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REVIEW

The Role of Bacterial Siderophores in Infection Therapy: From Anti-Infective Mechanisms to Therapeutic Advances

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Abstract: Siderophores are low-molecular-weight iron chelators that mediate microbial iron acquisition and critically shape host–pathogen interactions. This review highlights the structural diversity, regulatory networks, and virulence functions of bacterial siderophores, including their roles in overcoming host nutritional immunity, modulating immune responses, promoting biofilms, and coordinating metal homeostasis. We further discuss therapeutic strategies that exploit siderophore pathways, from "Trojan horse" siderophore–antibiotic conjugates such as cefiderocol to emerging non-antibiotic conjugates incorporating metal complexes, peptides, nucleic acids, vaccines, and nanomaterials. Beyond antibacterial applications, siderophores show promise in antifungal and antiparasitic therapies and as infection-specific imaging probes. Despite these advances, translational challenges—including adaptive resistance, pharmacokinetic instability, and competition with endogenous siderophores—limit clinical progression. Innovative approaches such as engineered siderophore scaffolds, multifunctional delivery platforms, and nanotechnology-enabled systems may help overcome these barriers. Overall, this review underscores the central role of siderophores in microbial pathogenesis and their growing potential as versatile platforms for next-generation anti-infective and diagnostic development.

Keywords: siderophores, iron acquisition, bacterial pathogenesis, anti-infective therapy, antimicrobial resistance

Introduction

Iron plays a pivotal role in the pathogenesis and progression of bacterial infections, serving as an indispensable element for bacterial growth and metabolism. Bacteria have evolved finely tuned regulatory systems to acquire iron from the host, thereby driving proliferation and facilitating infection.[1] In response to bacterial invasion, hosts employ stringent iron-withholding strategies to restrict pathogen growth by limiting the availability of free iron. This competitive tug-of-war between host iron sequestration and bacterial iron acquisition constitutes a central paradigm in bacterial infection research and therapeutic development.[2,3]

The widespread use of antibiotics—coupled with the alarming rise of resistant strains—has progressively eroded the efficacy of conventional antimicrobial agents, positioning antimicrobial resistance as a major global public health challenge.[4] In recent years, intensified investigations into bacterial iron metabolism and siderophore biology have spotlighted siderophore-based antimicrobial strategies. Siderophores, as the primary molecular tools for bacterial iron acquisition, outcompete host iron-binding molecules to sustain pathogen viability and virulence. Leveraging this unique property, the "Trojan horse" strategy has emerged: conjugating antibiotics to siderophores exploits active bacterial uptake pathways to achieve efficient intracellular drug delivery, thereby enhancing therapeutic potency.[5,6] The clinical success of cefiderocol—the first marketed siderophore–antibiotic conjugate—has validated the feasibility of this approach.[7,8]

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Beyond antibiotic delivery, accumulating evidence indicates that siderophore applications extend into broader and more innovative therapeutic domains. Siderophore–non-antibiotic conjugates are gaining considerable traction as a novel frontier. By coupling siderophores with metal complexes (eg, gallium or platinum), antimicrobial peptides, nucleic acids, or vaccine components, these multifunctional carriers enable efficient transport of non-traditional antimicrobial agents into bacterial cells, producing multifaceted effects such as enhanced outer-membrane penetration, disruption of metal homeostasis, or targeted immune activation.[9–11] Although these strategies currently show limitations in rational design, in vivo evaluation, and cross-pathogen applicability, they also offer distinctive advantages—particularly in combating multidrug-resistant strains, developing next-generation vaccines, and integrating diagnostic and therapeutic functions.[12]

Siderophore-based antimicrobial strategies thus represent a promising route to overcoming resistance barriers. By perturbing iron metabolism—especially through interventions targeting siderophore biosynthesis, transport, and functional pathways—these approaches not only impede pathogen proliferation and dissemination but may also mitigate the emergence of antimicrobial resistance.[13] Importantly, the rapid expansion of siderophore–non-antibiotic conjugate research unlocks new possibilities for precision therapy and diagnostics. Notably, siderophore applications are extending to fungal and parasitic infections, utilizing iron restriction to suppress pathogen growth, as well as serving as molecular probes for precise infection-site diagnosis and imaging.[14–17]

Recent translational advances further underscore this field's potential. Phase III clinical trials have demonstrated the efficacy of cefiderocol in treating ventilator-associated pneumonia caused by carbapenem-resistant *Enterobacterales*, with improved survival rates relative to best available therapy.[18] Meanwhile, innovative siderophore–nanoparticle hybrids have shown promise in preclinical models, enabling targeted photothermal ablation of biofilms in chronic infections. Complementarily, siderophore-based vaccines targeting uropathogenic *Escherichia coli* have progressed to animal challenge studies, reducing bacterial burdens by up to 99% without disrupting the gut microbiota.[19,20] Collectively, these multidimensional investigations highlight the unique value of siderophores in infection prevention and control.[4]

While previous reviews have primarily focused on the biochemical mechanisms of siderophore biosynthesis and iron chelation, the present review distinguishes itself by integrating mechanistic foundations with translational progress, emphasizing emerging clinical evidence and next-generation conjugate designs that bridge fundamental research with therapeutic implementation. To contextualize these developments, Figure 1 provides a concise historical timeline of landmark advances—from the discovery of bacterial siderophores to the clinical approval of cefiderocol—illustrating how decades of foundational research have converged to shape current therapeutic innovation. Building upon this framework, we present a comprehensive overview of siderophore biology, including host–pathogen iron competition, siderophore-mediated virulence, and immune evasion, followed by an in-depth analysis of recent advances in siderophore-based antimicrobial strategies and emerging applications in antifungal, antiparasitic, and diagnostic/imaging technologies (Figure 2). By integrating classical paradigms with cutting-edge discoveries, we aim to provide theoretical

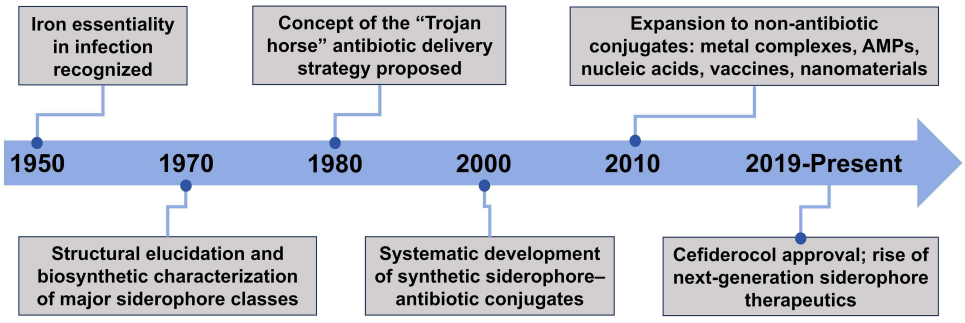

Figure 1 Timeline of major milestones in siderophore-based therapeutic development. Key advances include the discovery of bacterial siderophores (1950s), structural and biosynthetic characterization (1970s), the conception of the "Trojan horse" antibiotic delivery strategy (1980s), and the synthetic engineering of siderophore–antibiotic conjugates (2000s). The 2010s marked the expansion to non-antibiotic conjugates such as metal complexes, antimicrobial peptides (AMPs), nucleic acids, vaccines, and nanomaterials. Since 2019, cefiderocol approval has defined the clinical era of siderophore therapeutics, accompanied by progress in vaccines, nanoparticle-based theranostics, and AI-driven siderophore engineering. Created with Adobe Illustrator.

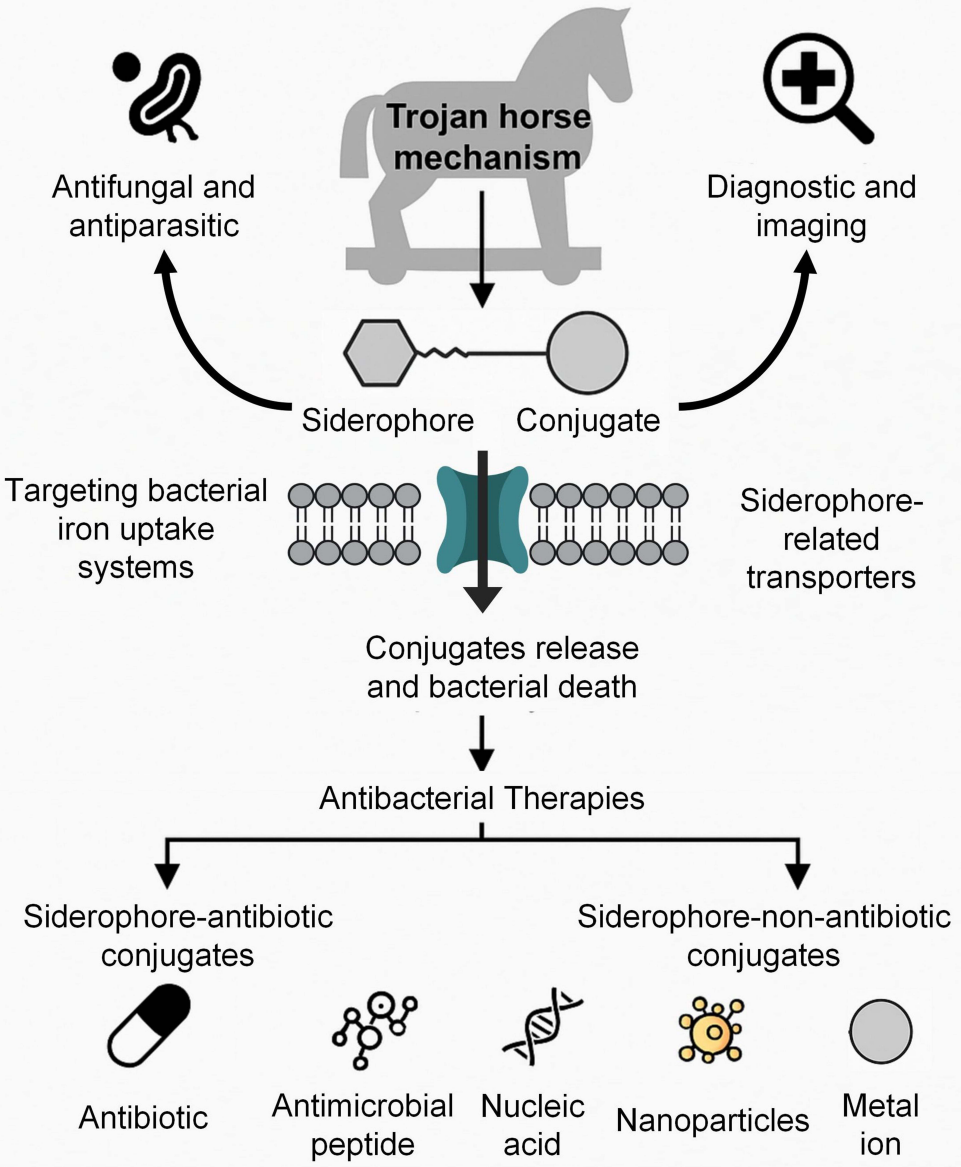

Figure 2 Current applications of siderophores in anti-Infection therapy. Created with Adobe Illustrator.

insights for elucidating siderophore mechanisms in infections and for guiding the development of innovative antimicrobial and diagnostic modalities.

