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Bacteriophages at the Chemistry Interface: Chemical, Genomic, and Structural Strategies for Targeted Therapeutics

Kanayo Samuel Okonji[1, 2*]

[1]Department of Chemistry, Federal University Oye-Ekiti, Ekiti State, Nigeria; [2]Department of Health Sciences, University of the People, Pasadena, California, USA.

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***Correspondence**
Email: kanayosamuelokonji63@gmail.com

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ABSTRACT

This review examines the molecular chemistry and structural biology of bacteriophages as emerging targeted therapeutics, focusing on how chemical and genetic engineering can enhance phage specificity and therapeutic potential to address antimicrobial resistance. A narrative review was conducted following the Assessment of Narrative Review Articles (SANRA) guidelines. Literature searches in PubMed, Scopus, and Google Scholar (2015–2026, with inclusion of earlier seminal studies where necessary) used terms including "bacteriophage", "phage therapy", "endolysin", "holin", "phage engineering", "chemical modification", and "genomics". Studies were included if they were relevant to phage structural biology, enzymatic lysis, chemical modification, genomic annotation, or therapeutic development. Non-English publications and standalone conference abstracts were excluded. Forty references met inclusion criteria. Bacteriophages show species- and strain-specific host recognition mediated by tail fiber and baseplate variation; furthermore, genome-packaging efficiency differs among phage types, influencing replication and burst size. Chemical modifications, including conjugation of polyethylene glycol (PEG) chains (PEGylation) and surface ligand conjugation, improve phage stability, circulation time, and bacterial targeting, while clustered regularly interspaced short palindromic repeats (CRISPR)-based engineering enables customized host specificity. Hybrid phage–nanoparticle systems further enhance delivery precision and biofilm penetration. Collectively, these findings show that rational design and molecular engineering can transform natural phages into programmable therapeutic agents. Bacteriophages can be chemically and genetically engineered to enhance specificity and therapeutic potential. Their structure–function relationships, enzymatic precision, and genomic adaptability position them as promising agents against multidrug-resistant pathogens. Integrating chemistry, bioinformatics, and synthetic biology supports next-generation phage therapeutics with improved targeting and efficacy; however, programmability currently relies on empirically guided engineering rather than fully predictable design frameworks, underscoring the need for continued mechanistic research.

INTRODUCTION

Antibiotic resistance remains a global health threat, with multidrug-resistant (MDR) infections rendering conventional therapies ineffective. Globally, antibiotic resistance was responsible for an estimated 1.27 million attributable deaths in 2019, with approximately 4.95 million deaths associated with bacterial resistance [1]. It has been projected that, under a range of modeling assumptions, antimicrobial resistance could result in up to 10 million deaths annually by 2050; however, this figure is a modeled projection with inherent methodological uncertainty [2]. In this context, bacteriophages (phages), viruses that infect and lyse bacteria, have re-emerged as promising alternatives due to their high host specificity, self-amplification at the site of infection, and microbiome-sparing properties [3, 4].

Structurally, tailed DNA phages are macromolecular assemblies that function as supramolecular nanomachines. Their infection cycle such as adsorption, DNA injection, replication, and lysis is governed by precise molecular interactions [5]. Unlike broad-spectrum antibiotics, phages recognize specific bacterial receptors through evolutionarily

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adapted tail fibers and baseplate proteins. These interactions mirror principles of molecular recognition observed in ligand–receptor binding systems [6].

Key to their antibacterial action is the lytic phase, during which holins forms programmed pores in the cytoplasmic membrane, permitting endolysins accumulated in the cytoplasm to access and degrade the peptidoglycan by cleaving specific bonds within the cell wall. The resulting weakening of the cell wall leads to osmotic lysis and release of progeny [7]. These enzymes exhibit bond-specific hydrolytic activity, typically mediated by conserved active-site residues or, in some cases, metal-dependent catalytic centers [8]. Their specificity reduces off-target effects and supports narrow-spectrum therapeutic use.

Recent advances in surface chemistry, such as PEGylation and ligand conjugation, have enhanced phage pharmacokinetics and bacterial targeting [9]. In parallel, genomic sequencing and computational tools now enable rapid phage annotation, host prediction, and personalized therapeutic development [10, 11].

