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Review Article

Helicobacter pylori and Gastric Cancer: A Potential New Paradigm of 3R (Remove, Remodel, Repair) Integrated Therapy Based on Nanomaterials

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Abstract

Helicobacter pylori infection represents a significant modifiable risk factor in the pathogenesis of gastric cancer. Nevertheless, conventional antibiotic treatments have increasingly proven inadequate due to challenges such as antibiotic resistance, microbial dysbiosis, and mucosal damage. In response to these issues, this review introduces an innovative intervention strategy based on the "nanotechnology-based 3R" approach (Remove *H. pylori*, Remodel the microenvironment, Repair the gastrointestinal tract), which aims to offer a comprehensive solution for managing *H. pylori* infection. This strategy comprises three principal components. Firstly, the utilization of pH/light/magnetic multi-responsive nanomaterials facilitates the precise eradication of the pathogen and its biofilm. Secondly, to address bacterial immune evasion, these nanomaterials are engineered to target and neutralize virulence factors such as VacA, thereby contributing to the reversal of the local immunosuppressive environment. Thirdly, the utilization of nanomaterials presents a promising approach for the concurrent repair of the mucosal barrier and the maintenance of intestinal microbiome homeostasis. Finally, this paper provides a comprehensive analysis of the specific mechanisms employed by typical nanomaterials, including metal-organic frameworks, charge-reversal nanoparticles, nanozymes, and antimicrobial peptide crystals. These mechanisms involve targeted microbial eradication, activation of autophagy, and the upregulation of tight junction proteins. Furthermore, the study delves into the critical roles played by multimodal external field stimulation and material–host interaction network analysis, which are essential for future clinical translation. Ultimately, this review suggests a potential roadmap for system-precision intervention that transcends the conventional "sterilization first" paradigm. Nonetheless, the current evidence regarding the efficacy and safety of this approach is predominantly derived from cell and mouse models. Therefore, its clinical applicability requires validation through studies involving large animal models and prospective clinical trials.

Keywords: *Helicobacter pylori*; Antibiotic-free; Integrative medicine; Gastrointestinal tract; Nanomaterial; Immune remodeling; Organ repair.

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Introduction

Gastric cancer remains one of the most prevalent and lethal major cancers worldwide, ranking fifth in new cases among all malignant tumors and third in mortality, and continues to pose a significant public health burden.[1] Gastric cancer is often diagnosed at an advanced stage, a characteristic that significantly increases the difficulty of treatment and leads to a high mortality rate.[2] A large number of epidemiological and molecular biological studies have shown that *H. pylori* infection is one of the most important modifiable risk factors for gastric cancer development, and

it has been classified as a Class I carcinogen.[3,4] *H. pylori* infection significantly increases the risk of gastric cancer through mechanisms involving chronic infection, immune dysregulation, and multiple carcinogenic pathways.[5,6] Studies have shown that *H. pylori* infection is one of the main causes of gastric cancer. It significantly increases the risk of gastric cancer by continuously inducing gastric mucosal inflammation, immune response disorders, and remodeling of the tumor microenvironment.[7] According to the "Fifth National Consensus Report on the Management of *H. pylori* Infection", the "Management of *H. pylori* Infection—Maastricht VI/Florence Consensus Report",[8] the IHPWG Consensus,[9] and the Kyoto Global Consensus in 2015, *H. pylori* infection is contagious and is a major controllable cause of gastric cancer. The Kyoto Consensus clearly stated that all infected individuals should receive eradication therapy to prevent the development of gastric cancer and reduce transmission, and that initial eradication treatment is critically important.[10] Numerous studies have shown that the decline in cancer incidence is closely related to the global reduction in *H. pylori* infection rates.[11] *H. pylori* infection can trigger a variety of gastrointestinal diseases, posing a serious threat to public health and increasing the medical burden.[12] The Department of Gastroenterology and Clinical Research Center of Shanghai Changhai Hospital, affiliated with Naval Medical University, led by Academician Zhaoshen Li and Director Yiqi Du, has long been committed to research on *H. pylori* prevention and control. Between 2021 and 2023, the team led a large-scale epidemiological survey covering 29 provinces, 10,735 families, and over 31,000 individuals nationwide. The results revealed that the individual *H. pylori* infection rate in China was 40.66%, whereas the family infection rate was as high as 71.21%. A previous study systematically demonstrated that "family clustering" is the core link in the transmission of *H. pylori*.[13] On the basis of the above data, the team, in collaboration with 57 centers in China, formulated the world's first "Chinese Consensus on the Control and Management of Family *H. pylori* Infection (2021 Edition)." This consensus proposes a comprehensive family intervention strategy of "screening—simultaneous eradication—follow-up," upgrading the "individual treatment" model to a "family management" model for the first time. It provides an evidence-based pathway and operational guidelines for reducing reinfection rates and preventing primary gastric cancer.[14,15] In 2023, Nobel laureate and discoverer of *H. pylori*, Professor Marshall, published an article in the journal Gut highly appraising China's proposed "family-based *H. pylori* screening-eradication" strategy, deeming it feasible and worthy of global promotion.[16] A nationwide multicenter long-term follow-up study confirmed that standardized eradication of *H. pylori* can significantly reduce the risk of gastric cancer.[17] Currently, the treatment strategy for *H. pylori* infection still involves multidrug combination regimens, typically including combinations of antibiotics, proton pump inhibitors, and bismuth agents.[8,18,19] The National Consensus on the Management of *H. pylori* Infection recommends bismuth quadruple therapy as the first-line regimen for eradicating *H. pylori* infection.[20] However, traditional antibiotic therapy faces many challenges in clinical application. On the one hand, antimicrobial resistance is increasingly severe. On the other hand, the extensive use of broad-spectrum antibiotics inevitably disrupts the balance of the gut microbiota, which may lead to long-term adverse metabolic and immune consequences.[21,22] Facing this clinical dilemma, it is urgent to break out of the "antibiotic-dominated" mindset and construct a systematic intervention strategy that takes into account pathogen clearance, microecological protection, and host immune remodeling.[23] In recent years, intelligent biomaterials, with their responsive advantages to pH, enzymes, light, magnetism, etc., have been able to precisely eliminate *H. pylori* in the stomach while synchronously repairing the mucosa and balancing the microbiota, providing the possibility for closed-loop management of "treatment-repair-homeostasis maintenance".[24] This strategy can not only effectively overcome the problem of antibiotic resistance but also avoid unnecessary interference with the gut microbiota.[25]

In recent years, the rapid development of nanomedicine has provided revolutionary tools for the precise intervention of *H. pylori* infection.[26,28] Specifically, the application of nanomaterials in the treatment of *H. pylori* infection is mainly reflected in the following three aspects: (1) directly enhancing the killing efficiency of drug-resistant bacteria through targeted delivery, sustained-release or controlled release, or physical penetration; (2) modulating the functions of immune cells to kill pathogens or eliminate bacterial toxins, thereby reshaping the inflammatory microenvironment of the stomach; (3) using mucosal repair factors or prebiotics/probiotics to simultaneously promote gastric tissue regeneration and the balance of the gut microbiota.[27–29] Building on the "Remove-Remodel-Repair" (3R) multidimensional synergistic mechanism, this article introduces a novel nanomaterial-mediated comprehensive therapeutic paradigm. This approach involves three sequential steps: initially, the efficient removal of pathogens (Remove), followed by the remodeling of the infected microenvironment (Remodel), and ultimately, the repair of damaged organs (Repair). The objective is to systematically manage *H. pylori* infections. Figure 1 illustrates the 3R strategy framework. Furthermore, we aim to integrate innovations across three dimensions, nanomaterials, immunology, and microecology, to propose and explore a potential new individualized non-antibiotic pathway for combating *H. pylori*.[30]

Remove *H. pylori*

Nanomaterials have demonstrated great potential in the precise elimination of *H. pylori*. By ingeniously combining material properties with the physiological characteristics of the pathogen, nanomaterials can achieve efficient targeted delivery and antibacterial effects.[31] pH-responsive materials take advantage of the unique pH characteristics of the gastric environment. For example, protonated polymers such as chitosan and tannic acid can release antimicrobial substances under acidic gastric conditions. This not only eliminates *H. pylori* but also protects the intestinal microbiota from disruption.[32] Enzyme-responsive materials leverage overexpressed enzymes at the site of infection, such as matrix metalloproteinases (MMPs), to achieve precise targeted release of drugs. Nanogels composed of ascorbyl palmitate (AP) can target inflamed sites and release drugs, thereby effectively combating *H. pylori*.[33] Nanomaterial-based phototherapy has also shown excellent performance. Photothermal agents such as gold nanostars (GNSs) can convert light energy into heat energy to disrupt the bacterial living environment. For example, the GNS@Ab constructed by Zhi *et al*.[34] could effectively kill drug-resistant *H. pylori* with the assistance of a near-infrared laser while maintaining the balance of the intestinal microbiota. Photosensitizers such as chlorin e6 (hereinafter referred to as Ce6) generate reactive oxygen species (ROS) under irradiation with specific laser wavelengths, causing irreversible damage to biomolecules through oxidation. The ZnO2-Ce6@lipo developed by Wong *et al*.[35] efficiently eradicated *H. pylori*. Sonodynamic therapy leverages the cavitation effect of ultrasound and the ROS generated by sonosensitizers to kill bacteria. For example, Fe-HMME@DHA@MPN can release Fe-HMME and HMME in