Siderophore Biology

Diversity and Classification of Bacterial Siderophores

Siderophores are low-molecular-weight, high-affinity iron-chelating agents secreted by bacteria under iron-limiting conditions, and their structural and functional diversity directly shapes bacterial survival strategies and pathogenic potential. Based on the nature of their iron-coordinating moieties, siderophores are generally classified into catecholates, hydroxamates, carboxylates, and mixed-type structures.[21]

Catecholate siderophores are characterized by a 2,3-dihydroxybenzoic acid (2,3-DHBA) core, exemplified by enterobactin produced by *Escherichia coli* and salmochelin synthesized by *Salmonella*. Hydroxamate siderophores—including desferrioxamine B from *Streptomyces* and aerobactin from *Klebsiella pneumoniae*—enable efficient iron uptake via specific outer membrane receptors such as IutA.[22,23] Carboxylate siderophores function particularly well in

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acidic microenvironments; for instance, staphyloferrin A from *Staphylococcus aureus* utilizes α-ornithine and citric acid moieties to hijack host transferrin.[24,25] Mixed-type siderophores integrate multiple functional groups, illustrated by pyoverdine from *Pseudomonas aeruginosa*, which incorporates catecholate and hydroxamate features. Beyond mediating iron acquisition, pyoverdine triggers host mitophagy, ultimately promoting host cell death.[26,27] Petrobactin produced by *Bacillus anthracis* represents a unique bis-catecholate siderophore capable of evading immune detection by host siderocalin.[28]

Siderophores and Bacterial Virulence

In addition to their fundamental role in iron acquisition, siderophores function as potent virulence determinants. Their structural heterogeneity reflects bacterial evolutionary adaptation to diverse host niches and is closely intertwined with pathogenicity (Table 1). Collectively, these mechanisms highlight the multifaceted contributions of siderophores to bacterial pathogenesis and form the conceptual foundation for antimicrobial strategies targeting iron metabolism.

Structural Diversity of Siderophores and Immune Evasion Mechanisms

Evidence indicates that structural variations among siderophores dictate their chelation efficiency and determine their capacity to evade host immune surveillance, thereby directly influencing pathogen survival and infectivity.[49] For example, petrobactin secreted by *Bacillus anthracis* utilizes its distinct bis-catecholate structure to avoid recognition by siderocalin, playing a central role in systemic anthrax infections.[28]

Moreover, bacteria exploit structural modifications to implement "stealth" strategies—such as the glycosylation of enterobactin into salmochelin—to circumvent sequestration by lipocalin-2, thus ensuring continued iron acquisition and promoting virulence.[50] In Gram-negative bacteria, such modifications are widespread; for instance, salmochelin production in *Salmonella* enables resistance to nutritional immunity–imposed iron restriction.[51] Similarly, pyoverdine from *Pseudomonas aeruginosa* possesses a fluorescent chromophore and diverse peptide chain variants that confer effective iron chelation while evading host iron-binding proteins. These properties support chronic infections, including those in cystic fibrosis airways.[52] Such structural attributes ensure siderophore non-redundancy and help define bacterial "replication niches" during infection.

Non-Classical Functions of Siderophores and Their Roles in Virulence

Beyond traditional iron sequestration, siderophores exert diverse non-classical functions that significantly shape bacterial virulence. Yersiniabactin from *Klebsiella pneumoniae* activates the host HIF-1α pathway, mimicking hypoxic microenvironments and promoting pulmonary infection progression.[38] Additionally, yersiniabactin binds non-iron metals such as Zn^{2+} and Cu^{2+}, compensating for deficiencies in zinc transport systems (eg, *znuABC*) and mimicking superoxide dismutase activity within phagocytes to protect bacteria from copper-induced ROS stress. This enhances survival during pneumonia and sepsis.[51]

Siderophores also facilitate biofilm formation; for example, pyochelin from *Pseudomonas aeruginosa* stabilizes extracellular polysaccharide matrices and supports robust colonization.[26,27] Pyoverdine in *P. aeruginosa* also regulates virulence gene expression via quorum sensing and promotes interbacterial competition under iron limitation by inhibiting the growth of competing microbes.[53] Within host cells, certain siderophores directly alter iron homeostasis. Enterobactin produced by *E. coli* chelates the host labile iron pool (LIP), suppressing macrophage antimicrobial activity. Its copper-binding capability further increases copper tolerance, reduces ROS accumulation, and strengthens virulence in multidrug-resistant strains.[51] Additionally, enterobactin dramatically enhances virulence under iron scarcity, whereas siderophore-deficient mutants exhibit profound attenuation.[23] Enterobactin also impairs immune defenses by inhibiting neutrophil extracellular trap (NET) formation and phagocytosis.[29] Moreover, siderophores confer protection against oxidative stress, further contributing to pathogen persistence.[54] Siderophores may also function as signaling molecules that modulate host transcriptional programs—upregulating apoptosis pathways while downregulating DNA repair and cell cycle genes—thereby disrupting host iron homeostasis and promoting infection dissemination.[50] In *Yersinia pestis*, yersiniabactin facilitates zinc acquisition to overcome *znuABC* deficiencies and enhances bacterial survival under Zn^{2+} limitation in both insect and mammalian hosts, supporting cross-species transmission.[51]

Table 1 Representative Bacterial Siderophores: Structural Features, Receptors, and Virulence Effects

Bacterium	Siderophore	Type of Siderophore	Key Structural Features	Primary Receptors	Virulence Effects	References
Escherichia coli	Enterobactin	Catecholate type	Tris(catecholate) trilactone	FepA, CirA, Fiu	Binds iron from plasma transferrin, promotes bacterial growth and infection; Evades Lipocalin-2 neutralization; Suppresses neutrophil activity, reduces ROS and NETs, promotes UTI	[29–31]
	Salmochelin	Catecholate type (glycosylated enterobactin)	C-glycosylated enterobactin core	IroN	Glycosylation enables immune evasion; Promotes colonization and invasion via IroN receptor	[32–34]
	Aerobactin	Hydroxamate type	Hydroxamate groups derived from lysine and citrate	IutA	Promotes growth in serum and urine	[35,36]
	Yersiniabactin	Mixed type	Phenolate & thiazolidine rings	FyuA	Enhances lung infection and spleen colonization	[37,38]
Salmonella enterica	Enterobactin	Catecholate type	Tris(catecholate) trilactone	FepA	Chelates intracellular iron, interferes with macrophage iron-dependent mechanisms	[39]
Staphylococcus aureus	Staphyloferrin A/B	Carboxylate type	Citrate and amine (ornithine/DABA) backbone	SirA (for Sbn)	Hijacks transferrin, promotes chronic infection and biofilm	[24,25]
	Autochelin	Not specified	Not fully characterized	Not specified	Involved in iron acquisition, enhances virulence	[40]
Pseudomonas aeruginosa	Pyoverdine	Mixed type	Fluorescent chromophore (quinoline) + strain-specific peptide chain	FpvA (type-specific)	Induces mitophagy and cell death; Green fluorescence useful for biosensing	[27]
	Pyochelin	Mixed type	Salicylate & cysteine-derived thiazolidine	FptA	Stabilizes biofilm matrix, promotes chronic infection	[41]
Klebsiella pneumoniae	Enterobactin	Catecholate type	Tris(catecholate) trilactone	FepA	Binds transferrin iron, promotes infection; Induces platelet mitophagy and apoptosis	[42]
	Yersiniabactin	Mixed type	Phenolate & thiazolidine rings	FyuA	Activates HIF-1α pathway, simulates hypoxia, promotes infection spread	[38]
	Aerobactin	Hydroxamate/Mixed type	Hydroxamate groups	IutA	Enhances iron uptake via IutA receptor, associated with hypervirulent strains	[23]
	Salmochelin	Catecholate (glycosylated enterobactin)	C-glycosylated enterobactin core	IroN	Chelates iron, increases replication, enhances virulence	[32–34]
Mycobacterium tuberculosis	Carboxymycobactin	Carboxylate type	Salicylate-derived with lipid tail	Not fully defined (IrtAB implicated)	Promotes macrophage survival, suppresses immune response	[43]
Bacillus subtilis	Bacillibactin	Catecholate type	Tris(catecholate) trilactone	FeuA	Strong Fe^{3+} chelation via trilactone structure	[44]
Vibrio cholerae	Vibriobactin	Catecholate type	Catecholate with norspermidine backbone	ViuA, VctA	Releases heme via hemolysin, enhances gut invasion; VitA receptor uptake	[45]
Bacillus anthracis	Petrobactin	Catecholate type	Bis(catecholate) with citrate spacer	FpuA (Fe^{3+}-petrobactin uptake)	Evades siderocalin, critical virulence factor	[46]
Streptomyces spp.	Desferrioxamine B	Hydroxamate type	Linear trihydroxamate	Not specified (diffusion/energy-independent uptake)	Clinical iron overload treatment; antimalarial	[22]
Yersinia pestis	Yersiniabactin	Mixed type	Phenolate & thiazolidine rings	Psn	Enhances virulence via Psn and *Irp2* genes	[47]
	Enterobactin	Catecholate type	Tris(catecholate) trilactone	FepA	Inhibits neutrophil activity, promotes intracellular survival	[29]
Listeria monocytogenes	Ferric citrate	Carboxylate type	Utilizes host citrate-Fe^{3+} complexes	Not specified	Reduces Fe^{3+} to Fe^{2+}; uses catecholamines as iron source	[48]

Regulatory Mechanisms of Siderophore Expression

Siderophores are high-affinity iron-chelating agents secreted by bacteria in iron-limiting environments, with their biosynthesis and expression governed by multilayered, finely tuned genetic regulatory mechanisms. These mechanisms enable bacteria to efficiently respond to iron availability, environmental cues, and host immune pressures, thereby optimizing iron acquisition, averting energy wastage, and enhancing pathogenicity or survival adaptability. Siderophore expression regulation encompasses transcriptional levels, post-transcriptional levels, and signal transduction systems, forming a complex network (Table 2). This integrated network is highly conserved across bacteria but exhibits species-specific adaptations to diverse ecological niches. This section will concisely outline these core mechanisms and their roles in pathogenic bacteria.

Global Transcriptional Regulators

Siderophore biosynthetic gene clusters are predominantly controlled by global transcriptional regulators, with the ferric uptake regulator Fur being the most conserved and extensively characterized. Under iron-replete conditions, Fur binds Fe^{2+} and interacts with Fur-box sequences in promoter regions to repress transcription of siderophore biosynthesis and transport genes, thereby preventing iron overload and mitigating oxidative stress. During iron starvation, Fur repression is relieved, leading to derepression of gene clusters—such as the *ent* genes encoding enterobactin and the *pvd* genes responsible for pyoverdine synthesis—and thereby promoting siderophore production. This negative regulatory paradigm is highly conserved among Gram-negative bacteria, including *Escherichia coli, Pseudomonas aeruginosa*, and *Burkholderia* spp (Figure 3A).[55,56,69,70] In *P. aeruginosa*, Fur regulates more than 50 iron-related genes, including the *pvd* and *pch* clusters encoding pyoverdine and pyochelin, ensuring their prioritized expression under iron limitation.[23,55] Similarly, in *Burkholderia*, Fur modulates malleobactin biosynthesis.[59]

Table 2 Multilevel Regulation Mechanisms of Bacterial Siderophore Expression

Regulation Level	Key Regulators	Mechanism	Representative Species	Target Genes/ Pathways	References
Transcriptional	Fur	Represses transcription under iron sufficiency; The inhibition is relieved under iron deficiency	*E. coli, P. aeruginosa, Burkholderia spp.*	*ent, pvd, pch, mba*	[55,56]
	DtxR	Represses siderophore expression with Fe^{2+}	*Corynebacterium spp.*	Catecholate siderophore genes	[57]
	Zur, Mur	Responds to Zn^{2+}/Mn^{2+}, indirectly regulates iron	Various species	Metal homeostasis genes	[58]
	MftR	Represses mbaS, relieved by xanthine	*B. thailandensis*	mba gene cluster	[59]
Environmental signaling	QS system (LasR etc)	Activates siderophore gene clusters at high density	*P. aeruginosa, V. harveyi*	*pvd, pch, vibF*	[60,61]
	Two-component systems (BfmRS etc).	Regulation of siderophore-related genes by sensing stress signals	*P. aeruginosa, S. oneidensis*	*pvd, fpv, pubABC*	[55,62]
	Host immune induction	Host proteins induce "stealth" siderophores	*E. coli, Salmonella spp.*	*iroBCDE*	[51]
Post-transcriptional	sRNAs (PrrF, RyhB)	Inhibit nonessential iron protein translation	*P. aeruginosa, E. coli*	*pchE, ent*	[63,64]
	CsrA/CsrB	CsrA inhibits mRNA translation; CsrB relieves	*S. oneidensis*	*pubABC*	[62]
Network coordination	Fur + sRNA	Coordinates transcription and translation	Multiple species	Siderophores and iron metabolism	[65]
	σ factors (MbaS etc).	Activates siderophore gene expression	*Burkholderia, fungi*	*mba*, NRPS genes	[66,67]
	Siderophore signaling	Regulates virulence gene expression	*P. aeruginosa* etc.	QS systems, virulence genes	[68]