The integration of chemical biology, synthetic biology, and bioinformatics is transforming phages into programmable therapeutic agents with enhanced specificity and clinical potential, thereby supporting precision medicine applications. This review outlines the structural, chemical, and genomic mechanisms that underpin the development of phages as targeted therapeutics.

Molecular architecture of bacteriophages

Bacteriophages, particularly those within the class *Caudoviricetes*, exhibit a conserved modular structure comprising a protein capsid, a tail apparatus for genome delivery, and tail fibers or baseplates that mediate host recognition [5]. These structures are stabilized by non-covalent interactions, such as hydrogen bonds, electrostatic forces, and hydrophobic packing, mirroring principles of supramolecular chemistry [12].

The capsid is typically icosahedral and encloses tightly packed double-stranded DNA. Internal pressure from DNA compaction, estimated at 40–60 atm (~4–6 MPa) based on experimental measurements, drives the initial ejection of DNA during infection [13]. This compacted state is stabilized by divalent cations and DNA–protein interactions that protect the genome in the extracellular environment [13, 14].

Within the class *Caudoviricetes*, phages are often informally categorized by morphology based on the former families *Myoviridae*, *Siphoviridae*, and *Podoviridae*. These morphotypes include contractile-tailed (myovirus), long non-contractile-tailed (siphovirus), and short-tailed (podovirus) phages. Tail fibers mediate host recognition by binding to specific surface receptors, which depend on bacterial cell envelope architecture. In Gram-negative bacteria, receptors typically include lipopolysaccharides, flagella, pili, and outer membrane proteins, whereas in Gram-positive bacteria, phages commonly target teichoic acids, lipoteichoic acids, or other exposed cell wall polymers. These ligand–receptor interactions are chemically selective and determine host range [15].

Figure 1 presents a schematic representation of a model tailed bacteriophage (myovirus morphotype), highlighting its icosahedral capsid enclosing double-stranded DNA, a contractile tail sheath, baseplate, and tail fibers. The tail fibers are depicted engaging specific bacterial surface receptors, such as lipopolysaccharides and outer membrane proteins, demonstrating molecular selectivity analogous to ligand–receptor binding interactions in biological and supramolecular systems.

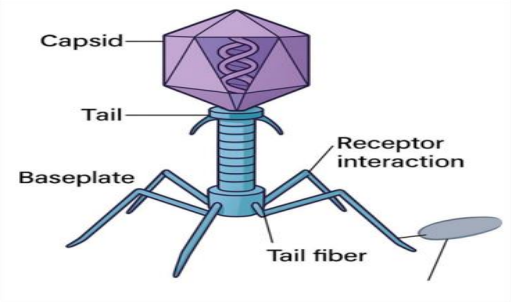


Fig. 1. Structural schematic of a tailed bacteriophage showing capsid, contractile tail, baseplate, and tail fibers binding to host receptors

Phage self-assembly is a chemically guided process involving scaffolding proteins, chaperones, and energy-dependent DNA-packaging motors. The resulting architecture functions as a targeting nanodevice, optimized through evolution for delivery precision and stability under adverse environmental conditions [16].

Understanding this architecture supports the rational design of phage-based therapeutics with enhanced infectivity, structural stability, and engineered surfaces for therapeutic use.

Mechanistic chemistry of phage–bacteria interactions

The phage–bacteria interaction is a multi-stage process governed by precise chemical recognition and structural transitions. Each step such as adsorption, genome injection, replication, and lysis demonstrates fine molecular coordination [17, 18]. The stepwise chemical and structural processes underlying phage infection are summarized in Figure 2: (1) adsorption via tail fiber ligand binding to the host receptor; (2) genome injection; (3) conformational change accompanying tail sheath contraction; (4) replication; (5) assembly of progeny virions; (6) holin–endolysin mediated lysis and virion release. Each stage emphasizes molecular interactions and catalysis.