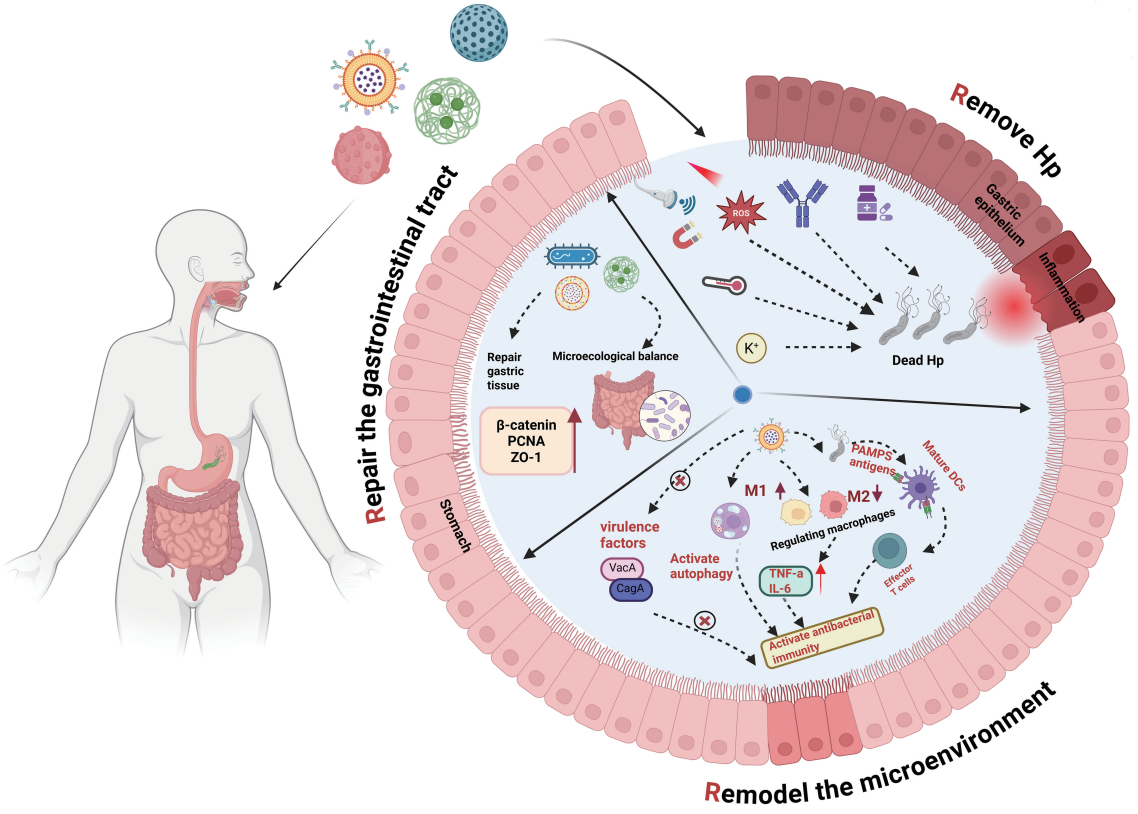

Fig. 1. Schematic diagram of 3R (Remove, Remodel, Repair) integrated therapy for *H. pylori* infection based on nanomaterials. Created with BioRender.com. *H. pylori*, *Helicobacter pylori*; IL-6, interleukin-6; PCNA, proliferating cell nuclear antigen; TNF-α, tumor necrosis factor-alpha; ZO-1, zonula occludens-1.

an acidic environment, generating singlet oxygen under ultrasound irradiation to achieve sonodynamic therapy.[36] Magnetic materials can generate local high temperatures under an alternating magnetic field, thereby disrupting the living environment of *H. pylori*. For example, the FeCo@G nanoheater can upregulate the expression of HSP70 under the action of an alternating magnetic field, thereby enhancing the body's resistance to *H. pylori* infection.[37] In addition, the development of multistimuli-responsive materials and multifunctional nanoplatforms has further enhanced therapeutic efficacy. For example, Pd(H)@ZIF-8@AP, which combines photosensitizers and pH-responsive materials, can achieve multiple precise strikes, thereby effectively eliminating *H. pylori* (Table 1).[33–36,38–44] The MSPLNP-Au-CB nanomaterial integrates diagnostic, therapeutic, and imaging functions, enabling precise localization and efficient eradication of *H. pylori*.[39] In summary, nanomaterials have shown significant advantages in precise targeting and efficient antibacterial activity against *H. pylori*. However, to further improve therapeutic efficacy and safety and promote their clinical application, the performance of nanomaterials still needs to be optimized.

Response mechanisms of nanomaterials for H. pylori clearance

The eradication of *H. pylori* using nanomaterials is achieved through sophisticated responses to either endogenous stimuli within the gastric microenvironment or precisely applied exogenous stimuli. These responsive mechanisms enable spatiotemporally controlled drug release, physical disruption of bacteria, or generation of bactericidal agents, thereby enhancing precision and reducing off-target effects. As summarized in Table 1, these strategies can be broadly categorized into endogenous stimulation (e.g., pH, enzymes, ROS) and exogenous/multimodal stimulation (e.g., light, ultrasound, magnetic field).

Nontargeted strategies for removal

Non-targeted (ligand-free) nano-strategies rely on bulk or environment-triggered actions to eradicate *H. pylori*. Lipid nanoparticles (such as liposomes) achieve drug delivery by physically encapsulating antibiotics (e.g., amoxicillin) or natural antibacterial lipids (e.g., linolenic acid). The membrane structure of liposomes can fuse with bacterial cell membranes, disrupting the integrity of the *H. pylori* cell membrane and thereby killing bacteria. For example, the liposome-encapsulated linolenic acid system (LipoLLA) designed by Obonyo *et al*.[45] was able to kill 99.9% of *H. pylori* after incubation at a concentration of 67 μg/mL for 30 m while also disrupting the cell membranes of its dormant forms (coccoid forms), and no drug resistance was induced within 10 days. Inorganic nanoparticles (such as zinc oxide and silver nanoparticles) leverage their unique physicochemical properties to release metal ions (Zn^{2+}, Ag^{+}) or generate ROS in the gastric acid environment, thereby exerting antibacterial effects.[46] Metal ions can bind to lipopolysaccharides on the *H. pylori* cell membrane, disrupting the cell membrane structure. Additionally, metal ions can form stable coordination bonds with nitrogen, oxygen, or sulfur atoms within bacterial cells, thereby interfering with the normal physiological functions of bacteria. ROS induce oxidative stress and damage bacterial cell membranes and DNA, thus achieving a bactericidal

Table 1. Nanomaterials for *H. pylori* removal *via* multi-response mechanisms

Stimulus types	External stimuli	Response mechanism	Representative material	Main model	Major limitations
Endogenous stimulation	Gastric acid (pH)	Gastric acid decompresses ZIF-8 → releases Zn^{2+} and H_2 → destroys *H. pylori* membrane + inhibits urease.	ZAN@CS MND,[40] Pd(H)@ZIF-8[41]	BALB/c mice, *H. pylori* SS1 strain; C57BL/6 mice	Mouse level only; long-term toxicity not assessed
	Enzyme	Enzymatic cleavage → site-specific release	AP-nanogel[33]; AP@CS@Lip@HKUST-1[41]	Mouse gastric mucosa sections +*H. pylori*26695 biofilm; ATCC 43504 + C57BL/6 mice	*In vivo* quantification missing; inter-individual variability unknown
	ROS	"ROS cleavage of borate ester bond → selective gel degradation of inflammatory site → targeted release of probiotics and repair factors"	L.reuteri@HTP[42]	C57BL/6 mice	Single model, insufficient conversion data, and lack of clinical validation
Exogenous stimuli/Multimodal response	NIR light	Photothermal + ROS oxidation	GNS@Ab,[34] ZnO2-Ce6@lipo[35]	*In vitro* drug-resistant *H. pylori* clinical isolate + mouse *H. pylori* SS1	Penetration ≤ 5 mm; light dose needs optimization
	Ultrasound	Cavitation + singlet oxygen	Ver-PLGA@Lec[43]	Mouse *H. pylori* SS1 biofilm infection model	Safe acoustic dose window not yet defined
	Alternating magnetic field kHz	Magnetothermal → local > 50 °C	FeCo@G[44]	*In vitro H. pylori* 26695 + mouse *H. pylori* SS1 model	Thermal injury threshold unclear
	Dual pH + light	Acid targeting + photo-ROS finish	Pd(H)@ZIF-8@AP[38]	Mouse *H. pylori* SS1 infection model	Scale-up stability not reported
	pH+Ultrasound	Gastric acid triggering → component release → Fenton reaction + sonodynamic synergy → self-enhanced generation of reactive oxygen species → precise sterilization	Fe-HMME@DHA@MPN[36]	C57BL/6 mice + *in vivo* cell experiments	Clinical translation is limited by the dependence of ultrasound equipment and the unknown long-term safety
	Tri-modal	Theranostic integration→ fluorescence	MSPLNP-Au-CB[39]	*In vitro H. pylori* 26695 + mouse *H. pylori* SS1 model	Batch-to-batch reproducibility to be verified

All models exclusively used *H. pylori* standard strains (SS1 or 26695) or clinical isolates; no surrogate bacteria were employed. NIR, near-infrared; ROS, reactive oxygen species.

effect. For example, the pH-sensitive GNSs (GNS@Ab) designed by Zhi *et al*.[34] could effectively kill *H. pylori* in the stomach, including drug-resistant strains, through a photothermal conversion process that generates heat with the assistance of a near-infrared laser. In addition, after complete eradication of *H. pylori* in vitro, most of the GNS@Abs can be excreted from the body without disrupting the balance of the gut microbiota (Table 1).[34] These non-targeted strategies involving nanomaterials also have significant advantages in reducing the emergence of drug-resistant strains, providing new ideas for future clinical treatments.