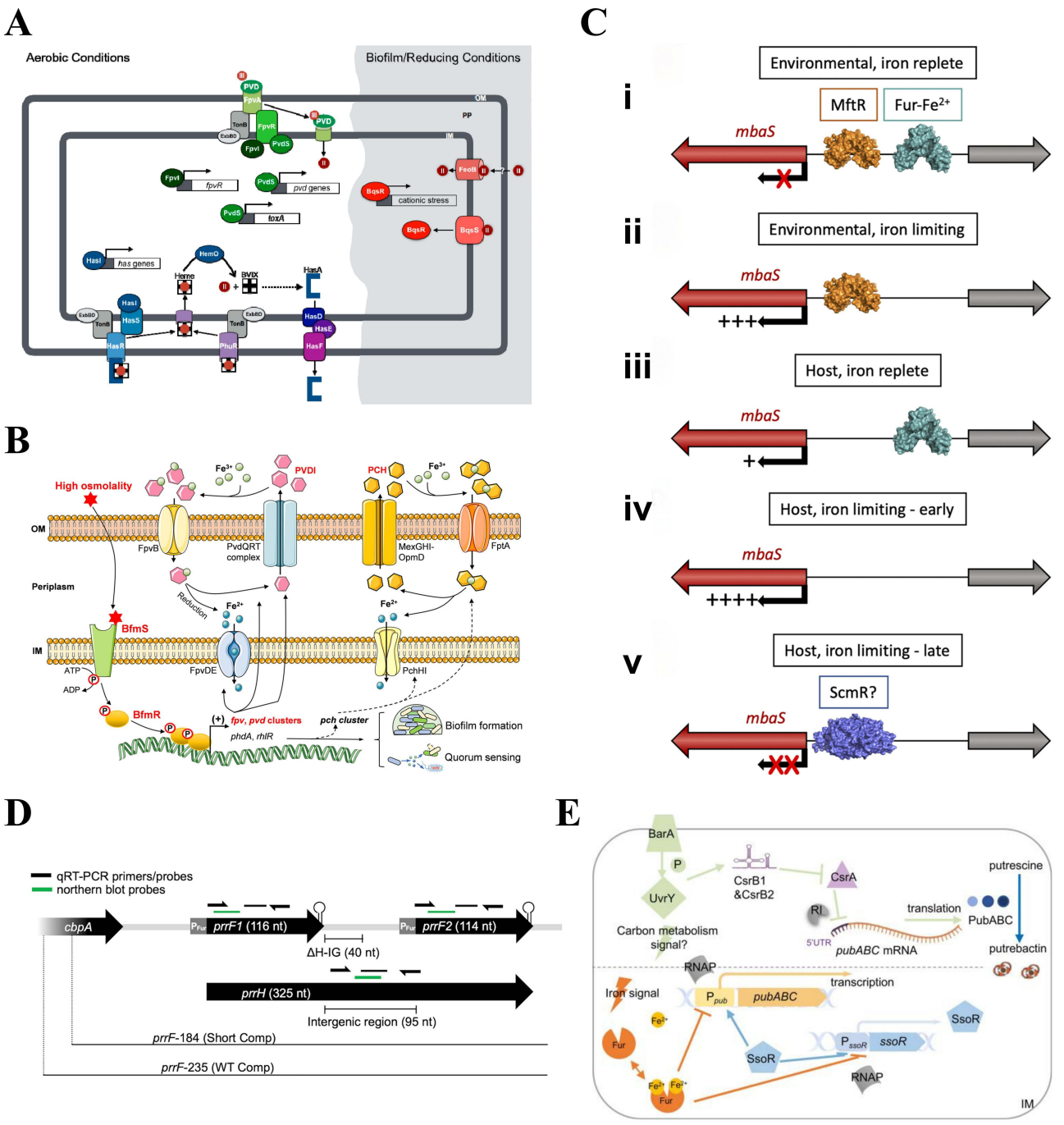

Figure 3 Multilayered regulatory networks of siderophore expression. (**A**) In *Pseudomonas aeruginosa*, iron availability is primarily sensed and regulated through ferric uptake regulator (Fur)–dependent signaling pathways. The Fur–Fe^{2+} complex modulates several downstream σ factors, including PvdS, which governs pyoverdine biosynthesis and toxin secretion, FpvI for pyoverdine uptake, and HasI for heme acquisition. Additionally, degradation products of the heme oxygenase HemO and the BqsSR two-component system under anaerobic or reducing conditions contribute to regulation, collectively ensuring preferential activation of the *pvd* and *pch* siderophore gene clusters under iron limitation to enhance iron uptake and virulence.[70] (**B**) BfmRS-mediated regulation of siderophore production in *Pseudomonas aeruginosa*. In response to osmotic stress, the BfmRS two-component system activates transcription of *fpv, pvd*, and *femARI* clusters to boost pyoverdine synthesis, while also modulating *rhl* quorum sensing and biofilm formation, indirectly affecting pyochelin levels.[55] (**C**) Host-specific regulation of siderophore biosynthesis by MftR in *Burkholderia thailandensis*. Under iron-replete conditions, MftR represses the σ factor *mbaS*; in the host environment, xanthine binding to MftR relieves repression, thereby activating malleobactin production. (i) During growth under iron-replete environmental conditions, *mbaS* is repressed by both Fur-Fe2+ and MftR. (ii) Iron limitation leads to dissociation of Fur and elevated expression of mbaS (and in turn the entire *mba* gene cluster). (iii) In a host environment, characterized by elevated urate levels, MftR dissociates, resulting in a modest increase in *mbaS* expression. (iv) In an iron-limited host environment, both Fur and MftR dissociate. (v) Accumulation of xanthine during stringent response may lead to ScmR-mediated repression of *mbaS* under conditions of high cell density.[59] (**D**) Posttranscriptional regulation by PrrF/PrrH sRNAs in *Pseudomonas aeruginosa*. Under iron limitation, PrrF1/2 repress nonessential iron-containing proteins to prioritize siderophore synthesis, while PrrH responds to heme to fine-tune *pchE* expression and enhance pyochelin production.[71] (**E**) Posttranscriptional regulation of siderophore synthesis by the CsrA/CsrB system in *Shewanella oneidensis*. CsrA represses translation of *pubABC* mRNA, while CsrB sRNA sequesters CsrA to relieve repression, enabling putrebactin biosynthesis under iron-limiting conditions.[62] Created with Adobe Illustrator.

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Beyond Fur, additional global regulators contribute to siderophore regulation. DtxR functions as a major transcriptional regulator in Gram-positive bacteria, controlling catecholate siderophore expression.[57] Moreover, expanded Fur-family proteins such as Zur (zinc uptake regulator) and Mur (manganese uptake regulator) modulate siderophore expression indirectly via polymetal homeostasis.[58] The diversity of these regulatory proteins reflects bacterial adaptation to complex, metal-rich environments.

Environmental and Host Signal Integration

Siderophore expression is further modulated by diverse environmental cues—iron availability, oxygen tension, pH gradients, and host-derived metabolites—integrated through sophisticated signal-transduction pathways that enable precise temporal and spatial regulation. In pathogenic bacteria, host-associated conditions such as iron restriction and nutritional immunity act as primary triggers of siderophore production (Figure 3B).[55] For example, in *Burkholderia thailandensis*, the malleobactin biosynthetic gene cluster is directly governed by the global transcriptional regulator MftR. Under iron-replete conditions, MftR represses *mbaS* (encoding the extracytoplasmic function sigma factor MbaS). Within host cells, however, MftR binds the purine metabolite xanthine, releasing this repression and activating malleobactin synthesis. This regulatory mechanism optimizes siderophore expression in host environments by preventing unnecessary energy expenditure while enhancing virulence traits such as biofilm formation and motility (Figure 3C).[59] MftR regulation may further synergize with other ligand-responsive transcriptional regulators, such as ScmR, which respond to cell density and purine metabolic status.[66]

Quorum sensing (QS) constitutes another essential environmental signaling mechanism that synchronizes siderophore production across bacterial populations. In *Pseudomonas aeruginosa*, QS regulators LasR and PqsR modulate pyoverdine and pyochelin production: high-density bacterial communities release autoinducers such as acyl-homoserine lactones, activating siderophore gene clusters to support iron acquisition and virulence factor secretion.[60,61] Additionally, in bacteria such as *Shewanella oneidensis*, the two-component system BarA/UvrY responds to iron limitation to activate the *pubABC* operon encoding putrebactin, while simultaneously integrating oxidative stress and nutritional cues.[62] Host immune factors—chiefly lipocalin-2 (LCN2)—bind bacterial siderophores, inducing the expression of "stealth" siderophores (eg, salmochelin) that evade immune sequestration.[51,69] These environmentally responsive mechanisms coordinate siderophore expression with dynamic infection contexts.

Post-Transcriptional Regulatory Mechanisms

In addition to transcriptional control, siderophore biosynthesis is shaped by post-transcriptional mechanisms including small RNAs (sRNAs) and translational repressors, which enable rapid adaptation to iron fluctuations. In *P. aeruginosa*, the PrrF sRNA system (PrrF1 and PrrF2) is induced under iron depletion and base-pairs with target mRNAs to repress translation of non-essential iron-consuming enzymes, thereby prioritizing limited iron for siderophore biosynthesis (Figure 3D).[63,71,72] PrrF-mediated suppression of metabolic enzymes indirectly enhances pyoverdine and pyochelin production. Heme-responsive sRNA PrrH further fine-tunes pyochelin expression (eg, *pchE*), modulated by light exposure and static culture conditions.[71] In *Escherichia coli*, the RyhB sRNA activates enterobactin biosynthesis during iron scarcity by repressing iron storage proteins.[64,73] Meanwhile, in *S. oneidensis*, the RNA-binding protein CsrA binds the 5′ UTR of *pubABC* transcripts to inhibit translation, whereas CsrB sRNA—activated by BarA/UvrY—neutralizes CsrA repression, thereby permitting putrebactin synthesis (Figure 3E).[62,74]

Collectively, these sRNA-mediated pathways constitute rapid, energy-efficient regulatory layers that complement transcriptional mechanisms to form multilayered control networks.[75] The siderophore regulatory network encompasses transcriptional, post-transcriptional, and epigenetic interactions. For instance, Fur often cooperates with sRNAs (eg, PrrF, RyhB) to orchestrate an "iron-sparing" response: Fur represses transcription while sRNAs fine-tune translation.[62,65] Two-component systems such as BfmRS in *P. aeruginosa* coordinate *pvd* and *fpv* expression in response to envelope stress.[55] In pathogens such as *B. thailandensis*, MftR-mediated regulation integrates siderophore biosynthesis with biofilm and motility pathways.[76]

Notably, in some bacteria—similar to fungal pathogens—siderophore regulation involves non-ribosomal peptide synthetases (NRPS) and extracytoplasmic function (ECF) sigma factors, expanding regulatory complexity.[66,67] Recent

findings further highlight non-classical functions of siderophores, including roles as signaling molecules influencing virulence and metal tolerance, adding further layers of intricacy to the regulatory landscape.[51,68] This regulatory diversity ensures efficient iron utilization under host conditions while minimizing immune detection and energy waste, collectively reinforcing pathogen survival and virulence.