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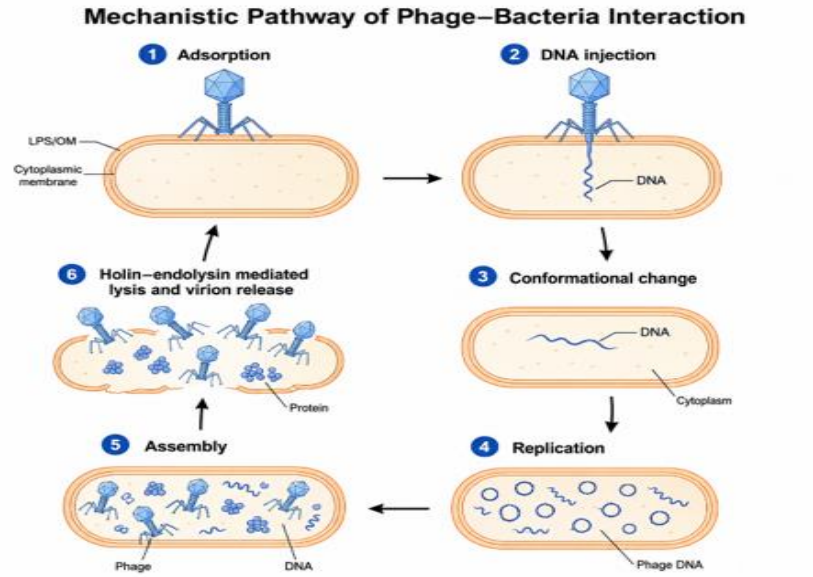


Fig. 2. Life cycle of a lytic bacteriophage, illustrating attachment, DNA injection, replication, and enzymatic lysis

Adsorption begins with reversible binding between phage tail fibers or receptor-binding proteins and bacterial surface molecules, such as lipopolysaccharides (LPS) and outer membrane proteins. These interactions rely on hydrogen bonding, hydrophobic effects, and electrostatic interactions, resembling classical ligand–receptor recognition mechanisms observed in supramolecular chemistry [6].

Upon irreversible attachment, conformational changes in the tail structure trigger genome injection. In contractile-tailed phages (myovirus morphotype) infecting Gram-negative bacteria, tail sheath contraction propels the hollow tail tube through the outer membrane, periplasm, peptidoglycan layer, and inner membrane, facilitating genome injection into the host cytoplasm. Although tail contraction itself occurs rapidly (milliseconds), complete DNA translocation can take from seconds to several minutes, depending on phage type and host conditions [19].

Following replication, phages initiate lysis through enzymes that degrade the host envelope. Holins form pores in the cytoplasmic membrane, enabling endolysins to access and degrade the peptidoglycan by cleaving glycosidic bonds (muramidase or glucosaminidase activity), amide bonds (amidase activity), peptide cross-links (endopeptidase activity), or catalyzing intramolecular transglycosylation (lytic transglycosylase activity); in Gram-negative hosts, spanins assist in disrupting the outer membrane. These enzymes exhibit site-specific catalysis, which limits off-target effects [20]. However, bacteria can rapidly develop resistance to phages through mechanisms such as receptor modification, restriction-modification systems, or CRISPR-Cas immunity [21].

The coordinated sequence of these steps highlights phages as efficient, highly selective molecular machines optimized through evolution for antimicrobial activity [18].

Enzymatic lysis: endolysins, holins, and catalytic strategies

Endolysins and holins orchestrate the final stage of phage infection, namely host cell lysis. Their enzymatic mechanisms are selective, enabling targeted bacterial killing [7].

1) Endolysins: As illustrated in Figures 3A–3E, endolysins are peptidoglycan hydrolases that cleave specific bonds within the bacterial cell wall and are commonly classified into five catalytic types: muramidases, glucosaminidases, amidases, endopeptidases, and lytic transglycosylases, based on their cleavage sites and catalytic mechanisms [8]:

(A) N-acetylmuramidases (lysozyme-type): Cleave the β-1,4 glycosidic bond between N-acetylmuramic acid (MurNAc) and N-acetylglucosamine (GlcNAc) (Figure 3A).

(B) Endopeptidases: Hydrolyze peptide cross-bridges between amino acid residues in the peptidoglycan (Figure 3B).