Targeted strategies for removal

Unlike bulk-action platforms, ligand-directed nanocarriers home to *H. pylori* surface epitopes or essential enzymes. For example, the pectin-coated liposomes prepared by Gottesmann *et al*.[47] significantly enhanced the bactericidal effect by utilizing the specific interaction between pectin and the surface structure of *H. pylori*. In addition, pH-responsive nanomaterials can release drugs in the acidic environment of the stomach, increasing the concentration of drugs at the site of infection, thereby enhancing the antibacterial effect and reducing the impact on the gut microbiota.[47] Jing *et al*.[48] were the first to use the unique urea channel UreI on the *H. pylori* membrane to design urea-chitosan/TPP nanoparticles. The carrier particles are approximately 230 nm in size and have pH-sensitive characteristics: almost no drug release in gastric acid (pH 1.2) but rapid drug release in the gastric mucosal layer (pH 6.0). This characteristic increased the local concentration of amoxicillin at the lesion by 14 times, and the antibacterial rate was close to 90% within 6 h. Competitive experiments revealed that the addition of urea significantly weakened the drug effect, confirming that the targeting molecule was indeed UreI and providing direct evidence for "drug-channel" lock-and-key delivery.[48] In a systematic review, Almarmouri *et al*.[49] pointed out that urease is a key enzyme for acid resistance in the stomach of *H. pylori*, which is not expressed by the host and the main symbiotic bacteria, so it has natural selectivity. The micromolar inhibitors (quercetin, thiocarbamide derivatives, metal complexes, etc.) collected by the authors can reduce the gastric bacterial load by 2–3 log in animal models without significantly changing the Shannon index of intestinal flora, thereby achieving efficient bactericidal activity and maintaining microecological homeostasis.[49] Targeted nanomaterials have significantly improved the treatment of *H. pylori* infection by precisely delivering drugs and inhibiting urease activity while reducing the occurrence of drug resistance and the impact on normal tissues, providing a new direction for clinical application.

Progressive selection framework for precise removal of nanomaterials

Although Table 1 systematically summarizes various responsive nanomaterials used for *H. pylori* clearance, from a clinical translation perspective, these strategies are not in the same mature echelon. Based on the four dimensions of oral feasibility, gastric retention efficacy, difficulty in large-scale production, and regulatory acceptability, we can divide the existing nanomaterials into three progressive levels: Tier 1: pH-responsive monofunctional nanomaterials. Representative systems include ZAN@CS MNDs and Pd(H)@ZIF-8.[40,41] Their primary advantage lies in exclusive reliance on intrinsic gastric acidity for triggering, requiring no external devices. Preclinical studies have demonstrated stomach-specific drug release and minimal perturbation of the gut microbiota. The principal bottleneck is no longer efficacy, but rather the absence of comprehensive long-term toxicity profiles.[40,41] Tier 2: Photothermal/sonodynamic/magnetothermal physical sterilization nanomaterials. Representative systems include GNS@Ab, Ver PLGA@Lec, and FeCo@G.[34,43,44] Their irreplaceable value resides in antibiotic-independent physical bactericidal mechanisms. Nevertheless, clinical translation is constrained by the fact that ultrasound/magnetic field devices have not yet been integrated into routine clinical pathways for *H. pylori* eradication.[34,43,44] Tier 3: Multimodal response nanomaterials. Representative systems include Fe-HMME@DHA@MPN. Despite their conceptual sophistication, definitive evidence of clinical endpoint benefits is lacking. At the current stage, such platforms should be positioned primarily as proof-of-concept models for mechanistic exploration.[36]

In summary, the trajectory of "orally administered single-stimulus responsive materials → physical sterilization-enhancing materials → multimodal theranostic platforms" constitutes a rational, stepwise translational roadmap for the field of nanomaterial-mediated *H. pylori* eradication.

Molecular targeting

Molecular targeting is a key strategy for the precise elimination of *H. pylori*. By precisely intervening in the key pathogenic factors or metabolic pathways of bacteria, molecular targeting clearance strategies provide new ideas for overcoming drug resistance and biofilm barriers. The virulence factors CagA, VacA, and T4SS are the core "weapons" of *H. pylori* pathogenesis.[50] *In vitro* studies have confirmed that small-molecule inhibitors can block the energy ATPase Cagα of the T4SS and inhibit the translocation of CagA, thereby reducing the release of IL-8 from epithelial cells and the inflammatory response.[50] Enzyme targeting: Urease is the key enzyme by which *H. pylori* resists gastric acid and is considered the "lifeline". After being covalently modified by silver nanoparticles, the half-maximal inhibitory concentration (IC_{50}) of the natural product quercetin is reduced from 42 μM to 1.8 μM, with no cross-inhibition of mammalian urease.[51] Immune microenvironment targeting: During *H. pylori* infection, cytokines such as IL-17, which are secreted by Th17 cells, play important roles in the immune response. However, the VacA toxin of *H. pylori* can induce myeloid cells in the gastric mucosa to differentiate into $CD25^+Foxp3^+$ regulatory T cells (Tregs), which inhibit protective inflammatory responses by releasing IL-10. Experiments have shown that mice depleted of $CD25^+$ Treg cells produce higher levels of IFN-γ in response to *H. pylori* stimulation, with massive infiltration of macrophages and T cells in the gastric mucosa, which aids in bacterial clearance.[52] Bacterial cell wall targeting: The hydroxyl groups in phenylboronic acid can reversibly covalently bind to peptidoglycan in the bacterial cell wall, thereby enhancing the ability of the material to recognize and target bacteria. For example, studies have shown that gold nanoparticles (AuNPs) modified with phenylboronic acid can specifically bind to peptidoglycan on the surface of gram-positive bacteria through this mechanism, disrupting the cell wall structure and leading to bacterial death.[53] Molecular targeting strategies demonstrate significant therapeutic potential by precisely intervening in key pathogenic factors, metabolic pathways, and the immune microenvironment of *H. pylori*. These strategies not only effectively inhibit bacterial virulence and survival but also enhance the host immune response and maintain microbiota balance. Multidimensional interventions, including the targeting of virulence factors, enzyme systems, immune microenvironments, and bacterial cell walls, provide new ideas for overcoming drug resistance and biofilm barriers and offer theoretical and technical support for the precise prevention and treatment of *H. pylori* infections.

Physical targeting

Physical targeting strategies activate the functions of nanomaterials through external physical stimuli (such as light, ultrasound, and magnetic fields) to achieve spatiotemporally controllable and precise elimination of *H. pylori* infections. In recent years, photoresponsive nanomaterials have shown great potential in antibacterial therapy through physical targeting mechanisms. Ti *et al*.[54] developed a CDs@ZIF-8 composite nanofiber membrane that triggers the production of ROS upon visible light exposure, disrupting bacterial membrane structures to achieve photodynamic sterilization. Gao *et al*.[55] constructed a black phosphorus-based nanoplatform (BP@EPL-LA) that generates ROS and nitric oxide under near-infrared light irradiation. It achieves pH-responsive targeting through charge reversal, enhancing electrostatic adsorption with bacterial membranes in the acidic infection microenvironment. This significantly improves sterilization efficiency and effectively clears drug-resistant bacterial biofilms *in vivo*, promoting tissue repair.[55] Ultrasound-responsive materials (such as Ver-PLGA@Lecithin) generate a large amount of ROS through sonodynamic therapy, disrupting biofilm structures and killing *H. pylori*. Liu *et al*.[43] reported that Ver-PLGA@Lecithin can effectively produce ROS under ultrasound triggering, clearing *H. pylori* from biofilms while having minimal impact on the gut microbiota. The diversity of the gut microbiota is maintained after treatment.[43] Magnetic materials (such as FeCo@G) generate heat through the magnetothermal effect under an alternating magnetic field, upregulating HSP70 in host cells and thereby inhibiting *H. pylori* colonization. Xia *et al*. demonstrated that FeCo@G has good stability in the acidic environment of the stomach. It destroys *H. pylori* cell membranes through heat generation and activates host defense mechanisms to achieve efficient sterilization. Within 24 h after treatment, 95% of the material can be excreted from the gastrointestinal tract, indicating high safety.[44] Moreover, the MC@PHDA hydrogel achieves physical targeting clearance of hepatocellular carcinoma by activating the photothermal effect of MoS_2 and the photodynamic action of Chlorella through spatiotemporally precise irradiation with 660 nm and 808 nm lasers, generating local hyperthermia and ROS. This light-controlled technique not only efficiently eradicates cancer cells but also protects surrounding normal tissues, highlighting the unique advantages of physical targeting in tumor therapy.[56] Physical targeting technology activates nanomaterials through external physical stimuli (such as light, ultrasound, and magnetic fields) to achieve precise elimination of *H. pylori* infections. This technology not only significantly improves the efficiency of *H. pylori* clearance but also reduces interference with the gut microbiota, demonstrating significant advantages and broad application prospects.

Environmental targeting

Environmental targeting strategies utilize the acidic microenvironment of the *H. pylori* colonization area to design pH-responsive nanodrugs, achieving precise drug release and activation at the site of infection.[57] Zhang *et al*.[58] devised a more straightforward "endogenous enzyme-mimicking" strategy. They synthesized fullerinol nanoparticles that undergo a pinacol rearrangement of vicinal hydroxyl groups into carbonyl moieties under the low-pH conditions of the stomach. This structural conversion leads to a marked increase in the surface C=O/C–O ratio, which effectively "switches on" the peroxidase-like activity of the fullerinol nanoparticles. Consequently, these activated nanoparticles can catalyze the generation of antibacterial species precisely at the site of *Helicobacter pylori* infection, enabling targeted bacterial eradication and biofilm disruption without inducing antibiotic resistance.[58] This mechanism of "environmental response–structural transformation–local amplification of sterilization" provides new ideas for the precise treatment of *H. pylori* infections.[59] Wang *et al*.[60] elaborated on the design and fabrication of mono- or multifactor-responsive nanoscale antibacterial systems by exploiting the unique microenvironmental features of the infection site, such as low pH, enzymes, toxins, and temperature. These intelligent systems can achieve precise drug release, surface charge reversal, and deep penetration at the site of infection, significantly improving the clearance efficiency of drug-resistant bacteria and their biofilms while reducing toxicity to normal tissues.[60] Moreover, the low-pH environment of the stomach provides a natural opportunity for the activation of pH-responsive materials. For example, ZnO_2 nanoparticles were shown to fully release Zn^{2+} ions in a gastric acid environment. These metal ions precisely target the cell membrane of *H. pylori*, disrupting its integrity and thereby disturbing bacterial metabolic activities, leading to bacterial death.[35] Similarly, the Bi-MOF@CS-Se nanodrug, with its unique metal–organic framework structure, rapidly dissociates and releases Bi^{3+} ions under acidic conditions. The Bi^{3+} ions effectively inhibit the key energy metabolism processes of *H. pylori* and enhance the permeability of the bacterial cell membrane, demonstrating excellent antibacterial efficacy. In the neutral intestinal environment, these materials exhibit good stability, avoiding disturbance to the gut microbiota and thus achieving protection of the intestinal microecology.[59] The inflamed gastric region is typically characterized by the overexpression of MMPs. Enzyme-responsive materials ingeniously exploit this feature to achieve precise drug release. For example, the AP@CS@Lip@HKUST-1 nanoplatform, with its outer AP hydrogel layer degrading under the action of MMPs, releases the loaded antibacterial components in an orderly manner. This on-demand release mechanism not only enhances the precision of antibacterial therapy but also significantly reduces the potential toxicity of drugs to normal tissues, achieving efficient and safe pathogen clearance. Moreover, the phosphatidic acid (PA) component in this material can activate the autophagy pathway in gastric epithelial cells, aiding in the clearance of intracellular bacteria and further enhancing the thoroughness of the antibacterial effect.[41] This intelligent responsive property enables the material to clear gastric pathogens while maintaining the stability of the intestinal microbiota, providing strong support for the balance of gastrointestinal microecology.