Bacterial Siderophores and Host Iron Competition

Hosts deploy a variety of iron-restriction strategies—integral components of innate immunity—to suppress pathogen growth. Iron-binding proteins such as transferrin, lactoferrin, and ferritin sequester free iron, drastically reducing its availability in host tissues.[77] To counter bacterial siderophores, immune cells secrete lipocalin-2 (LCN2), which binds and neutralizes siderophores such as enterobactin, thereby preventing bacterial iron reclamation.[78] LCN2 deficiency impairs neutrophil chemotaxis and disrupts macrophage cytokine responses, underscoring its essential immunoprotective role.[79]

Some pathogens—including *Bacillus anthracis*—circumvent LCN2 through "stealth" siderophores such as petrobactin.[80] To surmount host iron restriction, bacteria have developed multifaceted strategies. First, the high affinity of siderophores enables them to scavenge iron from host iron-binding proteins.[50] For example, enterobactin's iron affinity far exceeds that of host transferrin, rendering it an efficient iron-scavenging tool.[49] Second, some pathogens secrete multiple siderophores to augment iron acquisition capacity; for instance, Pseudomonas aeruginosa concurrently produces pyoverdine and pyochelin to address varying iron-limiting conditions.[26] Finally, certain pathogens modify siderophore chemical structures to evade immune recognition; for example, petrobactin's bis-catecholate architecture precludes LCN2 recognition, enabling successful circumvention of host immune assaults. This dynamic host-pathogen tug-of-war exemplifies the criticality of siderophores in infection processes.[81]

Anti-Infection Mechanisms of Siderophores

Siderophores, as potent iron-scavenging metabolites, play multifaceted roles in modulating bacterial infections and host immunity. They also represent promising targets for anti-infective interventions. Their anti-infection roles can be broadly categorized into three domains: siderophore-mediated "Trojan horse" strategies, iron competition and immune modulation, and inhibition of siderophore pathways. These strategies are increasingly supported by mechanistic and translational research (Figure 4).

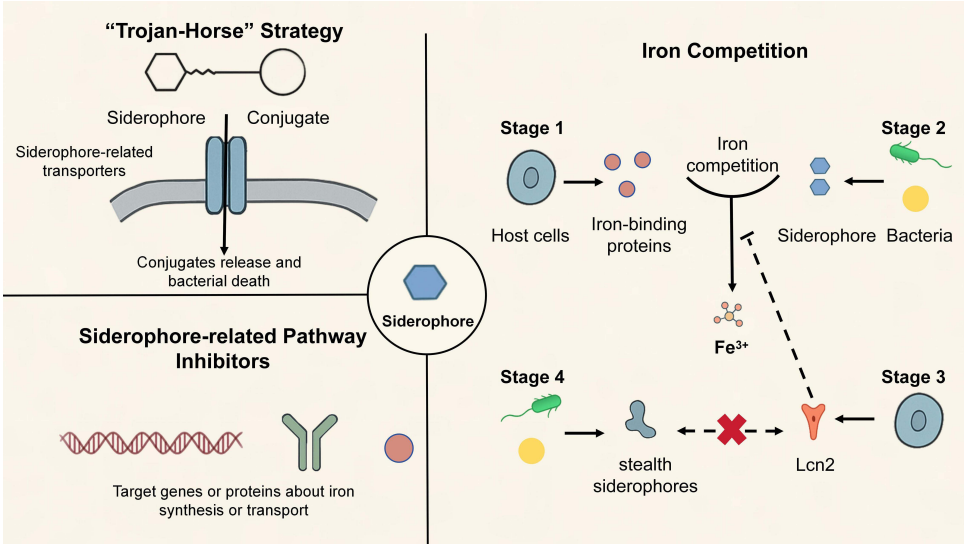

Figure 4 Anti-infection mechanisms of siderophores. 1) Siderophore-mediated "Trojan Horse" strategies. 2) Iron competition between host cells and bacteria. Stage 1: Host cells secrete iron-binding proteins (eg, lactoferrin) to restrict iron availability and suppress pathogen growth. Stage 2: Pathogens counteract by producing high-affinity siderophores that "pirate" iron from host proteins. Stage 3: Host cells release lipocalin 2 (Lcn2), a siderophore-binding protein that neutralizes bacterial siderophores and blocks their reuptake. Stage 4: Certain pathogens circumvent this defense by synthesizing "stealth siderophores" (eg, salmochelin, petrobactin) that evade Lcn2 recognition. Created with Adobe Illustrator.

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Siderophore-Mediated "Trojan Horse" Strategies

Siderophore–antibiotic conjugates constitute an emerging therapeutic paradigm that exploits bacterial iron transport pathways to deliver antibiotics across the outer membrane. This approach overcomes permeability barriers inherent to Gram-negative pathogens and has shown strong activity against multidrug-resistant (MDR) strains. Cefiderocol—the first approved siderophore–cephalosporin conjugate—utilizes its siderophore moiety to form iron complexes recognized by bacterial uptake systems. Once internalized, cefiderocol inhibits penicillin-binding proteins (PBPs), disrupting cell wall biosynthesis.[82] Clinical studies confirm cefiderocol's robust efficacy against carbapenem-resistant and MDR Gram-negative pathogens, offering therapeutic advancements for complicated urinary tract infections and hospital-acquired pneumonia.[18,83,84]

Siderophore-functionalized nanodrugs, such as gold nanoparticle–siderophore conjugates, further expand the therapeutic landscape. These targeted constructs markedly suppress *P. aeruginosa* growth—including resistant strains—achieving >95% bacterial reduction while lowering required antibiotic doses. In murine models, AuNP–NSC mitigates *P. aeruginosa*-induced skin lesions and prevents secondary sepsis-related organ failure.[19] These advances highlight innovative strategies to combat antimicrobial resistance.

Iron Competition and Host Immune Regulation

The tug-of-war over iron between host and pathogen represents a central axis of innate immune defense. During infection, bacterial pathogens depend on iron as an essential cofactor for replication and metabolic activity, whereas the host employs a repertoire of iron-sequestration strategies to reinforce antimicrobial protection. Accordingly, host immune cells such as neutrophils and macrophages secrete LCN2, which binds siderophore–iron complexes and prevents bacterial iron reacquisition.[85] In response to this iron restriction, pathogens upregulate siderophore biosynthesis and iron uptake systems as compensatory mechanisms.

Certain pathogens—most notably *Bacillus anthracis*—have evolved siderophores capable of evading LCN2 sequestration. Petrobactin, for example, exhibits chemical modifications that prevent LCN2 recognition, ensuring sustained iron uptake within the host environment.[80] In contrast, siderophores such as enterobactin from *Escherichia coli* are readily captured by LCN2, whereas its glycosylated derivative salmochelin escapes immune detection, thereby circumventing host iron-withholding strategies.[38,86]

To counter siderophore-mediated immune evasion, researchers are engineering LCN2 variants with expanded siderophore-binding spectra. Structure-guided protein design has yielded LCN2 derivatives capable of binding diverse siderophores—including those from *Pseudomonas aeruginosa* and even petrobactin from *B. anthracis*—thereby enhancing sequestration of multiple siderophore–iron complexes and improving antimicrobial performance.[87] Tailored LCN2 variants may eventually be optimized to target pathogen-specific siderophores as adjunctive therapies for acute or persistent infections. Nevertheless, these engineered proteins face several translational barriers, including immunogenicity, variable in vivo stability due to protease susceptibility, and inconsistent efficacy across infection models, necessitating comprehensive pharmacokinetic and long-term safety evaluations before clinical application.

Beyond regulating bacterial growth, siderophores exert additional virulence-associated effects. Enterobactin, for instance, targets the heme prosthetic group of host myeloperoxidase (MPO), inactivating enzymatic function and diminishing oxidative bactericidal capacity.[29] As MPO is a key iron-dependent peroxidase required for neutrophil-mediated killing, LCN2 binding of enterobactin helps maintain MPO functionality and enhances antimicrobial potency.[88] LCN2 is stored within neutrophil granules and released rapidly as a first-line response to infection. Moreover, infection induces additional LCN2 expression through Toll-like receptor (TLR) activation and cytokine signaling.[89] Despite these protective mechanisms, MPO inactivation and LCN2-mediated rescue differ markedly across tissues, infection contexts, and inflammatory states, highlighting the context dependence of siderophore–immune interactions.

Siderophores also modulate host immune signaling. Numerous studies show that siderophores induce cytokine and chemokine production—including IL-6, IL-8, CCL20, and LCN2—thereby promoting immune cell recruitment.[90,91] Enterobactin induces IL-8 expression in human respiratory epithelial cells,[92] while desferrioxamine (DFO) stimulates IL-8 production via p38 MAPK signaling in vitro.[93] Despite these effects, the magnitude and direction of immune activation vary

substantially with siderophore type, concentration, species, and tissue microenvironment. Excessive immune activation may exacerbate inflammation or tissue injury, complicating therapeutic exploitation of siderophore-induced immune responses.

Siderophores also activate transcription factors such as hypoxia-inducible factor–1α (HIF-1α). Under hypoxic or iron-limited conditions, prolyl hydroxylases responsible for HIF-1α ubiquitination lose essential iron cofactors, stabilizing HIF-1α and promoting transcription of antimicrobial genes—including antimicrobial peptides, inflammatory mediators, granule proteases, and phagocytosis-related factors.[94–96] HIF-1α activation also enhances macrophage phagocytosis via p38 MAPK and increases inducible nitric oxide synthase (iNOS) expression, thereby augmenting reactive nitrogen species production to combat intracellular pathogens.[97,98] However, in vivo variability in HIF-1α activity—shaped by oxygen gradients and iron availability—can lead to inconsistent antimicrobial outcomes. Importantly, many immunomodulatory effects attributed to siderophores in vitro may reflect iron chelation rather than siderophore-specific signaling. Mechanistic dissection is further complicated by variability across cellular models, infection contexts, and physiological states. Whether these immunological effects can be harnessed therapeutically—or pose risks of pathological hyperinflammation—requires careful investigation.

Intriguingly, siderophores also induce profound cellular responses by disrupting organellar iron homeostasis. Iron chelation triggers PINK1/Parkin-independent mitophagy, which supports mitochondrial quality control and enhances resistance to infection.[99] In *Caenorhabditis elegans*, inhibition of mitophagy increases susceptibility to *P. aeruginosa* infection and lethality, underscoring mitophagy's role as a protective host mechanism.[100] Yet translating siderophore-induced mitophagy into therapeutics is challenging due to model-dependent variability, uncertain efficacy in mammalian systems, and potential mitochondrial toxicity during prolonged iron depletion. Rigorous in vivo validation is therefore essential.

Overall, siderophores profoundly shape host–pathogen dynamics by modulating iron availability, immune responses, and cellular stress pathways. However, their functional consequences vary widely across species, models, and physiological contexts. Many discoveries stem from reductionist systems, and their relevance in complex in vivo settings remains unresolved. Thus, while siderophore–immune crosstalk represents an enticing frontier for therapeutic innovation, its inherent complexity necessitates cautious interpretation and systematic experimental validation before clinical translation.

Siderophore Pathway Inhibitors

Beyond exploiting siderophores as delivery vehicles, targeting the enzymatic machinery of siderophore biosynthesis or transport constitutes a promising anti-infective strategy. Non-ribosomal peptide synthetases (NRPSs) are central to many bacterial siderophore biosynthetic pathways, catalyzing the assembly and modification of siderophore precursors. Inactivating NRPSs effectively blocks siderophore production, severely compromising bacterial iron acquisition and competitive fitness.[101] A growing body of evidence demonstrates that natural products, synthetic inhibitors, and nanoparticles can effectively suppress siderophore biosynthesis, functionality, or transport.[27] Moreover, inhibition of transacetylases such as SidF and SidL—enzymes involved in siderophore biosynthesis in fungi—represents a promising avenue for antifungal drug development.[102] Siderophores also regulate quorum sensing and virulence factor expression.[2,60,68] In *P. aeruginosa*, pyoverdine modulates multiple virulence determinants, including exotoxin A and pyoverdine itself, which play central roles in pathogenicity. Thus, small-molecule inhibitors targeting siderophore-mediated signaling pathways may offer dual benefits: suppressing both iron acquisition and virulence expression. Together, these findings establish a robust foundation for the development of innovative therapeutics targeting siderophore pathways.