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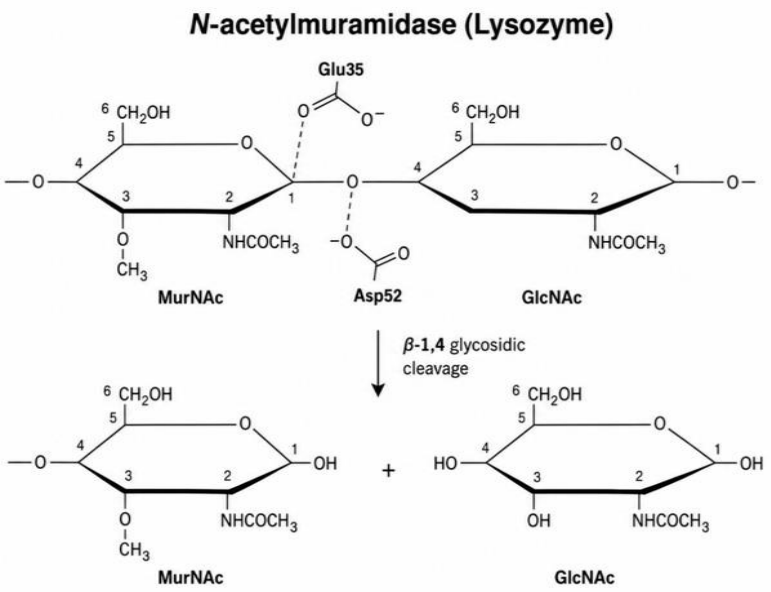


Fig. 3A. Glycosidase activity cleaves the β-1,4 linkage between *N*-acetylmuramic acid (MurNAc) and *N*-acetylglucosamine (GlcNAc) in the glycan backbone. This activity is exemplified by lysozyme-type enzymes, in which catalytic residues often include Glu and Asp.

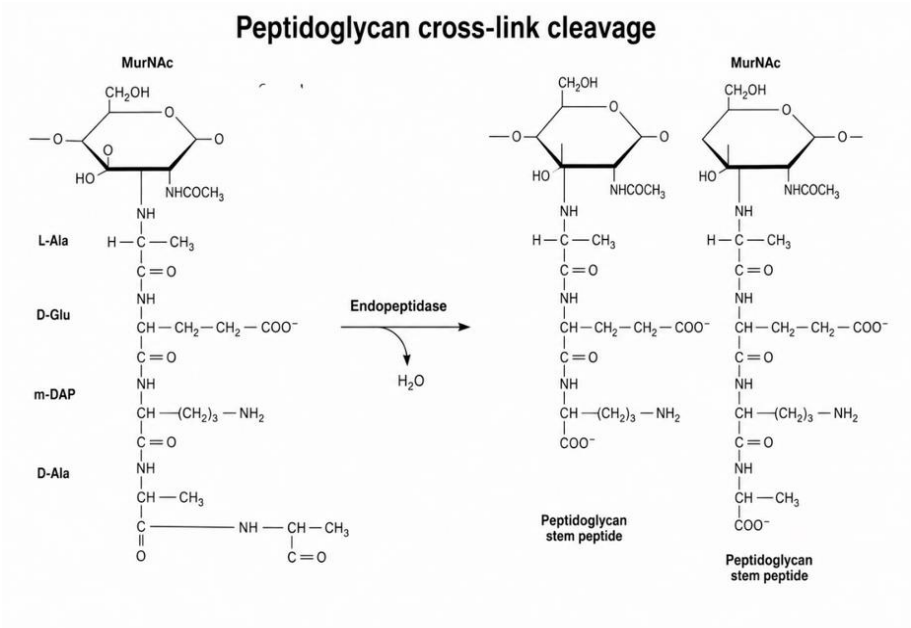


Fig. 3B. Endopeptidase activity hydrolyzes peptide bridges in cross-linked peptidoglycan, such as D-Ala–L-Lys linkages. Examples include lysostaphin and phage tail-associated muralytic enzymes

(C) Lytic transglycosylases: Similar to muramidases, but they catalyze cleavage through intramolecular transglycosylation, forming 1,6-anhydro rings at the cleavage site (Figure 3C).

(D) Amidases: Hydrolyze the amide bond between MurNAc and L-alanine at the start of the peptide stem (Figure 3D).

(E) Glucosaminidases: Cleave the β-1,4 glycosidic bond between GlcNAc and MurNAc in the peptidoglycan glycan backbone, on the GlcNAc side of the disaccharide repeat, whereas muramidases cleave on the MurNAc side (Figure 3E).

Each enzymatic class exhibits distinct active-site architectures and catalytic mechanisms, often involving acid-base catalysis, metal ion cofactors, and nucleophilic substitution. Their modularity and specificity make them attractive scaffolds for protein engineering and enzybiotic development [22].

Table 1 summarizes the catalytic types of endolysins and their mechanisms.