Remodel the microenvironment

Nanocarriers can efficiently adsorb virulence factors such as VacA excreted by *H. pylori* through a "capture-clear" strategy, thereby reshaping the gastric mucosal immune microenvironment. In the treatment of *H. pylori* infection, nanomaterials play an important role by reshaping the inflammatory microenvironment in the stomach. For example, the ZAN@CS MND nanodrug protonates and becomes positively charged in the acidic gastric environment, where it targets *H. pylori*, disrupts its cell membrane, and dismantles the biofilm structure. Moreover, this nanomaterial can modulate the immune response, increasing the number of $CD4^+$ T cells in the stomach and reducing the expression of proinflammatory factors. This strategy not only eliminates pathogens but also reshapes the microenvironment by regulating immune cell functions, providing new ideas for the treatment of *H. pylori* infection.[40]

Nanocarriers adsorb virulence factors

Nanocarriers can specifically adsorb the key virulence factor VacA of *H. pylori*, thereby significantly improving the host immune

microenvironment. VacA is one of the main virulence factors of *H. pylori* and can induce vacuolation in host cells and disrupt the integrity of cell membranes, thereby inhibiting the function of immune cells and weakening the host immune response.[61] By carefully designing nanocarriers with the ability to specifically adsorb VacA, it is possible to effectively reduce the damage caused by VacA to host cells and avoid the inhibitory effects of VacA on immune cells, thereby enhancing the host immune response. For example, Ver-PLGA@Lecithin nanoparticles have an adsorption rate of over 90% for VacA in the pH range of 2–7. They can block the binding of VacA to integrin β1, significantly downregulating the activation of the NLRP3/IL-1β axis.[43] Similarly, *H. pylori* outer membrane vesicles are rich in VacA, which can be synchronously adsorbed and delivered by chitosan-modified mesoporous silica nanoparticles along with antibiotics, thereby reducing the IL-8 storm induced by outer membrane vesicles.[62] In addition, polydopamine (PDA)-coated cerium oxide nanorods (PDA-CeO_2) can clear free VacA through electrostatic interactions, restore the M2 polarization of macrophages, and increase IL-10 levels.[63] These studies collectively demonstrate that nanoplatforms lay the foundation for immune homeostasis in the subsequent "remodeling-repair" process by "clearing" virulence factors.

Activating the innate immune response

The use of nanomaterials has emerged as a novel strategy for treating *H. pylori* infections by reshaping the immune microenvironment through the activation of the innate immune response. In recent years, nanomaterials have shown great potential in activating innate immunity. Research indicates that copper-based metal-organic frameworks (MOFs) nanomaterials can induce immunogenic cell death through photothermal therapy, releasing damage-associated molecular patterns and tumor-associated antigens. This process activates the maturation of dendritic cells (DCs), which in turn stimulates T cell-mediated immune responses, effectively suppressing tumor recurrence.[64] Nanomaterials can mimic pathogen-associated molecular patterns to activate pattern recognition receptors, such as Toll-like receptors (TLRs), on the surface of host cells.[65] This activation mechanism can induce immune cells to secrete proinflammatory cytokines (such as IL-6 and IL-1β) and enhance the phagocytic capacity of immune cells such as macrophages, thereby improving the clearance efficiency of *H. pylori*.[66] Specifically, certain nanomaterials bind to TLR4, thereby activating downstream signaling pathways, promoting inflammatory responses, and effectively inhibiting the growth of *H. pylori*. This process not only enhances the innate immune response but also provides the potential to reshape the gastric immune microenvironment.[67] In terms of reshaping the immune microenvironment, nanomaterials can serve as an immunomodulatory platform by regulating the proportion of immune cell subsets (e.g., enhancing type 1 helper T-cell responses and suppressing regulatory T-cell activity), thereby breaking the immune tolerance induced by *H. pylori*. For example, the nanomaterials mentioned by Liu *et al*.[68] can induce immunogenic cell death, releasing damage-associated molecular patterns to activate DCs and T cells, thereby enhancing antitumor immune responses. Similarly, Nowak *et al*.[69] demonstrated the role of MOF nanoparticles in delivering antisense oligonucleotides, which target PD-L1 to increase immune cell activity and inhibit tumor growth. These studies indicate that nanomaterials can not only clear pathogens by activating the innate immune response but also modulate the immune microenvironment to enhance immune cell function. In addition, nanomaterials can be used in combination with other therapies (such as antibiotics and vaccines) to increase therapeutic efficacy and reduce the risk of drug resistance. This potential is further highlighted in the treatment of *H. pylori*. For example, nanomaterials can be loaded with anti-*H. pylori* drugs or immune modulators to achieve targeted delivery, thereby increasing the local drug concentration and reducing systemic adverse effects. Moreover, by precisely controlling the composition and structure of nanomaterials, the immune microenvironment can be dynamically regulated to promote gastric mucosal repair.[70] In summary, the 3R strategy based on nanomaterials (removing pathogens, remodeling the immune microenvironment, and repairing tissue) offers a novel perspective for the treatment of *H. pylori* infection. By activating the innate immune response to eliminate pathogens and remodeling the immune microenvironment to promote tissue repair, this integrated therapeutic paradigm holds promise to overcome the limitations of traditional therapies and achieve breakthroughs in the prevention and treatment of *H. pylori*-related diseases (such as gastritis, gastric ulcers, and gastric cancer). Future research needs to further optimize the biocompatibility and targeting of nanomaterials and explore their safety and efficacy in clinical applications.

Promotion of adaptive immune responses

In recent years, the ability of nanovaccines to enhance antigen presentation and modulate the immune microenvironment has provided a solid theoretical and experimental basis for their "remodeling" role in the treatment of *H. pylori* infection.[71] Studies have demonstrated that the self-adjuvant lipopeptide vaccine *H. pylori*10 modified with Pam2Cys (based on the CagA antigen epitope) can effectively activate DCs and multiple pattern recognition receptors, such as TLR2/NLR/RLR, when administered *via* intranasal mucosal immunization in mice. This activation induces a robust Th1 and Th17 T-cell response, significantly expands memory $CD4^+$ T cells, and elicits a specific secretory IgA antibody response in the gastric mucosa, gut, and saliva. The use of *H. pylori*10 alone can reduce *H. pylori* colonization in the stomach by approximately 10-fold, and its combination with *H. pylori*4 shows even better efficacy, indicating that this vaccine strategy holds great promise for inducing protective immunity and eliminating pathogens.[72] A large-scale retrospective analysis revealed that *H. pylori* infection acts as a "double-edged sword" in gastric cancer immunotherapy. Among patients with Epstein–Barr virus-negative, microsatellite-stable gastric cancer, those who were positive for *H. pylori* and who received anti-PD-1/PD-L1 therapy exhibited significantly prolonged immune-related progression-free survival. The tumor microenvironment in these patients is characterized as an "immunologically hot tumor," with increased PD-L1 expression and infiltration of nonexhausted $CD8^+$ T cells, indicating that *H. pylori* infection can enhance immune responses and improve therapeutic outcomes. Conversely, in mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) colorectal cancer and esophageal squamous cell carcinoma, *H. pylori* positivity was associated with shorter immune-related progression-free survival, possibly due to its interference with immune recognition or regulatory mechanisms. The status of *H. pylori* infection can serve as an important predictive factor for the immunotherapy response. Future studies should consider cancer type and molecular characteristics to individually assess whether the eradication of *H. pylori* is necessary to optimize immunotherapy strategies.[73] Using IFN-γ gene knockout mice and their derived gastric epithelial cell line GSM06, it was found that IFN-γ significantly enhances the expression of MIP-2 (the murine homolog of IL-8) and inducible nitric oxide synthase mRNA during *H. pylori* infection, indicating

its role in mediating Th1-type immune responses and promoting gastric mucosal inflammation. Pretreatment with IFN-γ increases COX-2 expression in infected cells but does not significantly alter COX-2 levels *in vivo*. One study demonstrated that IFN-γ is an important regulator of *H. pylori*-induced gastric inflammatory responses.[74]