Therapeutic Applications

Antibacterial Therapy

Siderophore–Antibiotic Conjugates

The research landscape surrounding siderophore–antibiotic conjugates (SACs) charts a coherent progression from fundamental mechanistic discoveries to clinical translation, firmly anchored in the "Trojan horse" strategy. This paradigm leverages bacterial iron uptake systems to overcome outer membrane permeability barriers and selectively target multidrug-resistant Gram-negative pathogens (Table 3). Foundational insights stem from naturally occurring sideromycins

Table 3 Siderophore–Antibiotic Conjugates

Antibiotic Class	Conjugate Name	Siderophore Type	Mechanism of Action	Antibacterial Activity	Development Status/Clinical Limitation	References
tRNA synthetase inhibitor	Albomycin	Trihydroxamate	Peptidase cleavage after transport releases active moiety; Inhibits protein synthesis	MIC 100× lower than ampicillin in *E. coli*	Natural product	[104]
Aminoglycosides	Salmycins	Trihydroxamate	Iron reduction triggers intramolecular release	MIC 10 nmol L^{-1} for resistant *staphylococci/ streptococci*	Natural product	[104]
β-Lactams	Trihydroxamate-β-lactam	Synthetic trihydroxamate	Mimics Albomycin's iron-chelation	Delays *E. coli* growth	Lab research	[105]
	Tri-catechol-amoxicillin	Synthetic catechol mimic	Acetylated catechol as prodrug; Iron-dependent transport	MIC 0.05–0.39 μmol L^{-1} (*P. aeruginosa*) under iron limitation	Lab research	[106]
	Enterobactin-ampicillin	Natural enterobactin (Ent)	Enhances recognition and selectivity	MIC 1000× lower (*E. coli*)	Lab research	[107]
	Glycosylated Ent-β-lactam	Mono/di-glycosylated Ent	Mimics salmochelin; Iron-mediated transport	1000× more potent (*E. coli*)	Lab research	[108]
	Mono-catechol-aminopenicillin	Simplified mono-catechol	Bacterial uptake via recognition	30–60× lower MIC than piperacillin (*P. aeruginosa*)	Lab research	[109]
	Cefiderocol	Simplified mono-catechol	Siderophore transport; Diffuse by porin and inhibits cell wall synthesis	Effective against carbapenem-resistant strains	FDA approved (2019)	[12,82,110,111]
Monobactams	Pirazmonam	Hydroxypyridone	Imidazolinone linker; Iron transport	MIC 0.5 μg·mL^{-1} (*P. aeruginosa*) vs 4 μg·mL^{-1} for aztreonam	Early research	[112]
	U-78608	Hydroxypyridone	Triazolone linker optimized	MIC_{90} = 2 μg·mL^{-1} (*P. aeruginosa*)	Early research	[113]
	MC-1	Hydroxypyridone	Propanediol replaces methyl for better uptake	MIC_{90} = 0.5 μg·mL^{-1} (*P. aeruginosa*)	Preclinical	[114]
	BAL30072	Hydroxypyridone	Aminothiazole side-chain modified	MIC_{90} = 4/8 μg·mL^{-1} (*P. aeruginosa*/ *A. baumannii*)	Phase I halted (hepatotoxicity)	[115]
Quinolones	Ciprofloxacin-Pyochelin	Natural Pyochelin	Acetal linker cleavage releases drug	MIC_{90} = 0.6 μmol·L^{-1} (*P. aeruginosa* PAO1)	Premature linker hydrolysis	[116]
	"Trimethyl-lock"-Ciprofloxacin	Synthetic siderophore	Iron reduction triggers lactonization	Weaker than free ciprofloxacin	Needs cleavage optimization	[117]
	Ent-Ciprofloxacin	Natural enterobactin	IroD esterase releases drug	Pathogen-specific inhibition (*E. coli*)	Dependent on IroD	[118]
	Ent-SS-Ciprofloxacin	Natural enterobactin	GSH reduces disulfide bond	Effective in dense *E. coli* colonies only	Disulfide instability	[119]
	Tri-catechol-Ciprofloxacin	Synthetic tri-catechol	Piperazine linker improves uptake	MIC = 8 μg·mL^{-1} (*P. aeruginosa*)	Lower than parent drug	[120]
Oxazolidinones	Linezolid-Catechol	Synthetic catechol	Non-cleavable linker; Direct inhibition	MIC = 128 μmol·L^{-1} (*P. aeruginosa*)	Limited activity	[121]
	Oxazolidinone-Pyochelin	Natural Pyochelin	Unclear cleavage mechanism	Poor activity	Research discontinued	[122]
	Cephalosporin-Oxazolidinone	Synthetic catechol	β-lactamase releases drug	Active against ADC-1 β-lactamase-expressing *A. baumannii*	Lab research	[123]
Broad-spectrum	Desferridanoxamine-Triclosan	Natural Desferridanoxamine	Phenolic bond cleavage releases triclosan	Similar to free triclosan	Risk of extracellular premature cleavage	[124]
Glycopeptides	Di-catechol-Teicoplanin	Synthetic di-catechol	Inhibits A. baumannii cell wall synthesis	MIC = 0.8 μmol·L^{-1} (vs 25 μmol·L^{-1})	Lab research	[125]

such as albomycin and salmycins, in which trihydroxamate siderophores are covalently linked to potent antibacterial domains. These conjugates hijack native iron import pathways to traverse the outer membrane, subsequently releasing active payloads within the cell and exhibiting substantially enhanced antibacterial activity compared with their parent molecules.[103] Building on these natural precedents, extensive efforts have focused on constructing synthetic SACs, with β-lactam conjugates emerging as the most successful class due to their periplasmic targets and compatibility with siderophore-mediated transport.

Cefiderocol—the first approved siderophore–cephalosporin conjugate—exemplifies the success of this approach. Designed specifically to combat infections caused by carbapenem-resistant Gram-negative pathogens, cefiderocol employs three synergistic mechanisms: (1) enhanced permeation through outer membrane iron uptake pathways; (2) efficient periplasmic delivery of the β-lactam payload to inhibit cell-wall synthesis; and (3) intrinsic stability against carbapenemases and extended-spectrum β-lactamases.[126] Its monocatecholate motif coordinates Fe^{3+} and selectively engages TonB-dependent receptors such as PiuA in *Pseudomonas aeruginosa* and CirA/Fiu in *Escherichia coli*, thereby conferring exceptional potency against refractory pathogens.[12,82,110,111] The clinical approval of cefiderocol constitutes the first definitive validation of siderophore-guided antibiotic delivery.

Biomimetic siderophore engineering has further diversified the SAC repertoire. Glycosylated enterobactin–β-lactam conjugates that recapitulate salmochelin architecture exhibit exquisite specificity for *E. coli* strains expressing the IroN receptor, enhancing antibacterial activity by more than three orders of magnitude.[108,118] For cytoplasm-targeting antibiotics such as quinolones and oxazolidinones, a variety of cleavable linkers have been devised. Acetal-linked ciprofloxacin–pyochelin conjugates retain activity against *P. aeruginosa* but suffer from premature hydrolysis ex vivo.[116] In contrast, ortho-hydroxycinnamic acid linkers featuring a trimethyl-lock motif enable iron-triggered lactonization and payload release, offering a refined strategy for intracellular drug activation.[117] Enzyme-responsive systems, such as enterobactin–ciprofloxacin conjugates cleaved by pathogen-specific IroD esterases, further highlight the potential for selective activation.[118] Additionally, siderophore conjugation has been exploited to broaden the spectrum of certain antibiotics. A bis-catecholate teicoplanin conjugate, for instance, exhibits potent activity against *Acinetobacter baumannii*, reducing MIC values from 25 μmol/L to 0.8 μmol/L.[125]

Despite the clinical success of cefiderocol, growing epidemiological and molecular evidence indicates that Gram-negative bacteria are rapidly evolving resistance mechanisms that compromise SAC efficacy. TonB-dependent receptor (TBDR) loss or alteration is among the most prominent mechanisms. Clinical isolates of *Enterobacter cloacae, Klebsiella pneumoniae*, and *P. aeruginosa* recovered during cefiderocol therapy often display loss-of-function mutations or downregulation of *cirA, fiu, piuA*, and *piuD*, resulting in significantly impaired siderophore-mediated transport and increases in MIC exceeding an order of magnitude.[127–129] These observations underscore the dependence of SAC activity on intact iron acquisition pathways.

A second major resistance mechanism involves β-lactamase-mediated degradation. Although cefiderocol is engineered to evade many serine carbapenemases, several metallo-β-lactamases (MBLs)—including NDM-1, NDM-5, and VIM variants—efficiently hydrolyze the cephalosporin core.[130–132] Clinical failures in NDM-producing *Enterobacterales* correlate with the high catalytic efficiency of these enzymes. In *A. baumannii*, PER-type β-lactamases synergize with TBDR downregulation to produce high-level resistance, often with MICs >32 mg/L.[133]

Beyond enzymatic degradation, cell envelope remodeling and efflux pump upregulation further contribute to resistance. Changes in lipooligosaccharide structure, porin loss, or global iron-regulation (eg, Fur, PvdS) alter siderophore receptor expression, reducing SAC uptake.[134,135] Overexpression of efflux systems—such as MexAB-OprM in *P. aeruginosa* and AdeABC in *A. baumannii*—diminishes intracellular cefiderocol accumulation, whereas efflux-deficient mutants regain susceptibility.[136,137] Collectively, these multifaceted resistance pathways highlight bacterial capacity to simultaneously impair siderophore recognition, weaken β-lactam stability, and restrict periplasmic drug delivery.

These challenges emphasize the need for next-generation SACs capable of engaging multiple receptors, resisting MBL hydrolysis, and limiting efflux susceptibility. Incorporating mechanistic insights into receptor promiscuity, linker chemistry, and drug activation will be crucial for designing more durable SAC platforms.

Contemporary obstacles include optimizing linker design to ensure in vivo stability while maintaining efficient intracellular release, and developing strategies to bypass receptor downregulation or efflux activation. MC-1, for

instance, leverages specific TBDRs to bypass porin-mediated resistance.[114] Safety concerns, such as hepatotoxicity associated with BAL30072, further reinforce the importance of meticulous toxicological evaluation.[115] Looking ahead, pathogen-tailored siderophore scaffolds, multifunctional conjugate designs, and AI-driven optimization are poised to accelerate the development of the next generation of SAC candidates. Although most SACs remain in preclinical or investigational stages, the strategy holds transformative potential for reshaping antibacterial chemotherapy in an era of escalating resistance.

Siderophore–Non-Antibiotic Conjugates

Siderophore–non-antibiotic conjugates represent a powerful and versatile extension of the "Trojan horse" paradigm, exploiting bacterial iron acquisition machinery to deliver unconventional antimicrobial payloads—including metal complexes, peptides, nucleic acids, vaccines, and nanomaterials—across the Gram-negative outer membrane (Table 4). Beyond facilitating cellular entry, these constructs reprogram bacterial iron metabolism, disrupt redox balance, or activate host immunity, enabling multimodal therapeutic activity against drug-resistant pathogens.[138,139] Distinct from siderophore–antibiotic conjugates, these non-antibiotic variants often prioritize multifunctionality, integrating imaging, immunomodulation, or photodynamic therapy. However, they must overcome challenges including iron competition, linker stability, and the biochemical heterogeneity of infection microenvironments. As the field transitions from mechanistic proof-of-concept to preclinical validation, notable advancements have emerged in xenometal-based therapeutics and siderophore-targeted vaccines.