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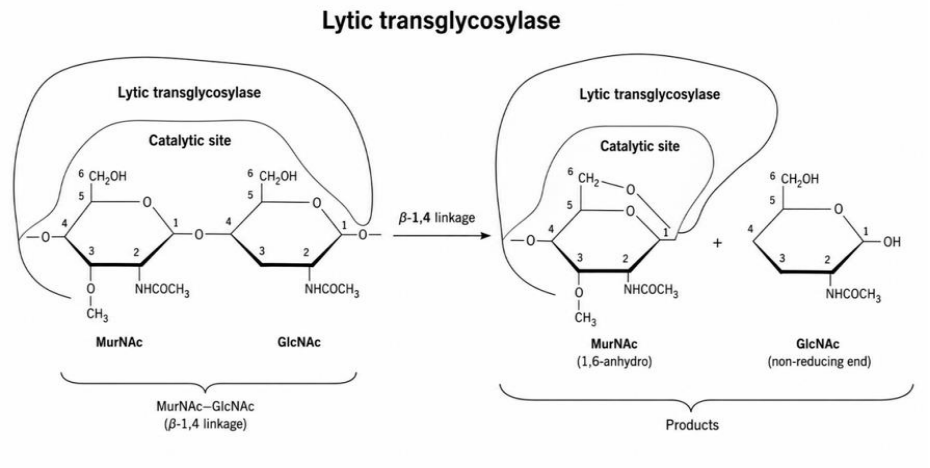


Fig. 3C. Lytic transglycosylase activity breaks β-1,4 linkages between MurNAc and GlcNAc while forming a 1,6-anhydro ring on MurNAc. Catalysis typically involves an acid/base residue facilitating intramolecular ring closure

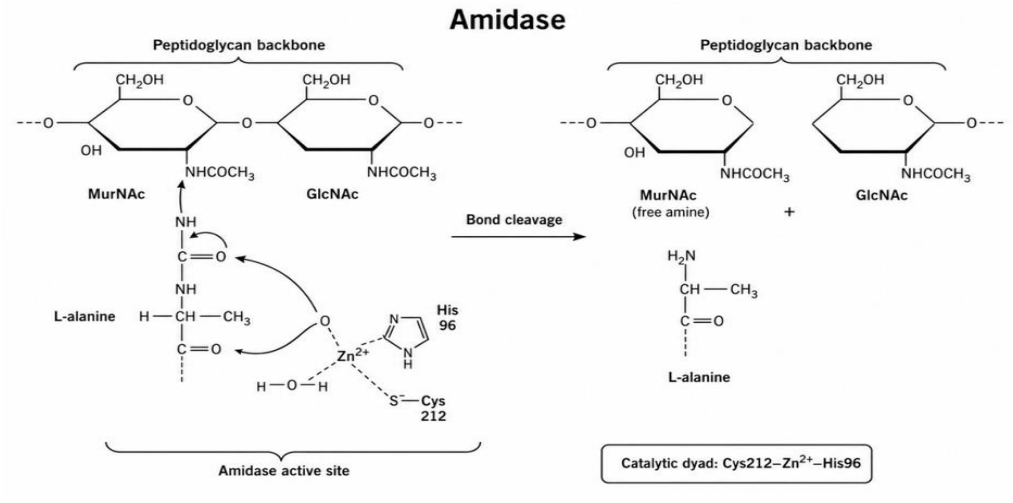


Fig. 3D. Amidase activity hydrolyzes the amide bond between MurNAc and L-alanine in the stem peptide. Representative enzymes include *N*-acetylmuramoyl-L-alanine amidases

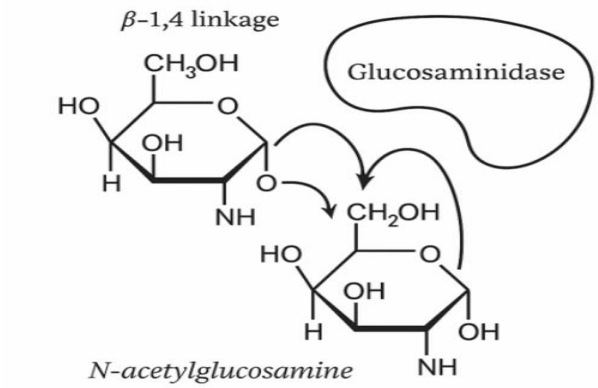


Fig. 3E. Glucosaminidase activity cleaves β-1,4 bonds between GlcNAc and MurNAc within the glycan backbone, contributing to peptidoglycan degradation. Examples include phage-associated glucosaminidases such as those found in *Bacillus* and *Streptococcus* phages, as well as other muralytic enzymes with GlcNAc-side specificity.