Regulating the function of immune cells

In recent years, with the widespread application of nanotechnology in the biomedical field, its potential in immune regulation and inflammation treatment has gradually attracted attention. In the chronic infection microenvironment of *H. pylori*, the maturation of DCs is impeded, macrophages are polarized toward the M2 phenotype, and Tregs are overexpanded. These factors collectively constitute the pathological basis of immune evasion and persistent inflammation.[75,76] In a colitis model, PSB@NP-FA nanoparticles remodeled the immune microenvironment by regulating macrophage polarization and T-cell responses. Although colitis and *H. pylori* gastritis differ in inflammatory context, the core strategy, using stimuli-responsive nanomaterials for localized delivery of immunomodulators, remains conceptually relevant. For *H. pylori* infection, analogous platforms could be designed to target the gastric mucosa and counteract *H. pylori*-induced immune suppression.[77] The research team of Liao Lan and Wei Junchao synthesized chiral AuNPs *via* the GSH reduction method. They demonstrated that L-AuNPs selectively activate macrophage autophagy, drive M2 anti-inflammatory polarization, and remodel the pro-osteogenic immune microenvironment, significantly enhancing bone regeneration efficiency. This study not only highlights the potential of nanomaterials to precisely regulate immune cell functions through stereoselectivity but also provides new insights for immune regulation in the field of orthopedics.[78] In addition, macrophage membrane-coated nanoparticles leverage "homotypic homing" to enrich the infection site and precisely enter macrophages *via* the mannose pathway. This triggers a ROS storm and a cascade of pro-inflammatory cytokines, driving macrophages to polarize toward the M1 phenotype, thereby effectively eliminating intracellular bacteria. These nanoparticles subsequently present antigens to activate T cells, bridging innate and adaptive immunity. This process reshapes the local immune microenvironment, enabling self-clearance of the infection and preventing recurrence. This approach offers a new paradigm of "cellular immune reprogramming" for the treatment of deep-seated infections.[79] In summary, the nanoplatform provides a robust cellular basis for the integrated treatment of *H. pylori* infection in the "remodeling" phase of the 3R paradigm through multinode coordinated regulation of "DC–macrophage–Treg cells". These studies not only reveal the important role of nanomaterials in remodeling the immune microenvironment but also offer new strategies and theoretical foundations for the treatment of *H. pylori* infection and related diseases.

Inhibiting immune evasion mechanisms

In cancer treatment, inhibiting autophagy can enhance therapeutic efficacy, but it may upregulate PD-L1, leading to tumor immune evasion.[80] However, the *H. pylori* virulence factor CagA degrades p53 *via* multiple pathways, thereby relieving its transcriptional activation of miR-34a. This, in turn, inhibits the targeted degradation of PD-L1 mRNA by miR-34a, leading to significant upregulation of PD-L1 in gastric cancer cell-derived exosomes.[81,82] These exosomes, enriched with PD-L1, circulate throughout the body and bind to PD-1 on the surface of $CD8^+$ T cells, blocking their proliferation and the secretion of IFN-γ, TNF-α, and IL-2. This weakens the antitumor immune response and creates a persistent immunosuppressive microenvironment, facilitating immune evasion and the progression of *H. pylori*-related gastric cancer.[83] For *S. aureus* infection, the Hb Naf@RBCM nanoparticles disrupted bacterial immune evasion by simultaneously inhibiting antioxidant pigment synthesis and eliminating the bacterial H_2S shield. Although *H. pylori* employs distinct evasion mechanisms (e.g., VacA-mediated Treg induction), this multimodal strategy illustrates how nanocarriers can concurrently target multiple bacterial survival pathways—a design principle relevant for developing comprehensive anti-*H. pylori* platforms.[84] In an orthopedic implant infection model, LAOIR nanoparticles accurately remove biofilms and induce local transient hypoxia by photoexcited singlet oxygen. The hypoxic microenvironment can inhibit lipoteichoic acid-mediated immune tolerance and prolong the survival of neutrophils. Oxygen recovery triggers "immune conversion", which enhances NETosis, phagocytosis, and the expression of inflammatory factors (IL-6, IL-1β) and chemotactic receptors (CCR2, CXCR2), thereby promoting the recruitment of immune cells. This oxygen-regulated cycle blocks bacterial immune escape and achieves bacteria–immune synergy. Although the strategy is derived from implantation-associated infection, it reveals the core mechanism of spatiotemporal regulation of nanomaterials to dynamically reshape the infection microenvironment and reprogram the immune response, which provides an important conceptual framework for the development of innovative therapies against *H. pylori* gastric mucosal biofilms. However, materials and strategies should be adapted to the acidic gastric environment and the biological characteristics of *H. pylori*.[85]

Activating autophagy to clear intracellular bacteria

Intracellular bacteria are among the important factors contributing to *H. pylori* resistance.[86] In traditional antibiotic therapy, the ability of *H. pylori* to invade gastric mucosal epithelial cells and form a protective niche within the cells allows it to evade the bactericidal effects of antibiotics, making intracellular bacteria challenging to treat.[87] In recent years, novel therapeutic strategies based on nanomaterials have offered potential solutions to this problem. For example, the AP@CS@Lip@HKUST-1 platform, with its core component PA, can induce lysosomal acidification and activate the host cell autophagy pathway, thereby promoting the clearance of intracellular *H. pylori*. Specifically, PA promotes calcium ion efflux, which activates the conversion of the autophagy-related protein LC3B, thereby enhancing the formation and degradation capacity of autophagosomes and achieving precise clearance of intracellular bacteria.[41] Similarly, when activated by ultrasound, the ICG@FCS nanoplatform generates singlet oxygen ($^1O_2$), which not only disrupts the cell wall and membrane structure of *H. pylori* but also induces autophagy, thereby increasing the host cell clearance efficiency of intracellular bacteria. Experiments have shown that after treatment with ICG@FCSs combined with ultrasound, the expression level of the 16S rDNA of *H. pylori* significantly decreases, and the expression of the autophagy marker protein LC3B-II increases, further confirming the ability of the platform to clear intracellular bacteria through autophagy activation.[88] The G3M@GaPP nanoflower dismantles intracellular bacterial immune evasion through a triple strategy: mannose-mediated active uptake by macrophages and induction of M2 polarization, which increases phagocytosis and creates an anti-inflammatory environment; a positively charged shell layer that promotes endosomal rupture and releases GaPP in acidic compartments, where Ga^{3+} competes with Fe^{2+} to chelate protoporphyrin IX, blocking bacterial iron me-

tabolism enzymes and triggering "Trojan horse"-style starvation death; and laser-activated GaPP that generates ROS for photodynamic therapy, which directly oxidizes bacterial membranes and nucleic acids. *In vitro* and *in vivo* models have shown that this platform is more efficient at clearing intracellular drug-resistant bacteria than free GaPP and antibiotics and is less likely to induce drug resistance. This provides a new nonantibiotic paradigm for combating persistent intracellular infections.[89] These studies demonstrate that nanomaterials can clear intracellular bacteria by activating autophagy mechanisms, providing new therapeutic ideas for overcoming *H. pylori* resistance and laying the foundation for the complete eradication of *H. pylori*.

Repair the gastrointestinal tract

In recent years, nanomaterials have shown unique advantages in the field of gastrointestinal protection, especially in achieving significant progress in the treatment of inflammatory bowel disease. The multifunctional nanocomposites represented by YMD@MPDA can synergistically alleviate intestinal inflammation and restore tissue function through five major mechanisms: antioxidant stress (MnO_2 nanozymes clear ROS), immune regulation (H_2S induces M2 polarization of macrophages), barrier repair (upregulation of tight junction proteins), targeted delivery (yeast cell wall-mediated enrichment at inflamed sites), and microbiota reshaping (inhibition of harmful bacteria and promotion of probiotic growth).[90] Nanomaterials are emerging as cutting-edge tools in gastrointestinal protection research. They function through multiple synergistic mechanisms: first, direct antibacterial activity, where metallic and nonmetallic nanoparticles can disrupt pathogenic bacterial membranes or induce oxidative stress; second, intelligent delivery systems, which protect drugs and probiotics for stable release in the gastrointestinal environment; third, responsive release, which precisely controls the release of active components on the basis of changes in pH, enzymes, or temperature; and fourth, the modulation of the gut microbiota, which promotes the colonization of beneficial bacteria, inhibits the proliferation of pathogenic bacteria, and enhances barrier function. Despite challenges related to stability and safety, nanotechnology shows broad prospects in gastrointestinal disease intervention, with the potential to realize personalized and precise therapeutic strategies in the future.[91] In terms of modulating the gut microbiota, nanomaterials can release short-chain fatty acids to provide nutrients for beneficial bacteria while inhibiting the growth of *H. pylori*, thereby restoring the balance of the gut microbiota and maintaining intestinal health. Yogurt-derived hybrid membrane vesicles exert gastrointestinal protective effects through a four-pronged mechanism of "antiadhesion, barrier repair, immune regulation, and microbiota reshaping." These vesicles fuse bacterial outer membrane vesicles with milk fat globule membrane vesicles, competitively blocking the adhesion of *H. pylori*, upregulating ZO-1 and lipid rafts to increase epithelial integrity, inhibiting IL-8 release, reducing neutrophil infiltration, and promoting macrophage clearance of apoptotic cells to rapidly repair mucosal damage. Moreover, hybrid membrane vesicles enrich beneficial bacteria such as *Blautia*, maintaining the homeostasis of the gastric microbiota.[92] In the field of skin care, CH. PYLORIS hydrogel combined with polyacrylamide and sodium alginate, loaded with Chlorella, provides mechanical support and a proliferative microenvironment, significantly promoting wound healing and tissue repair.[93] The bioactivity of NV released from NV@BSA-GEL hydrogel leads to effective ROS scavenging and good immune regulatory activity and promotes cell proliferation and migration of fibroblasts and vascular endothelial cells.[94] This nanotechnology strategy overcomes the bottleneck of antibiotic resistance and provides a new paradigm for the precise intervention of gastrointestinal infections and barrier dysfunction.