Metal complexes constitute one of the most mature and rigorously explored classes of siderophore–non-antibiotic payloads. Siderophore conjugation enables xenometals such as gallium and platinum to mimic ferric iron, entering bacteria through TonB-dependent receptors and subsequently disrupting essential iron-driven pathways, causing growth inhibition or cytotoxicity (Figure 5A and B). Galbofloxacin, a Ga(III)-complexed ciprofloxacin analog delivered via linear desferrichrome, exhibits an MIC_{98} of 93 nM against *Staphylococcus aureus*, outperforming ciprofloxacin (0.9 μM) and yielding significant bacterial load reduction and survival benefits in murine soft-tissue infection models.[140] Similarly, PEG–desferriamine:gallium (PEG–DG) conjugates potentiate vancomycin activity against *Pseudomonas aeruginosa*, increasing membrane permeability and demonstrating activity against multidrug-resistant isolates.[141] These xenometal agents enter via TonB-dependent systems, liberate metal ions intracellularly, and synergize with photothermal/photodynamic strategies to enhance bactericidal effects.[149] Platinum(IV)–siderophore conjugates expand this platform further. Enterobactin–Pt(IV) constructs (eg, d-Ent-Pt(IV)) achieve ~72% growth inhibition and induce DNA damage in *E. coli* under iron-limited conditions, yielding >10-fold increases in intracellular Pt accumulation with reduced mammalian cytotoxicity.[142] Payload-dependent selectivity has also been observed: platinum conjugates preferentially target Gram-negative bacteria, causing DNA lesions and morphological disruption.[143] Transcriptomic studies indicate that xenometal–siderophore constructs disrupt iron uptake and siderophore biosynthesis pathways in *S. aureus*, positioning them as candidates for narrow-spectrum therapies.[150] Despite their promise, xenometal conjugates face translational challenges. Metal–ligand stability varies in physiological fluids, premature metal release may increase host toxicity, and competition with endogenous metal-binding pathways may reduce therapeutic precision. Furthermore, in vivo pharmacokinetics, biodistribution (including hepatic and renal accumulation), and long-term biocompatibility remain insufficiently characterized. Systematic toxicological and pharmacokinetic studies are urgently needed to advance these constructs toward clinical translation.

Short antimicrobial peptides (AMPs) benefit markedly from siderophore-guided delivery. Peptides such as $K(RW)_3$—ordinarily inactive against Gram-negative bacteria due to outer-membrane exclusion—demonstrate potent antibacterial activity when conjugated to desferrioxamine or hydroxypyridinone scaffolds. These conjugates achieve MICs of 2 μM against *P. aeruginosa* in iron-limited conditions through FoxA-mediated uptake followed by membrane disruption (Figure 5C).[144] Parallel strategies have enabled nucleic acid therapeutics to penetrate Gram-negative bacteria. Catecholate-mimetic siderophore carriers transport antisense oligonucleotides or plasmids intracellularly with >80% delivery efficiency, enabling gene silencing through TonB-dependent uptake and endosomal escape (Figure 5E).[145] This represents a significant breakthrough in overcoming the longstanding permeability barrier of Gram-negative pathogens to genetic therapeutics.

Table 4 Siderophore–Non-Antibiotic Conjugates

Functional Category	Delivery Format	Representative Strategy	Target Bacteria	Mechanism of Action	Effect	Challenge	References
Metal metabolism disruption	Metal complex conjugate	Desferrichrome-Ga(III)-Ciprofloxacin (Galbofloxacin)	*S. aureus*	Iron competition, inhibits iron enzymes	MIC_{98} = 93 nM; superior to ciprofloxacin (0.9 μM); effective in mice	Iron competition, metal stability	[140]
	Polymer-metal conjugate	PEG-DG-Ga(III)	*P. aeruginosa*	Enhanced permeability + vancomycin synergy	Effective on resistant strains, MIC significantly reduced	Nano-structure design complexity, long-term safety	[141]
	Pt(IV) conjugate	Ent-Pt(IV)	*E. coli*	10× increased Pt uptake, reduced toxicity	72% inhibition, less toxic	Pt-loading strategy, stereochemistry	[142]
	Pt(IV) conjugate	d-Ent-Pt(IV)	G^- bacteria	DNA damage + morphological change	Activity depends on Pt load	Linker stability	[143]
Membrane disruption	Peptide conjugate	DFO-$K(RW)_3$, Hydroxy-Py-$K(RW)_3$	*P. aeruginosa*	FoxA-mediated transport, membrane lysis	MIC reduce to 2 μM, broad-spectrum potential	G^- FoxA expression heterogeneity	[144]
Nucleic acid delivery	Nucleic acid conjugate	Catechol-Fe(III)-ASO/Plasmid	G^- bacteria	Antisense silencing of resistance genes	>80% delivery efficiency, high specificity	Delivery system targeting	[145]
Photothermal/ Multimodal therapy	Nanostructure conjugate	AuNP-NHC-Fe(III)	MDR *P. aeruginosa*	Imaging + intracellular sterilization	>90% efficacy; diagnostic + therapeutic	Nanoparticle metabolism, uptake specificity	[19]
Biofilm inhibition	Small-molecule hybrid	Benzothiazole-hydroxamate-Fe (III)	*P. aeruginosa*	QS inhibition + iron disruption	IC_{50} = 0.4 μM; antibiotic synergy	Pharmacokinetic stability	[138]
Targeted immune vaccines	Siderophore-vaccine conjugate	Gluco-MAA-Crm197	*Salmonella*	Targets iron system for immunity	Strong protection; spares commensals	Need to confirm microbiome compatibility	[146]
	Siderophore-vaccine conjugate	Ybt-CTB, Aerobactin-CTB	*UPEC* (*E. coli*)	Induces immunity via iron uptake inhibition	100× reduction in bacterial load	Complex multivalent design	[20]
Diagnosis and treatment	Multivalent chelate probe	DOTAM-Fe(III)-Ab-^{68}Ga	G^+/G^- bacteria	PET imaging + antimicrobial delivery	Simultaneous diagnosis + treatment	Radiolabeling optimization needed	[147]
Suicide triggering	Peptide conjugate	TonB-Peptide-Fe(III)	*P. aeruginosa*	PfeA/PirA-mediated transport; induces programmed death	MIC reduce to 0.1 μM	Limited wild strain efficacy	[148]

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Nanotechnology significantly broadens the therapeutic repertoire of siderophore conjugates. Siderophore-functionalized gold nanoparticles (eg, AuNP–NHC–siderophores) selectively target *P. aeruginosa* through receptor-mediated internalization and integrate photothermal imaging with >90% bactericidal activity (Figure 5D).[19] Benzothiazole–hydroxamate hybrids further exploit siderophore mimicry to inhibit biofilms by sequestering iron and disrupting quorum sensing. These constructs exhibit IC_{50} values as low as 0.4 μM in *P. aeruginosa* models and synergize with tobramycin or ciprofloxacin to enhance activity (Figure 5F).[138,151] Despite their promise, nanoparticle-based siderophore platforms encounter substantial translational barriers. Biodistribution and clearance vary widely across nanomaterial classes; particle size, surface charge, and ligand density critically influence bacterial targeting versus host cell uptake; and interactions with the innate immune system introduce additional variability in vivo. Furthermore,

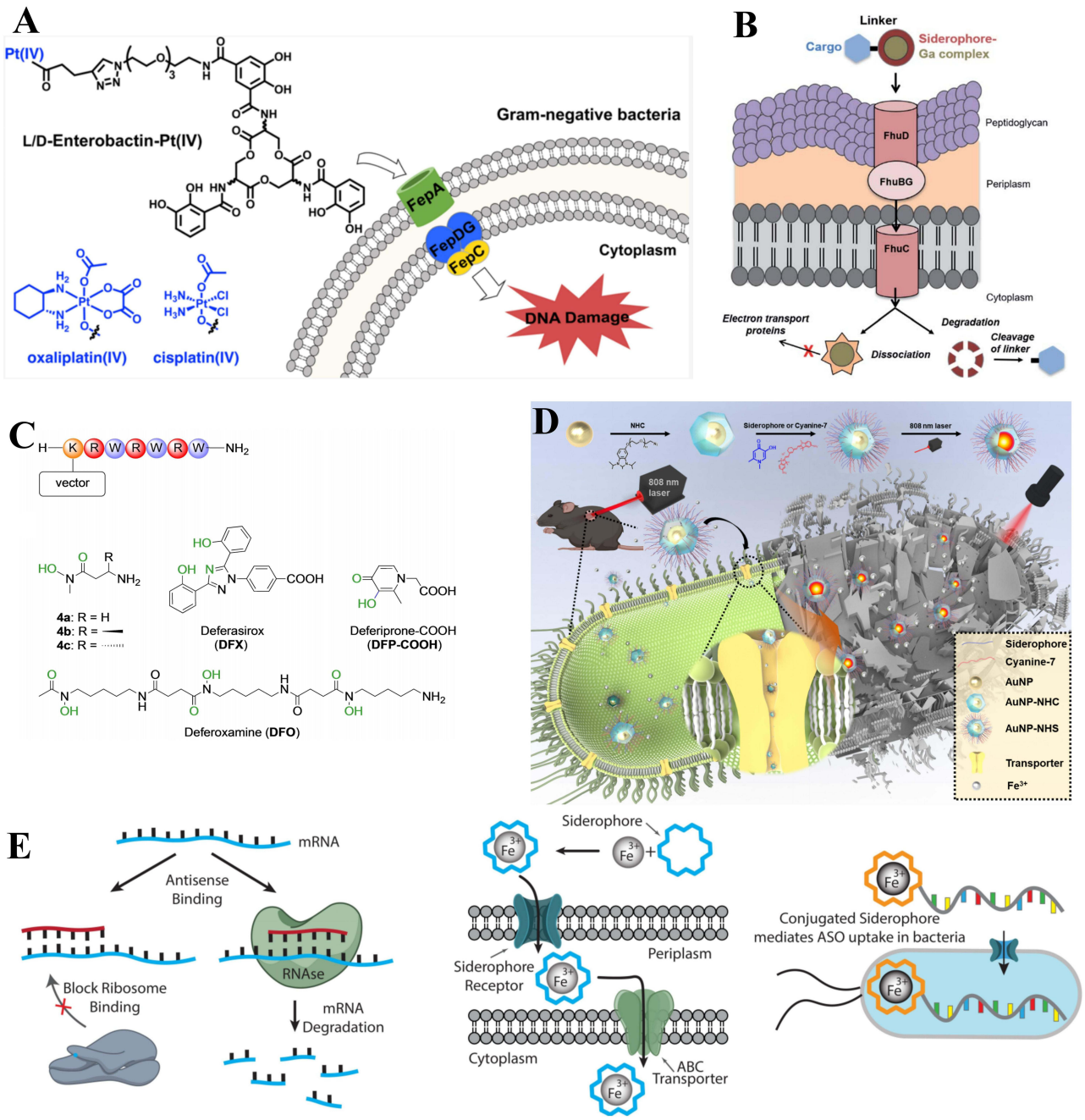

Figure 5 Continued.