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Table 1. Classification of endolysin catalytic types

Catalytic type	Cleavage target	Mechanism
N-acetylmuramidase (lysozyme-type)	β-1,4 bond between MurNAc and GlcNAc	Hydrolysis
Endopeptidase	Peptide cross-bridges	Hydrolysis
Lytic transglycosylase	β-1,4 bond between MurNAc and GlcNAc	Transglycosylation (intramolecular; forms 1,6-anhydroMurNAc)
Amidase	Amide bond between MurNAc and L-alanine	Hydrolysis
Glucosaminidase	β-1,4 bond between GlcNAc and MurNAc	Hydrolysis

Note: MurNAc, N-acetylmuramic acid; GlcNAc, N-acetylglucosamine. Muramidases and glucosaminidases cleave the same β-1,4 glycosidic linkage in the glycan backbone but at different positions within the disaccharide repeat: muramidases cleave on the MurNAc side, releasing MurNAc as the reducing sugar, whereas glucosaminidases cleave on the GlcNAc side, releasing GlcNAc as the reducing sugar.

2) Holins: Holins are small, integral membrane proteins that form pores at a genetically programmed stage during phage replication. Pore formation through oligomerization enables endolysins to access the peptidoglycan. In Gram-negative hosts, additional proteins such as spanins are required for disrupting the outer membrane [23].

Endolysins and holins are being engineered into several therapeutic formats:

A) Enzybiotics: Recombinant antimicrobial enzymes, typically derived from endolysins, that exhibit selective activity toward target bacterial species, thereby minimizing off-target effects [24].

B) Fusion constructs: Endolysins linked to targeting peptides for enhanced bacterial specificity.

C) Engineered holin peptides: Designed amphipathic peptides that mimic natural holins for controlled membrane permeabilization and drug delivery [23, 25].

Together, endolysins and holins form a bond-specific and temporally regulated antibacterial strategy.

Phage engineering and surface chemistry

Modern chemistry and bioengineering have enabled the reprogramming of phages into customizable delivery platforms. Key strategies such as ligand conjugation, PEGylation, phage display, and phage–nanoparticle hybrids are summarized in Table 2.

Table 2. Surface engineering strategies for bacteriophages

Strategy	Therapeutic purpose	Method
PEGylation	Prolongs circulation time	Covalent attachment of PEG
Ligand conjugation	Targets specific bacteria	Click chemistry; amide or thiol coupling
Phage–nanoparticle hybrids	Guided delivery, imaging, and therapy	Conjugation to gold or magnetic nanoparticles
Phage display	Ligand screening	Genetic fusion with coat proteins (pIII or pVIII)

Note: PEG, polyethylene glycol; pIII, minor coat protein; pVIII, major coat protein. Phage display is a genetic engineering technique rather than a chemical modification *per se*, but is included here as a complementary surface engineering strategy.

Surface protein engineering. Researchers have functionalized phage capsid and tail proteins using click chemistry, such as copper-catalyzed azide-alkyne cycloaddition (CuAAC) or strain-promoted azide-alkyne cycloaddition (SPAAC), amide bond formation, or thiol–maleimide conjugation, to attach targeting ligands, imaging agents, and stimuli-responsive moieties [26].

PEGylation. PEGylation of phage particles enhances circulation time and reduces immune clearance; however, its effects on tissue distribution and infectivity depend on the degree and site of modification [9, 27].

Phage display. Phage display is most commonly implemented in filamentous phage platforms such as M13. This technique involves genetically fusing peptides or proteins to coat proteins (*e.g.*, pIII or pVIII) to screen for ligands that bind specific targets, including bacterial receptors and tumor antigens [28].

Advanced phage engineering strategies

Phage-nanoparticle hybrids. Hybrid constructs merge phages with synthetic materials:

A) Gold–phage constructs have been developed for photothermal ablation of biofilms.

B) Magnetic–phage constructs enable guided drug delivery.

c) Drug–phage hybrids are engineered to co-deliver therapeutic agents, such as antibiotics or biofilm-degrading enzymes, thereby enhancing bacterial killing and matrix disruption [29].

