercial production[221]. The complex, multistep synthetic procedures required to fabricate such "advanced" therapeutic devices are difficult and costly to scale up from laboratory-scale synthesis to the GMP-compliant levels needed for clinical manufacturing. Ensuring consistent particle size, shape, and functionality across batches is challenging yet critical for reliable clinical performance; moreover, long-term stability, shelf life, and appropriate sterilization methods for such complex devices represent significant financial and technical hurdles[221]. Ideally, new antimicrobials would be developed with an optimal balance—between molecular complexity and structural simplicity in their design. Future antimicrobials would meet urgent clinical needs while remaining affordable to produce, scalable in manufacturing, and scientifically rigorous[221].

6.2.3. The resistance paradox: Evolutionary and ecological risks

The paradigmatic view of nanomaterials as "defense-proof by design" is challenged by the fact that, despite avoiding conventional resistance mechanisms, new evidence suggests organisms may evolve resistance in response to repeated application. For example, prolonged contact with AgNPs results in increased expression of cellular efflux systems[222]. Particularly worrisome is the finding that certain metal-based nanomaterials induce oxidative stress at subtoxic concentrations, which can cause mutations as well as damage cell membranes—potentially enabling horizontal gene transfer of resistance genes from one bacterial population to another[223]. Note that such a scenario should be considered when evaluating the indirect amplification of resistance spread during risk assessment or mitigation planning.

In summary, novel antimicrobial nanomaterials are moving from theoretical concepts to actual treatment options. To accomplish this, expertise from materials scientists, microbiologists, immunologists, and clinicians must be combined to establish robust testing protocols, adopt standardized assays, and pursue the development of formulations that balance efficacy with realistic manufacturing requirements and long-term patient safety. By following the above-mentioned comprehensive approach, these emerging technologies can become viable medical tools when conventional antibiotic drugs are no longer effective.

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Author contributions

Zhipeng Li and Jianliang Shen conceived the review topic. Zhipeng Li drafted and edited the manuscript. Yutong Li, Zhiyong Liao, and Jianliang Shen revised the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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