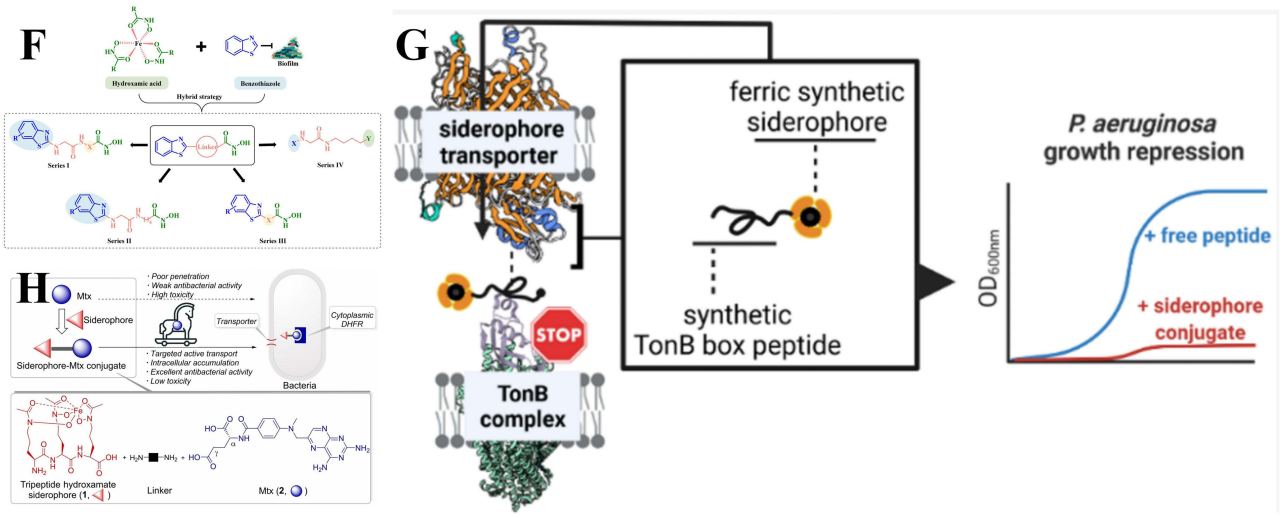

Figure 5 Strategies for siderophore-based non-antibiotic conjugates. (**A**) Siderophore–platinum (IV) conjugates reveals differing antibacterial activity and DNA damage depending on the platinum cargo.[143] (**B**) Galbofloxacin, a Ga(III)-desferrichrome-ciprofloxacin conjugate with a cleavable serine linker, is internalized into S. aureus via active transport through the ferrichrome uptake system.[140] (**C**) Schematic representation of the K(RW)3 peptide and structures of the siderophore vectors. Siderophore conjugation enhances the antibacterial activity of K(RW)3 peptides against *Pseudomonas aeruginosa* by exploiting bacterial iron uptake pathways. The most potent conjugates, P1-DFP and P1-DFX, function as "Trojan Horse" antibiotics, where the siderophore vector (iron chelator) facilitates delivery of the antimicrobial peptide into the cell.[144] (**D**) A siderophore-functionalized nanodrug based on a gold nanoparticle construct (AuNP-NSC; Gold nanoparticle_N-heterocyclic_Siderophore_Cyanine7), offering an innovative treatment modality against drug-resistant bacterial pathogens.[19] (**E**) Antibacterial ASO-siderophore conjugates exploit the bacterial siderophore-mediated iron uptake pathway to deliver antisense oligomers (ASOs) into bacteria. By conjugating a synthetic siderophore to peptide nucleic acid (PNA) or phosphorodiamidate morpholino oligomer (PMO) antisense agents targeting the essential *acpP* gene in *Escherichia coli*, these constructs achieve potent antibacterial activity through efficient internalization.[145] (**F**) Design of benzothiazole conjugated hydroxamic acid derivatives as dual-acting biofilm inhibitors.[151] (**G**) TonB box peptides were designed and coupled with synthetic siderophores in order to facilitate their uptake into bacteria in up to 32 synthetic steps. The study illustrated a variant of cellular suicide where a transporter imported its own inhibitor and demonstrated that artificial siderophores could import cargo with molecular weights up to 4 kDa.[148] (**H**) Design of siderophore-methotrexate conjugates.[152] Created with Adobe Illustrator.

challenges in scalable and reproducible manufacturing, regulatory qualification of complex nanostructures, and long-term safety assessments—including potential organ accumulation—remain significant obstacles to clinical implementation.

One of the most compelling emerging directions involves siderophore-based vaccines and theranostic platforms. These constructs target pathogen iron acquisition pathways to elicit narrow-spectrum immunity while sparing the commensal microbiota. For example, gluco-methyl anthranilate (Gluco-MAA) conjugated to carrier proteins protects mice against *Salmonella enterica*, reducing hepatic and splenic burdens and improving survival.[146] Similarly, yersiniabactin- and aerobactin-based vaccines reduce bacterial loads by ~100-fold in murine in vivo urinary tract infection models by neutralizing siderophores and inhibiting iron uptake.[20] Theranostic siderophore probes such as ^{68}Ga–DOTAM constructs enable PET imaging of infections in both Gram-positive and Gram-negative pathogens while simultaneously delivering antimicrobial payloads.[147] Notably, siderophore–peptide conjugates targeting TonB can induce lethal self-destruction ("suicide") in *P. aeruginosa*. Transport via PfeA and PirA yields MICs as low as 0.1 μM (Figure 5G).[148] These findings underscore the broad applicability of siderophore conjugation across prophylactic, diagnostic, and therapeutic modalities.

Despite these promising advances, siderophore–non-antibiotic conjugates face substantial translational barriers. Competition from endogenous siderophores, heterogeneous receptor expression, and restricted penetration within complex infection microenvironments can markedly reduce cellular uptake.[148,153] Moreover, activity against wild-type clinical isolates is frequently diminished, particularly in strains with low or variable expression of cognate siderophore receptors.[138,154] The performance of these conjugates is further shaped by linker architecture, stereochemical configuration, and stability within biological matrices—parameters that remain insufficiently explored.[142,143]

Although these systems exhibit striking in vitro potency and mechanistic sophistication, in vivo evaluation remains limited and fragmented (Table 5). Most candidates have undergone only preliminary assessment in murine infection or immunization models, with scarce data regarding pharmacokinetics, metabolic stability, potential off-target interactions, or efficacy in polymicrobial and biofilm-associated infections. These gaps—compounded by the competitive iron landscape in vivo and dynamic modulation of siderophore receptor expression during infection—underscore the need for rigorous preclinical characterization before meaningful clinical progression can occur.

Table 5 In vivo Validation Status of Leading Siderophore–Non-Antibiotic Conjugates and Key Barriers to Clinical Translation

Candidate	Type	Model	Outcomes	Hurdles	References
Ga-D2 (gallium-desferrichrome-ciprofloxacin)	Metal complex	Murine biodistribution (CBJ mice, IV injection)	Renal clearance; 13% intact in urine at 1h; Efficient bacterial uptake in vitro	Metabolic instability; Limited efficacy data; Requires enhanced stability for infection models	[155]
GaCi (gallium citrate)	Metal formulation	Murine wound infection (neutropenic BALB/c mice; topical treatment versus *K. pneumoniae* infection)	0.5–1.5 log CFU reduction; Faster wound closure; Reduced inflammation/biofilm	Topical only; Not siderophore-specific; Systemic safety unaddressed	[156]
cBSA-Ybt/Aer (yersiniabactin/aerobactin-cBSA)	Vaccine	Murine UTI (CBA/J mice; intranasal immunization; transurethral challenge versus *UPEC*)	10-126-fold reduction in urine/kidney burdens; Reduced inflammation	Carrier-dependent; undetectable antibodies; Model-specific; Needs human validation	[20]
Gluco-MAA-carrier	Vaccine	Murine infection (mice; immunization versus *Salmonella* challenge)	Reduced hepatic/splenic loads; Elevated survival	Limited to enteric pathogens; Commensal impact unknown; Preclinical only	[146]
KLH-Ent (enterobactin-KLH)	Vaccine	Dairy cows (subcutaneous immunization)	Elevated Ent-specific IgG/IgG2 in serum/milk; No adverse effects	Immunogenicity only; No demonstrated efficacy against infection; Translation to humans unclear	[157]

Future research should prioritize engineering siderophore mimics with enhanced receptor affinity and improved serum stability, integrating nanotechnology to optimize biodistribution and intracellular delivery,[19] and conducting systematic evaluations against high-priority ESKAPE pathogens.[138,140] Collectively, siderophore–non-antibiotic conjugates represent a transformative extension of the Trojan horse strategy, enabling selective, multimodal anti-infective interventions. Continued innovation in this domain is poised to expand antibiotic-repurposing opportunities (eg, methotrexate–siderophore conjugates; Figure 5H) and accelerate the development of integrated vaccine–therapeutic–diagnostic platforms, offering substantial promise for future clinical translation.[152]

In summary, siderophore-based therapeutic strategies diverge into two principal paradigms: conjugates incorporating traditional antibiotics and those employing innovative, non-antibiotic payloads. Table 6 provides a comparative overview of these approaches, outlining their mechanisms of action, developmental trajectories, and the unique challenges that shape their translational potential.

Antifungal and Antiparasitic Therapy

Siderophores also hold substantial therapeutic potential in antifungal and antiparasitic applications. As high-affinity iron chelators, siderophores disrupt fungal iron metabolism by depleting accessible iron pools essential for growth, reproduction, and metabolic homeostasis. Many fungi actively import siderophores; however, because these molecules are non-metabolizable iron traps, their internalization leads to intracellular iron starvation, thereby exerting potent antifungal effects.[158] Furthermore, siderophores exhibit synergy with established antifungal agents such as amphotericin B. For example, siderophores produced by strain GZDF3 markedly enhance antifungal inhibition against selected species, providing a conceptual foundation for developing novel biocontrol agents.[159] Siderophores may also function as targeted delivery vehicles, transporting antifungal drugs or fluorescent probes into fungal cells through receptor-mediated uptake, thereby improving specificity and therapeutic efficiency. VL-2397, a siderophore-like antifungal compound, exemplifies this strategy by entering fungal cells via the Sit1 transporter to exert potent activity.[160] Building on such insights, structural modification of siderophore scaffolds or synthesis of siderophore analogs has yielded advanced antifungal candidates, including ASP2397 and AS2488053 derived from MF-347833.[161]

In antiparasitic therapy, siderophore analogously interfere with parasite growth by targeting iron-dependent metabolic pathways. Several plant-derived secondary metabolites demonstrate antiparasitic activity through iron metabolic

Table 6 Comparative Overview of Siderophore-Based Conjugate Strategies: Antibiotic versus Non-Antibiotic Approaches

Conjugate Class	Core Mechanism	Typical Examples	Current Translational Status	Key Advantages	Major Challenges & Limitations
Siderophore–antibiotic conjugates (SACs)	"Trojan Horse" delivery: Exploits bacterial iron-uptake systems to transport conjugated antibiotics into cells, overcoming permeability barriers	β-Lactams (eg, Cefiderocol); Quinolones; Monobactams; Glycopeptides	One FDA-approved drug (Cefiderocol); Several candidates halted in clinical trials (eg, BAL30072); Majority in preclinical/ exploratory stages	Directly addresses outer membrane permeability in Gram-negative bacteria; Potent activity against multidrug-resistant (MDR) pathogens clinically validated; Builds upon known antibiotic pharmacophores	Bacterial resistance: Downregulation or mutation of siderophore receptors; Linker design: Balancing extracellular stability with efficient intracellular release; Toxicity: Some candidates exhibit off-target toxicity (eg, hepatotoxicity); Competition: Endogenous siderophores can reduce conjugate uptake
Siderophore–non-antibiotic conjugates	Utilizes the siderophore as a delivery vector for diverse, non-traditional antimicrobial agents that disrupt bacterial viability through alternative mechanisms	Metal ions (Ga^{3+}, Pt^{4+}); Antimicrobial Peptides (AMPs); Nucleic acids (ASOs); Vaccine components; Diagnostic probes (^{68}Ga).	Predominantly in preclinical research; Some imaging probes (eg, ^{68}Ga-TAFC) in clinical evaluation for diagnosis; No therapeutic conjugates approved	Novel mechanisms of action independent of traditional antibiotic targets, potentially delaying resistance; Multifunctionality: Enables combined diagnosis and therapy (theranostics), immune modulation (vaccines); Potential for narrow-spectrum, pathogen-specific therapies	Complex design and synthesis, especially for multifunctional conjugates; Limited in vivo efficacy data in complex infection models compared to SACs; Unclear pharmacokinetics and safety profiles for many novel payloads; Strong competition from native, high-affinity siderophores

disruption, highlighting the therapeutic relevance of targeting iron flux.[162] As carrier molecules, siderophores can selectively transport antiparasitic agents into parasites, thereby increasing drug efficacy while minimizing host toxicity. A ferritin-based delivery system developed by Bhatt et al achieved substantial parasite clearance in *Plasmodium* efficacy assays, illustrating the power of iron-targeted strategies.[163] Moreover, siderophore-inspired synthetic analogs and derivatives exhibit robust in vitro antiparasitic activity, charting new directions for drug development targeting iron-dependent parasitic physiology.