Mechanisms of local sterilization and targeted therapy

The targeting property of nanomaterials is reflected mainly in their ability to actively recognize *H. pylori*, which is due to the specific ligands or materials modified on their surface.[40] Nanomaterials achieve local sterilization and targeted therapy in the stomach through a dual mechanism of "carrier localization + active release": organic pH-sensitive liposomes and chitosan nanoparticles can control the release of antibiotics in the gastric acid microenvironment, protecting drugs and reducing off-target effects. Inorganic metal particles such as silver and gold can generate ROS through surface plasmon resonance or ion release, disrupting bacterial membranes and still possessing bactericidal power against drug-resistant strains. If further conjugated with antibodies or ligands, they can recognize *H. pylori* precisely, achieving high-concentration enrichment at the infection site and significantly reducing interference with the intestinal microbiota, providing a new strategy to overcome antibiotic resistance.[95]

The Pd(H)@ZIF-8@AP nanoplatform achieves local sterilization and targeted therapy through multiple mechanisms. First, the negatively charged AP hydrogel on the outer layer can be electrostatically adsorbed to the inflamed site and degraded by highly expressed MMPs, achieving targeted release at the site of inflammation. The released Pd(H)@ZIF-8 degrades in the acidic environment of the stomach to release Zn^{2+} and hydrogen gas. Zn^{2+} disrupts the membrane structure of *H. pylori* and inhibits its urease activity, enhancing the sterilization effect of gastric acid. Hydrogen gas, on the other hand, modulates the immune response and reduces oxidative damage. This material acts precisely at the site of infection, killing *H. pylori* while significantly reducing the impact on the gut microbiota, demonstrating good targeting ability and biocompatibility.[33] For example, a team led by Professor Jianjun Dai from China Pharmaceutical University developed the protonatable metal-based nanodrug ZnO-Ag-mercaptoacetamide@chitosan (ZAN@CS MNDs). Through the protonation charge reversal mechanism, it achieves active targeting and local sterilization in the gastric acid environment. The surface coating of chitosan endows it with the ability to penetrate the gastric mucosal barrier. Once in the acidic microenvironment, the ZAN core protonates and becomes positively charged, which electrostatically adsorbs to the negatively charged *H. pylori*, enhancing local retention. ZAN subsequently releases Zn^{2+}, Ag^{+}, and ROS, which disrupt bacterial membrane structures and degrade biofilm components (such as polysaccharides, proteins, and DNA), resulting in efficient sterilization. Moreover, the activity of the chitosan coating is reduced in the neutral environment of the intestine, avoiding interference with the gut microbiota and ensuring the targeting and safety of the treatment.[40] PtCo@G@H2A, as a novel cascade nanozyme, has demonstrated excellent local sterilization and targeted therapeutic capabilities in the treatment of *H. pylori* infections. This nanozyme achieves precise localization through a dual-targeting strategy: on the one hand, it utilizes the specific binding of heme to the HugZ protein on the surface of *H. pylori*; on the other hand, it relies on the charge reversal mechanism in the gastric acid environment, which makes its surface positively charged and allows it to electrostatically adsorb to the negatively charged bacterial membrane, enhancing retention and enrichment at the site of infection. Once in the acidic microenvironment, PtCo@G@H2A ac-

tivates peroxidase-like activity, catalytically generating ROS and further oxidizing L-arginine to release nitric oxide, which disrupts the bacterial membrane structure and induces bacterial death. This mechanism does not rely on antibiotics and thus holds promise for effectively circumventing antibiotic resistance. Additionally, the material can rapidly regain its negative charge in the neutral intestinal environment, avoiding interference with the gut microbiota, thereby demonstrating good targeting ability and biocompatibility and providing strong support for the development of new anti-infection strategies.[96] Owing to their precise local sterilization and targeted therapeutic mechanisms, nanomaterials represent a promising therapeutic advancement in the treatment of *H. pylori* infections. They can serve as intelligent carriers for antibacterial agents or functional molecules, responding to the acidic gastric microenvironment and achieving site-specific enrichment for efficient bacterial clearance. This approach significantly reduces reliance on traditional antibiotics and helps circumvent the risk of drug resistance. Moreover, nanosystems exhibit marked microbial selectivity. They can effectively clear *H. pylori* while largely sparing beneficial gut microbiota, which helps preserve ecological balance and reduce treatment-related adverse effects. This targeted strategy thus enhances both the safety and efficacy of treatment while also furnishing crucial technological underpinnings for future integrated therapies against *H. pylori*.

Mucus barrier enhancement mechanism

H. pylori infection initially disrupts the gastric mucus layer, leading to the reverse diffusion of hydrogen ions, inflammatory infiltration, and epithelial damage.[97] In recent years, nanomaterials have achieved reconstruction of mucus barrier function on the basis of the 3R concept through a cascade strategy of "penetration-adhesion-construction." The gastric mucus layer is approximately 500 μm thick, with pores smaller than 200 nm, and traditional drugs have a retention time of only 15 min. Nanomaterials achieve reconstruction of mucus barrier function through the following three stages: (1) Penetration: Shu *et al*.[98] developed a Cu-MOF@NF platform in which surface modification with fucoidan conferred a weak negative charge and hydrophilicity to the nanoparticles. This significantly reduced electrostatic interactions with the gastric mucus layer, thereby enabling efficient mucus penetration. (2) Adhesion: Cu-MOF@NF self-assembles into positively charged nanobrushes in gastric acid, competitively blocking the Lewis b-binding domain on *H. pylori* flagella and reducing adhesion by 82%. Moreover, its fucoidan component activates the EGFR-PI3K-AKT pathway, stimulating MUC5AC secretion and restoring mucus thickness to 91%. Concurrently, released Cu^{2+} penetrates the mucus, degrades biofilm polysaccharides, and disrupts the planktonic–biofilm cycle to prevent recurrence. Together, these actions reconstruct the mucosal barrier and establish an antibiotic-free strategy for effective *H. pylori* clearance.[98,99] (3) Reconstruction: Sonosensitive ICG@FCS generates ROS under ultrasound activation, efficiently disrupting the biofilm structure of *H. pylori* (extracellular polymeric substances) and eliminating its destructive effect on the epithelial barrier. The treatment significantly upregulated the expression of the tight junction proteins claudin-1 and occludin by 2.3-fold and 1.9-fold, respectively, restoring the integrity of intercellular connections. Moreover, the permeability of FITC-dextran was significantly reduced from 35.2% to 5.7%, indicating a substantial decrease in barrier permeability. This process, by clearing pathogens, inhibiting inflammation, and activating cellular repair pathways, reshapes the structure and function of the gastric mucosal barrier, achieving a transition from "destruction-repair" to "enhancement-homeostasis" and providing a new strategy for enhancing the mechanism of the mucus.[88]

Antioxidant and anti-inflammatory mechanisms

Nanomaterials exhibit both anti-inflammatory and antioxidant effects in combating *H. pylori* infection. Metallic nanoparticles (Ag, Au, and ZnO) achieve antibacterial effects by disrupting the bacterial membrane, releasing metal ions, and inducing the generation of ROS.[98] Moreover, nanocarriers such as chitosan and liposomes can deliver anti-inflammatory components, inhibit the activation of NF-κB, reduce the levels of proinflammatory factors such as IL-8 and TNF-α, block neutrophil infiltration, and alleviate inflammatory responses.[100] Nanozymes exhibit peroxidase-like activity in gastric acid, where hydrogen peroxide (H_2O_2) generates hydroxyl radicals (·OH). These radicals directly kill bacteria, degrade bacterial cell wall polysaccharides, and reduce the release of endotoxins, thereby achieving a triple synergistic effect of antibacterial, anti-inflammatory, and antioxidant actions.[101] In a gastric acid environment, the FPB-Co-Ch cascade nanozyme effectively alleviates oxidative stress by activating SOD/CAT/POD activity to convert bacteria-derived ROS into oxygen. The oxygen-rich environment inhibits the growth of microaerophilic *H. pylori*, reduces the release of its virulence factor VacA, blocks the NF-κB signaling pathway, downregulates the proinflammatory factors IL-1β and IL-6, and upregulates the anti-inflammatory factor TGF-β, thereby exerting a significant anti-inflammatory effect. Additionally, this nanozyme reduces apoptosis in GES-1 cells, restores the expression of the tight junction proteins ZO-1 and occludin, and promotes gastric mucosal repair. This "ROS clearance-inflammation inhibition-repair promotion" cascade reaction is confined to the stomach, avoids interference from the intestinal microbiota, and provides a novel, antibiotic-free, and microbiota-friendly therapeutic strategy for drug-resistant *H. pylori* infections.[102] *H. pylori* infection activates the NF-κB and AP-1 pathways, thereby inducing the expression of proinflammatory cytokines such as IL-8 and TNF-α. Simultaneously, this bacterium secretes antioxidant enzymes such as catalase and superoxide dismutase to eliminate ROS produced by the host, increasing its ability to resist host oxidative killing. This mechanism allows it to maintain long-term colonization and promote the progression of gastric diseases.[36] Additionally, *H. pylori* can induce the activation of the Nrf2 pathway, thereby enhancing the cellular antioxidant defense capacity and alleviating inflammatory damage, thus promoting its long-term colonization of the stomach as well as its participation in the occurrence and development of gastric diseases.[103]

Mechanisms of microbial community regulation

H. pylori infection can significantly disrupt the gastrointestinal microbiota, reduce microbial diversity, increase the abundance of potentially pathogenic bacteria such as Proteobacteria, and decrease the levels of beneficial bacteria such as Bifidobacterium and Lachnospiraceae, which are known to produce short-chain fatty acids.[104,105] Eradication therapy for *H. pylori* further exacerbates dysbiosis, which is characterized by a reduction in commensal bacteria and an expansion of opportunistic pathogens. These alterations in microbial communities may modulate the host's inflammatory response and metabolic homeostasis through the regulation of metabolic products such as short-chain fatty acids and lipopolysaccharide.[106] The latest systematic reviews further highlight that while eradication therapy effectively eliminates the pathogen, it significantly exacerbates microbial dysbiosis, characterized by decreased α diversity and altered β diversity, indicating the broad

impact of antibiotics on commensal bacteria. The concurrent use of probiotics has been shown to effectively mitigate treatment-related microbial disturbances, promote the recovery of beneficial bacteria, inhibit the overgrowth of pathogenic bacteria, improve gastrointestinal symptoms, and increase the eradication rate. These findings underscore the critical role of microbiota modulation in the management of *H. pylori* infection.[107] Nanomaterials precisely modulate *H. pylori* communities through multiple mechanisms: metal nanoparticles release silver/gold ions to trigger oxidative stress and damage bacterial membranes; liposomes encapsulating linoleic acid disrupt membrane structures; and pH-responsive carriers enable targeted drug release in the gastric acid environment, minimizing off-target effects. Additionally, nanocarriers protect probiotics against gastric acid, facilitating their colonization and competitive inhibition of pathogens, thereby restoring the gastric microbiota balance.[91] Studies have revealed that gastric-derived *Lactobacillus plantarum* XB7 exerts its effects through the secretion of bioactive factors. These factors inhibit the activation of the NF-κB and c-Jun signaling pathways induced by *H. pylori*, downregulate the expression of IL-8, and reduce neutrophil infiltration, thereby regulating interbacterial interactions. XB7 delays the colonization of *H. pylori* and decreases local and systemic levels of TNF-α and CINC-1, improving tissue pathology. These findings suggest that XB7 modulates microbial communities and immune homeostasis in a bidirectional manner by targeting the host inflammatory network and competing for ecological niches.[108]