Synthetic phages. *De novo* synthesis of phage genomes and structural proteins has enabled the design of synthetic phages with enhanced host specificity, potentially reduced immunogenicity, and customized payloads [30]. These developments demonstrate phages as chemically programmable platforms, bridging nanotechnology and targeted medicine (Figure 4).

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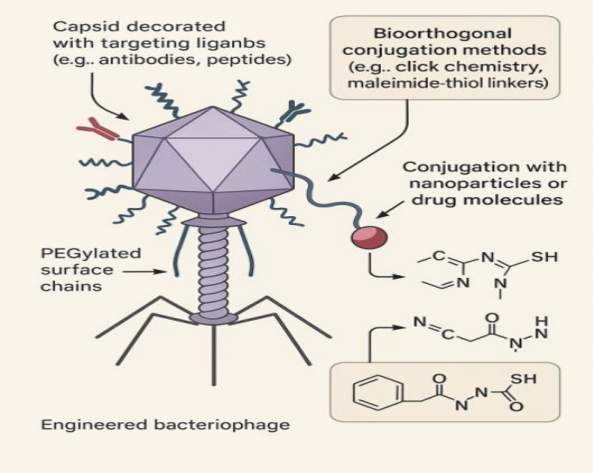


Fig. 4. Chemical modification strategies of phage surfaces, including PEGylation, ligand conjugation, and nanoparticle hybridization.

Therapeutic applications and challenges

Phage therapy is increasingly evaluated in clinical settings, particularly against multidrug-resistant pathogens.

Infectious diseases. Phage therapy has shown promising results in treating sepsis, cystic fibrosis-associated pulmonary infections, and chronic wounds. A landmark case study supports the use of personalized cocktails tailored to the patient's bacterial isolate [31], though large-scale randomized controlled trials are still needed for regulatory approval and clinical adoption.

Biofilm disruption and engineered delivery. Phages produce depolymerases and other matrix-degrading enzymes that disrupt the biofilm extracellular matrix, thereby facilitating phage penetration and enhancing bacterial killing. Phage preparations have also been incorporated into engineered delivery systems, including hydrogels and wound dressings, to improve biofilm disruption and therapeutic activity [32].

Targeted drug and gene delivery. In preclinical models, engineered phages deliver CRISPR–Cas antimicrobials for targeted bacterial genome editing [3], co-delivered antibiotics or antimicrobial peptides [29], and ligand-targeted imaging agents or gene therapy payloads [32].

Challenges. Despite these promising applications, several barriers limit clinical translation:

A) Rapid clearance by immune cells, primarily cells of the mononuclear phagocyte system (MPS), such as Kupffer cells in the liver and splenic macrophages, can limit phage circulation time and bioavailability.

B) Variable tissue distribution complicates achieving therapeutic concentrations at infection sites.

C) The lack of standardized regulatory pathways, including harmonized international frameworks and guidance specific to phage-based medicinal products, remains a major barrier to clinical implementation and broader adoption [33].

Current approaches to address these challenges include PEGylation to improve circulation and immune evasion [9], susceptibility-matched phage libraries for optimized host targeting [11], and computationally guided phage selection using machine learning and bioinformatics tools [10, 11].
Phages represent adaptable, precision-guided therapeutic agents with significant potential for targeted clinical applications [4, 31].

Genomics and bioinformatics in precision phage therapeutics

Genomic tools have transformed phage discovery and design into a rational, data-driven process. Table 3 lists commonly used bioinformatics tools for phage genome annotation and host prediction.

Table 3. Commonly used bioinformatics tools for phage genome analysis

Tool	Function	Input	Output
BV-BRC	Genome annotation	Phage genome	Gene annotations, tRNAs, CRISPR elements
Prokka	Genome annotation	Prokaryotic genome	Annotated genome
PHASTER	Phage detection	Bacterial genome	Prophage identification
PhageAI	Host prediction	Phage genome	Predicted host range
HostPhinder	Host prediction	Phage genome	Host strain prediction
RAST	Genome annotation	Bacterial genome	Subsystems-based annotated genome

Phage genome sequencing and annotation. Platforms such as Pharokka enable rapid phage genome annotation by identifying coding sequences, tRNAs, structural proteins, CRISPR-associated elements, and other functional gene categories using phage-specific databases and optimized algorithms [34]. Phages selected for therapy are strictly lytic to ensure efficient bacterial killing and to avoid the risk of transferring virulence factors or antibiotic resistance genes, a risk particularly associated with lysogenic (temperate) phages [34]. Figure 5 illustrates the genomics-informed precision phage therapy pipeline.