Diagnostic and Imaging Applications

Siderophore-based diagnostic and imaging technologies have recently demonstrated remarkable promise in infectious disease detection, leveraging the overexpression of pathogen iron uptake systems for site-specific visualization. In invasive pulmonary aspergillosis (IPA) models, Petrik et al utilized ^{68}Ga-labeled triacetylfusarinine C (TAFC) to achieve highly selective and sensitive positron emission tomography (PET) imaging in rats, clearly distinguishing infected from healthy tissues.[164] Subsequent investigations validated the in vivo stability, low nonspecific binding, and precise localization of ^{68}Ga-TAFC and ^{89}Zr-TAFC in *Aspergillus fumigatus*, highlighting strong preclinical potential.[15] For *Pseudomonas aeruginosa* infections, ^{68}Ga-labeled pyoverdine probes enable highly specific PET imaging through siderophore-mediated uptake, outperforming conventional imaging agents such as ^{18}F-FDG and ^{68}Ga-citrate in specificity and background noise suppression.[165] Beyond radionuclide-based probes, siderophore scaffolds have been adapted for fluorescent imaging. DOTAM–siderophore–fluorophore

conjugates developed by Mark et al facilitate rapid and accurate in vivo detection of *P. aeruginosa*, offering high specificity and real-time visualization capabilities.[147] In biosensing, siderophore-derived high-affinity metal-binding motifs have been incorporated into optical and electrochemical sensor platforms, enabling ultrasensitive detection of Fe^{3+} and Al^{3+} for environmental monitoring and biomedical diagnostics.[15,166] Despite these promising advances, several challenges impede widespread translation. Variations in pathogen siderophore dependency, suboptimal in vivo stability, and potential immunogenicity limit universal applicability. To overcome these barriers, future research should prioritize structural optimization to enhance biocompatibility, improve targeting precision, and development of multimodal imaging tools integrated with therapeutic functionalities. Such innovations will be crucial for achieving precision diagnostics, early detection, and personalized management of infectious diseases.

Emerging Therapeutic Strategies

Despite the considerable therapeutic promise of siderophore-based anti-infective strategies, their clinical translation remains constrained by pharmacokinetic (PK) liabilities and unwanted perturbation of host iron homeostasis.[167] PK instability arises from rapid renal filtration, extensive plasma protein binding, competitive iron exchange with transferrin or lactoferrin, and susceptibility of siderophore motifs to enzymatic degradation or oxidative cleavage.[12] Concurrently, exogenous siderophores may disrupt host iron balance by mobilizing ferritin-bound iron, competing with immune iron-withholding mechanisms, or promoting Fenton chemistry–mediated oxidative stress.[168] Overcoming these interrelated challenges requires actionable, engineering-oriented solutions that enhance stability, specificity, and biocompatibility in vivo.

Nanocarrier-based delivery systems have emerged as a powerful strategy to improve the PK profile of siderophore therapeutics. Polymeric nanoparticles, liposomes, ferritin nanocages, and metal–organic frameworks (MOFs) can shield siderophore ligands from premature iron exchange and serum degradation while prolonging circulation time and enabling controlled release at infection sites.[169–171] Encapsulation also reduces the likelihood of siderophore sequestration by host iron-binding proteins, thereby preserving high-affinity interactions with bacterial TonB-dependent receptors. Such platforms further enable co-delivery of siderophores with antibiotics or metal mimetics, enhancing intracellular accumulation and sustaining pharmacodynamic efficacy.

Parallel advances in artificial siderophore engineering provide additional solutions to specificity and toxicity constraints. By tuning chelation denticity, modifying donor groups (eg, hydroxypyridone, catechol–hydroxamate hybrids), or introducing salmochelin-like glycosylation, synthetic siderophores can evade host iron proteins while maintaining selective recognition of microbial receptors such as CirA, IroN, and PiuA/PfeA.[103,172] Computational and AI-guided scaffold optimization now enables rational prediction of stability, receptor binding affinity, and resistance avoidance, accelerating the design of species-targeted siderophore therapeutics.

Mitigating host iron toxicity is another central consideration. Conditional activation strategies—including pH-sensitive masking groups, pathogen-enzyme–triggered ligand unmasking, or microenvironment-responsive chelation—minimize unintended disruption of systemic iron pools.[4] Metal-mimetic approaches, particularly gallium substitution (Ga^{3+}), exploit bacterial iron acquisition pathways while avoiding iron-associated redox cycling and oxidative stress. Gallium-based siderophore conjugates have demonstrated strong antimicrobial activity with significantly improved safety.[173]

Hybrid systems integrating nanocarrier delivery, artificial siderophore scaffolds, and metal mimetics represent a forward-looking paradigm for constructing siderophore therapeutics with optimized PK performance, pathogen specificity, and host compatibility. Collectively, these emerging strategies transform siderophore-based therapeutics from passive "Trojan horse" systems into programmable, precision-designed platforms capable of navigating the complex iron ecology at the host–pathogen interface. Such advancements are poised to overcome long-standing PK and toxicity barriers and enable durable clinical translation.

Challenges, Limitations, and Future Directions

In the realm of infectious disease research, siderophores have emerged as pivotal targets for anti-infection therapeutics owing to their critical roles in modulating pathogen proliferation and host immune responses. Nonetheless, their clinical deployment encounters multifaceted challenges, encompassing bacterial adaptive evolution and resistance, hurdles in clinical translation, and the imperative for innovative siderophore designs alongside combination therapy paradigms.

Current Limitations and Challenges

The development and application of siderophore-based therapeutic strategies are constrained by several interconnected scientific and translational hurdles. A detailed discussion of these limitations is crucial for framing future research directions.

Hurdles in Clinical Translation and Standardization

A primary limitation is the incomplete clinical translation of siderophore-based concepts into widely available therapeutics. Despite promising preclinical data, cefiderocol remains the only SAC approved for clinical use, highlighting a significant bottleneck in moving from bench to bedside. This gap underscores the complexity of replicating in vitro success in human patients, where pharmacokinetics, pharmacodynamics, and safety profiles present unique challenges.[5] Furthermore, the field suffers from a lack of standardized evaluation methods for siderophore conjugates. Disparities in assay conditions, iron-chelation models, and efficacy metrics across studies complicate direct comparisons between candidate molecules and hinder the establishment of robust structure-activity relationships, slowing optimized drug design.

Biological and Pharmacodynamic Variability

The efficacy of siderophore-armed therapies is fundamentally influenced by pathogen biology, which introduces substantial variability. Variability in siderophore receptor expression among bacterial strains of the same species can lead to inconsistent drug uptake and efficacy, potentially allowing for treatment failure and the selection of resistant populations with downregulated receptors.[174]

Additionally, competition with endogenous siderophores during therapy poses a significant pharmacodynamic challenge. Pathogen-produced native siderophores, with typically very high affinity for their cognate receptors, can outcompete therapeutic conjugates for receptor binding and iron import, thereby diminishing the drug's effective concentration at its intracellular target.

Bacterial Adaptive Evolution and Resistance Mechanisms

Foremost, bacterial adaptive evolution and resistance constitute cardinal impediments to siderophore-targeted interventions. Iron is indispensable for bacterial viability, with pathogens secreting siderophores—often orchestrated via quorum sensing—to scavenge this nutrient from the host milieu. Prolonged exposure to siderophore antagonists or deprivation tactics may propel bacteria toward adaptive evolution through genetic mutations, horizontal gene transfer, or phenotypic plasticity. For instance, resistant strains may recalibrate iron uptake systems,[175,176] amplify alternative metal acquisition pathways (eg, manganese or copper),[177,178] or augment hijacking of host iron storage mechanisms to withstand iron sequestration stresses.[179] Moreover, the evolutionary pressure from SACs like cefiderocol can select for mutations in the siderophore receptor proteins themselves, rendering the pathogen insensitive to the conjugate.[174] Such evolutionary adaptations not only erode the efficacy of siderophore-based antimicrobial strategies but also potentially engender novel resistance phenotypes, exacerbating the prevailing antibiotic resistance crisis.

Pharmacokinetic and Stability Concerns

The clinical translation of siderophore-based strategies is further hampered by specific pharmacokinetic and stability issues. Limited in vivo stability of specific conjugates is a critical concern, as premature degradation or metabolism of the linker connecting the siderophore to the warhead (eg, an antibiotic) can sever the "Trojan horse" mechanism, releasing the active payload prematurely and reducing targeted delivery. Secondly, the pharmacokinetic attributes of siderophore antagonists in vivo—such as abbreviated half-lives, suboptimal tissue penetration and targeting, or limited selectivity across bacterial taxa—curtail their broad applicability.[5] The intricate host-pathogen interplay also renders iron metabolism interventions unpredictable; for example, host iron homeostasis mechanisms—such as hepatic hepcidin regulation—

may elicit compensatory feedback to siderophore antagonists, modulating their therapeutic outcomes.[180] Safety concerns, particularly the nonspecific effects of iron chelators that may precipitate host cellular iron deficiency and compromise innate immune functions, also remain a significant barrier.[181]

Future Directions

To overcome the aforementioned limitations, future research must focus on innovative platforms and strategic combinations.

Design of Next-Generation Siderophore Conjugates and Delivery Systems

Pursuing intelligent, multifunctional siderophore platforms is essential. This includes the development of novel conjugates with enhanced in vivo stability through the use of robust, enzymatically resistant linkers and siderophore mimetics. The creation of artificial chelators tailored to specific taxa or even broad-spectrum "universal" siderophore motifs could help bypass competition with endogenous siderophores and address receptor variability. Furthermore, advanced delivery systems—such as nanocarriers co-loaded with siderophore conjugates and iron-sequestering agents—aim to enhance the specificity, durability, and localized concentration of iron deprivation tactics.

Advancing Combination Therapies and Host-Pathogen Integrated Approaches

Combination therapies emerge as a pivotal strategy for amplifying efficacy and curbing resistance. Co-administration of SACs with other antibiotics or with pure siderophore antagonists (to saturate and block native uptake pathways) can heighten bacterial susceptibility and diminish the viability of resistant strains. Moreover, siderophore-host immunity synergies (eg, iron-modulated immunotherapy) are gaining traction. This involves leveraging host iron homeostasis perturbations to bolster innate immune cell bactericidal activity or integrating targeted vaccines against critical bacterial iron uptake systems to thwart pathogen nutrient acquisition. Establishing standardized preclinical evaluation frameworks will be crucial for reliably assessing these novel strategies.

These emergent paradigms, directly addressing current limitations, furnish expansive prospects for siderophore utilization in anti-infection modalities, potentially heralding breakthroughs against recalcitrant resistant infections.

Conclusion

Siderophores play a central role in bacterial iron acquisition, immune evasion, and virulence, making them valuable targets for anti-infection therapies. Through mechanisms such as the "Trojan horse" strategy, inhibition of iron competition, and modulation of host immune responses, siderophore-based approaches offer innovative solutions to combat multidrug-resistant infections. Cefiderocol, as the first FDA-approved siderophore-antibiotic conjugate, has set a significant precedent, demonstrating transformative potential in treating Gram-negative bacterial infections.

This review provides a novel synthesis by integrating traditional siderophore biology with the latest advances in synthetic conjugates, imaging probes, and vaccine platforms. Unlike conventional antibiotic strategies, we present a unified framework for siderophore-based therapeutics, expanding their application beyond drug delivery to include non–antibiotic conjugates that target bacterial iron metabolism, enhance diagnostic imaging, and modulate immune responses. By combining insights from iron biology, synthetic biology, and nanotechnology, we highlight the versatility of siderophores in addressing the challenges of antimicrobial resistance.

Future research should focus on optimizing siderophore conjugate designs, enhancing their specificity and stability, and expanding their use in precision therapy and diagnostics. The integration of emerging technologies such as synthetic biology and immunoengineering will be critical in advancing siderophore-based therapies, providing a powerful toolkit for combating resistant pathogens and improving patient outcomes. This review underscores the transformative potential of siderophore-based strategies in infection control and diagnostics, offering a comprehensive roadmap for future innovations in the fight against antimicrobial resistance.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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