Mechanisms of tissue repair and regeneration

Nanomaterials reconstruct tissue microstructures and restore physiological functions through multiscale and multimodal synergistic actions. As a new type of biomedical material, microalgae can significantly promote the regeneration of various tissues and organs.[109] Recent studies have revealed that the key mechanisms involve three main aspects: the regulation of cell fate, the remodeling of the immune microenvironment, and the precise activation of signaling pathways.[110–112] Inorganic nanomaterials leverage the electrical conductivity, antibacterial properties, and magnetic responsiveness of metals and carbon nanotubes to increase cell adhesion and protein adsorption, release bioactive ions to stimulate differentiation, and promote angiogenesis and collagen remodeling through photothermal stimulation. Magnetic targeting improves the homing of stem cells, thereby synergistically driving the repair and functional regeneration of soft tissues such as the skin, nerve, and myocardium.[113] Taking titanium dioxide nanotubes as an example, their nanoscale surface topography induces mesenchymal stem cells to form elongated pseudopodia that align in parallel. This activates mechanotransduction mediated by Yes-associated protein, which significantly upregulates the expression of alkaline phosphatase, osteocalcin, and osteopontin, thereby accelerating osseointegration.[114] Bioactive materials can target the delivery of drugs, control their release, and eliminate biofilms, thereby blocking the proinflammatory factors of *H. pylori* and reducing gastric mucosal damage. They also modulate immune responses and ROS levels, promoting epithelial repair and angiogenesis. This enables gastric tissue regeneration and microbiota reconstruction, providing a new strategy for combined anti-infection and tissue repair therapy.[115] The Fu-GaLip@KP nanocapsules restore lysosomal acidification and enhance autophagy to clear intracellular bacteria, block the CagA-NF-κB pathway, and inhibit ROS as well as inflammatory factors such as IL-8 and TNF-α, thereby reducing oxidative stress and mucosal damage. They also reshape the balance of the gut microbiota and promote the morphological repair of gastric epithelial cells, achieving multidimensional regeneration of gastric tissue and microbiota reconstruction following *H. pylori* infection.[116] Nanomaterials can also promote tissue regeneration by remodeling the immune microenvironment. For example, the graphene-chitosan-PDA (5QCS-1GO-PDA) multifunctional nanohybrid coating can release ROS in a sustained manner, suppress proinflammatory M1-type macrophages, induce M2-type polarization, and significantly upregulate IL-10, thereby creating an immune microenvironment conducive to tissue regeneration.[117] To address the clinically severe issue of methicillin-resistant *Staphylococcus aureus* infection in wounds, Xiao *et al*.[118] designed a PCL@Cu2+-PDA nanofiber dressing that leverages the low pH in the early stages of infection to trigger the release of Cu^{2+}, which rapidly eradicates *Staphylococcus aureus* and activates M1 macrophages for antibacterial activity. The resulting increase in ROS prompts PDA to scavenge free radicals, inducing M1-to-M2 polarization and sustainably upregulating IL-10. This remodeling of the immune microenvironment accelerates infection clearance, collagen deposition, and angiogenesis, achieving synergistic repair that inhibits bacterial growth, resolves inflammation, and regenerates tissue.

3R integration strategy

Nanomaterials demonstrate significant advantages in the treatment of gastrointestinal inflammation through the "3R integration" strategy—removal, remodeling, and repair.[119,120] For example, the protonated composite nanomedicine ZAN@CS can target and eradicate *H. pylori* in a gastric acid environment with a 100% sterilization rate. It achieves precise antibacterial activity by disrupting biofilm structures while avoiding interference with the gut microbiota.[40] Second, in the mechanisms of immune regulation and inflammation remodeling, nanomaterials achieve the reconstruction of immune homeostasis by modulating macrophage polarization and inhibiting inflammatory pathways such as the NF-κB pathway.[121–123] For example, the YMD@MPDA nanocomposite clears ROS and releases H_2S through MnO_2, inhibits the NOX4 and p38 MAPK pathways, and promotes the polarization of macrophages toward the M2 phenotype, thereby alleviating inflammation and remodeling the immune microenvironment.[90] Finally, in terms of gastric mucosal repair and intestinal microbiota protection mechanisms, nanomaterials can serve as carriers for growth factors or form protective gel layers to promote the proliferation and migration of epithelial cells, thereby accelerating mucosal repair. For example, nanomaterials can target the delivery of epidermal growth factor and other factors to promote the proliferation and migration of gastric mucosal epithelial cells, accelerating gastric mucosal repair. Moreover, their pH-responsive release characteristics can minimize interference with the intestinal microbiota, maintaining microbial homeostasis and achieving synergistic regulation of gastric mucosal protection and the microbiota.[124] In addition, certain nanodelivery systems can achieve targeted drug release in the stomach through pH-responsive or enzyme-triggered mechanisms, avoiding disruption of the intestinal microbiota and thereby protecting microbial homeostasis.[125]

Targeted elimination mechanism

In inflammatory or tumor microenvironments, excessive ROS, cellular debris, and proinflammatory factors pose significant barriers to remodeling and repair. Nanomaterials overcome these obstacles through a three-step targeted elimination mechanism: "recognition–capture–catalysis". First, recognition is the key to targeted

elimination by nanomaterials. Through surface modification with antibodies, peptides, or glycoproteins, nanocarriers can actively recognize and bind to receptors such as ICAM-1 and CD44 that are highly expressed in the lesion area, achieving active targeting.[126] ② Capture: Nanoparticles achieve targeted bacterial capture through surface functionalization. Cationic modifications utilize the negative charge of bacterial membranes to generate electrostatic adsorption. Ligands such as vancomycin and nucleic acid aptamers can specifically bind to bacterial wall glycoproteins or toxins. Antibody–antibiotic conjugates leverage the complementary structure of antigen–antibody interactions to achieve high-affinity capture. Additionally, coating nanoparticles with neutrophil or platelet membranes endows them with biomimetic properties, prolonging circulation time and enabling active recognition of inflammatory sites, thereby significantly increasing capture efficiency and targeting accuracy.[127] ③ Catalysis: HCeOx-D@PM utilizes a hollow mesoporous ceria core to scavenge ROS catalytically and suppress inflammation. The platelet membrane shell targets damaged alveoli, achieving efficient catalytic clearance in high-ROS-load areas.[128]

Immune regulation and inflammation remodeling mechanisms

Nanomaterials can precisely regulate innate and adaptive immunity in spatiotemporal dimensions through their size, morphology, surface chemistry, and responsiveness to the microenvironment, thereby achieving "inflammatory remodeling." The core mechanisms include ROS neutralization and immune cell phenotype conversion.[129] For example, nanomaterials such as polydopamine, melanin-like particles, and CeO_2 are rich in phenolic hydroxyl groups or oxygen vacancies, which can effectively scavenge excessive ROS, block the NF-κB/NLRP3 inflammasome signaling pathway, and promote the polarization of macrophages from the proinflammatory M1 phenotype to the reparative M2 phenotype. This helps alleviate chronic inflammation in conditions such as colitis and diabetic wounds.[117] The NLRP3 inflammasome is a multiprotein complex in the cytoplasm and an important component of the innate immune system. Carboxylated multiwalled carbon nanotubes block the assembly of the NLRP3 inflammasome through their surface negative charge, reducing the release of IL-1β and IL-18 and inhibiting ischemia–reperfusion neuroinflammation. This achieves "blocking"-level immune regulation and inflammation remodeling.[130] Metal ions such as Cu^{2+} and Sr^{2+} activate HIF-1α and upregulate VEGF/IL-4, inducing the polarization of macrophages toward the M2 phenotype while inhibiting NF-κB-mediated inflammatory signaling. This reshapes the bone immune microenvironment into a pro-repair state, achieving "reprogramming"-level immune regulation and defect repair.[131] In summary, nanomaterials reshape the inflammatory microenvironment through a three-tier mechanism of "clearance–blocking–reprogramming", providing precise therapeutic strategies for cancer, metabolic inflammation, and tissue regeneration.

Mechanisms of gastric mucosal repair and intestinal microbiota protection

In recent years, significant progress has been made in research on gastric mucosal repair and intestinal microbiota protection *via* nanomaterials, providing a new paradigm for the precise intervention of gastrointestinal diseases. The Pd(H)@ZIF-8 nanoplatform releases hydrogen and Zn^{2+} in the acidic environment of the stomach, which synergistically disrupts the membrane structure of *H. pylori* and inhibits urease activity, achieving precise antibacterial effects. Moreover, hydrogen scavenges ROS, downregulates the NF-κB signaling pathway, promotes the proliferation of GES-1 cells, and upregulates ZO-1 and occludin-1, thereby repairing the gastric mucosal barrier. 16S rRNA sequencing revealed that, after treatment, the intestinal α diversity and microbial structure of the mice were not significantly different from those of the antibiotic-treated mice, confirming the ability of the former to maintain intestinal microbiota homeostasis while eradicating pathogens.[59] The BiG@MC microcapsules, with a shell composed of gallic acid–BiIII metal phenolic networks, disintegrate in gastric acid to release bismuth ions and natural polyphenols. This action synergistically eradicates *H. pylori* and forms a protective film on the ulcer surface. The microcapsules significantly downregulated inflammatory factors and promoted CD31-positive angiogenesis, thereby accelerating gastric mucosal repair. Both *in vitro* and *in vivo* experiments revealed no significant changes in the α diversity or community structure of the gut microbiota, indicating the dual goals of targeted antibacterial activity and protection of microbial homeostasis.[132] Inspired by octopus suckers, suction-cup-like hydrogel micromotors continuously generate hydrogen in gastric acid to drive autonomous migration and firmly adhere to the ulcer surface. They release drugs to repair the gastric mucosa, significantly downregulating IL-6 and TNF-α while upregulating IL-10, thereby reducing inflammation and promoting healing. Their micrometer-scale size and negatively charged surface reduce intestinal exposure, avoiding microbial disturbance and achieving the dual goals of antibacterial activity and microbiota protection.[133] Through the aforementioned mechanisms, nanomaterials can achieve 3R integration of pathogen elimination, microenvironment remodeling, and tissue repair, providing a novel integrated prevention and treatment paradigm for *H. pylori* infection.

In summary, the independent roles of nanomaterials in pathogen removal, microenvironment remodeling, and tissue repair have been elaborated. However, their true therapeutic potential lies in the synergistic integration of these three components into a coherent paradigm. To clarify the conceptual progress and unique advantages of this integrated 3R strategy compared with traditional methods, we provide a comparative analysis in Table 2.[5,7,8,10,21,22,24,25,40–42,92,134–155]

From "strategy comparison" to "paradigm shift": The irreplaceability of 3R integrative therapy

Table 2 systematically compares conventional antibiotics, probiotic adjunctive therapy, and 3R nanotechnology across six dimensions: core strategy, targets of action, drug resistance risk, immune regulation, microbiota impact, and tissue repair. However, concluding merely that "3R therapy outperforms the others across all dimensions" would obscure its most fundamental paradigm shift—namely, that the 3R strategy redefines the therapeutic endpoint of *H. pylori* management from "bacterial negativity" to "gastrointestinal functional homeostasis."

The fundamental limitation of conventional antibiotic therapy lies not in its inability to kill bacteria, but in the fact that its chain of action terminates upon bacterial death. Probiotic adjunctive therapy, while attempting to mitigate microbiota injury, represents passive, post hoc repair. By contrast, the 3R nanotherapeutic strategy achieves the following: In the temporal dimension: sequential intervention of "eradication–remodeling–repair", rather than a single time-point strike; In the spatial dimension: expansion of the therapeutic battlefield from "the pathogen alone" to the "pathogen–host interface–microenvironment" tripartite system; In the biological dimension: a transition from "exogenous drug intervention" to "reactivation of the host's intrinsic repair capacity". Based on

Table 2. Evolution from conventional to integrated 3R nanotherapeutic paradigms in *H. pylori* management

Dimension of contrast	Traditional antibiotic therapy	Adjunctive probiotic therapy	3R nanotherapeutic (Remove-Remodel-Repair)
Core strategy	The eradication of *H. pylori* in gastric mucosa was achieved by a combination of potent acid inhibition and sufficient dosage and course of dual antibiotics[8,134,135]	Enhancing efficacy and attenuating toxicity, ecological escort, stabilizing intestinal flora, and reducing adverse effects[8,10]	It is a systematic integrated treatment of "remove, remodeling, and repair" trinity
Targets of action	Key structures unique to bacteria, such as the cell wall, ribosomes, and DNA replicases, kill bacteria by selectively attacking these targets[8,134]	Pathogen colonization sites, host microbiota homeostasis and immune balance[136]	Multiple targeting mechanisms: *H. pylori* cell membrane/biofilm (e.g. ROS, metal ions)[40,137]; Immune cells (e.g., macrophages, T cells)[138]; Mucosal repair signaling pathways (e.g., EGF, HSP70)[139]
Drug resistance	Drug resistance rates continue to rise[21,22]	no[8,134]	Low risk of resistance: Non-antibiotic mechanisms (such as ROS, photothermal, sonodynamic, and metal ions) were used to kill bacteria and avoid traditional antibiotic resistance pathways[24,25]
Immune regulation	Yes, but with a negative immune regulatory effect[139]	Local immunoregulatory function[140]	Systemic immune remodeling: enhanced antigen presentation and phagocytosis.[92] It promoted the polarization of M1 macrophages.[141] It can induce specific immunity as a vaccine carrier[142,143]
The impact on gut microbiota	Disrupting the intestinal flora[21,22]	Maintain the ecological balance of the intestine[144]	Precise protection and repair: pH/ enzyme response release: drugs are only activated in the acidic or infectious microenvironment of the stomach, reducing interference with the neutral environment of the gut.[40] Targeted sterilization: nano-material specificity combined with *H. pylori* to reduce the non-human damage to symbiotic bacteria[41]; Immunomodulation: reduce systemic inflammation and indirectly maintain the stability of intestinal flora[42]
Repair of gastric tissue	No[145]	Indirect repair has little effect[146]	Active, targeted and multi-level repair[42,146]
Potential mechanisms for prevention of gastric cancer	Single path: "Pathogen removal only"[147]	Potential and indirect[147]	Multi-targets and multi-dimensions. Eradication of *H. pylori*: elimination of *H. pylori* by non-antibiotic mechanisms to reduce the source of carcinogenesis[5,7,40,137]; Reversing precancerous lesions: promoting the repair and reversal of atrophic and intestinal metaplastic mucosa[148,149]; Enhanced immune surveillance: reshaping the immune microenvironment, activating T cells and NK cells, and improving immune clearance[142,143] Targeted regulation of carcinogenic pathways: such as the delivery of siRNA or small molecule inhibitors through nanocarriers to interfere with β-catenin, NF-κB and other signaling pathways[141,150]
Clinical transformation challenge	Antibiotic resistance and poor patient compliance[21,22]	Efficacy evidence and standardization deficiency. The mechanism of action is complex and varies greatly among individuals[151]	Multicomponent system complexity[152]; Due to the lack of clear regulatory review pathways and accepted clinical endpoint standards, clinical translation is difficult[153–155]

the above analysis, we propose the following tiered prioritization framework for 3R strategies: First-line priority strategy: Nanoplatforms possessing dual functionality of self-responsive eradication and immune remodeling, with well-defined oral bioavailability (e.g., AP@CS@Lip@HKUST-1).[41] These systems offer integrated therapeutic benefit without escalating systemic complexity. Synergistic/adjunctive strategy: VacA-adsorbing nanomaterials (e.g., Ver PLGA@Lec) deployed in combination with standard regimens to reverse localized immunosuppression.[43] This approach is particularly indicated for patients infected with VacA-high-expressing strains or those presenting with severe active gastritis. Reserve/exploratory strategy: Tissue-regenerative nanomaterials (e.g., Fu GaLip@KP).[116] Current evidence is primarily derived from murine models. Advancement to clinical trials should be contingent upon the establishment of mucosal repair kinetic profiles in large-animal models.

Based on the above analysis, the fundamental contribution of 3R integrative therapy lies not in incremental optimization, but in reframing the core problem and efficacy paradigm of *H. pylori* intervention. The essence of this paradigm shift is the elevation of therapeutic goals from the singular task of "pathogen eradication" to the systems-level endeavor of "host homeostasis reconstruction." Accordingly, strategy prioritization must transition from a hierarchy based on "technical complexity" to a tiered framework anchored by the dual benchmarks of "translational cost-effectiveness" and "evidence maturity." Only by completing this cognitive leap—from strategy comparison to paradigm shift—can 3R nanotechnology truly transcend the conceptual constraints of conventional antibiotics and advance from proof of concept toward clinical practice.

Conclusions

Gastric cancer remains a major global health challenge, largely attributable to persistent *H. pylori* infection. Traditional antibiotic-based therapies face increasing limitations due to drug resistance, microbiota disruption, and the lack of mucosal repair mechanisms. This review proposes a nanomaterial-mediated 3R integrated strategy, which offers a multidimensional approach for the systematic management of *H. pylori* infection. As Table 2 demonstrates, this paradigm shifts the therapeutic endpoint from bacterial eradication alone to gastrointestinal functional restoration—a distinction that separates 3R nanotherapeutics from both antibiotics and probiotic adjuncts.

The Remove phase leverages nanomaterials for precise pathogen clearance through targeted, stimuli-responsive mechanisms—such as pH-, enzyme-, light-, or magnetic-activated mechanisms—that enhance bactericidal efficacy while minimizing off-target effects and preserving the gut microbiota.

In the Remodel phase, nanomaterials actively reshape the gastric immune microenvironment by neutralizing virulence factors, modulating immune cell functions, and countering bacterial immune evasion, thereby creating a conducive setting for tissue recovery.

The Repair phase employs nanocarriers to restore mucosal integrity, alleviate oxidative stress and inflammation, regulate microbial communities, and promote tissue regeneration, collectively supporting gastrointestinal homeostasis.

By integrating these three dimensions, the 3R nanotherapeutic paradigm shifts from empirical antibiotic use toward precision-integrated intervention. However, its clinical translation remains at an early stage, with current evidence primarily derived from cellular and animal models. Future efforts should focus on optimizing nanomaterial biocompatibility, elucidating material–host–pathogen interactions, and advancing preclinical validation through large-animal studies and prospective clinical trials. Through interdisciplinary collaboration, this approach holds promise for overcoming antibiotic resistance and microbiota disruption, ultimately contributing to safer and more effective strategies for *H. pylori* management within an integrative medical framework.

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Conflict of interest

Prof. Yiqi Du serves as Editor-in-Chief, and Prof. Jie Gao serves as an editorial board member of *Cancer Screening and Prevention*. The authors have no other conflicts of interest to note.

Author contributions

Study conceptualization & framework establishment (JW, HW), figure design & visualization (JW, HW, TZ), Original Draft (JW, HW), revision & content development (JW, TZ, YW, CC, XW, HC), critical review & academic oversight (CY, JG, YD). All authors have made significant contributions to this study and have approved the final manuscript.

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