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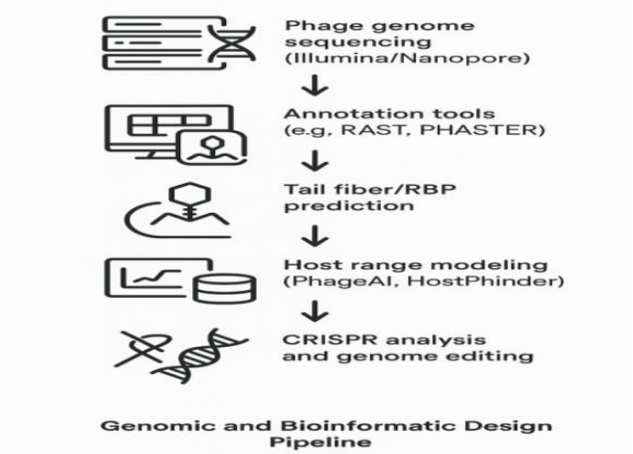


Fig. 5. Workflow of personalized phage therapy: pathogen isolation, sequencing, phage matching, and patient-specific formulation

Comparative genomics and host range prediction. Candidate therapeutic phages can be prioritized using computational tools. For example, HostPhinder predicts bacterial host genus based on tail fiber and genomic features, thereby accelerating selection without extensive wet-lab screening [35].

CRISPR–phage co-evolution. Bacterial CRISPR arrays serve as archives of prior phage infections. Conversely, phages evolve via mutations in protospacer or PAM sequences, or acquire anti-CRISPR (Acr) proteins to evade immunity [36].

Synthetic genome engineering. Using λ Red recombineering and CRISPR-based editing, researchers can reprogram phages to delete lysogeny genes, insert therapeutic payloads, or alter host tropism [37].

Toward personalized phage therapy. A growing clinical pipeline is establishing patient-specific pathogen sequencing and phage matching; however, production timelines remain variable and can extend well beyond initial estimates in complex cases. This approach will provide a foundation for scalable, precision phage therapy [38].

LIMITATION

This narrative review has several limitations. First, it relies on available literature from databases such as PubMed, Scopus, and Google Scholar, which may introduce database and selection bias. Second, the review follows the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines [39], which are designed for narrative rather than systematic reviews; nonetheless, some relevant studies may have been overlooked. Third, the reliance on published articles means that unpublished data, ongoing studies, or preprints not indexed in these databases may not have been included. Fourth, as a single-author review, it may reflect individual interpretive biases not mitigated by multi-reviewer consensus. Despite these limitations, this review provides a comprehensive overview of the chemical, structural, and genomic aspects of bacteriophages relevant to targeted therapeutics.

CONCLUSION AND OUTLOOK

Bacteriophages, foundational in molecular biology since the mid-20th century, are now being developed as chemically programmable precision therapeutics [40]. Their modular architecture, lytic enzymes, and genetic tractability support the development of targeted therapies with the potential to overcome resistance to conventional antibiotics [4, 31]. This review has highlighted how modern chemistry, structural biology, and genomics converge in the development of phages as next-generation antimicrobials.

Recommendations emerging from this review include fostering interdisciplinary collaboration between chemists, structural biologists, and microbiologists; leveraging phages' modular architecture for therapeutic design; building curated libraries of phage structural elements and catalytic domains; developing regulatory pathways suited to customizable biologics; and incorporating computationally guided selection and genomic matching to optimize therapeutic regimens. These recommendations are grounded in the evidence synthesized throughout this review. Phages offer a promising solution in the fight against antimicrobial resistance. They are precise, adaptable, and potentially customizable.

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CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest associated with this manuscript.

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AI DISCLOSURE

The authors declare that ChatGPT (OpenAI) was used solely for language polishing and grammar refinement during the preparation of this manuscript. The scientific content, data interpretation, analysis, and conclusions were developed independently by the authors, who take full responsibility for the integrity of the work.

DATA AVAILABILITY

All data analyzed in this study were derived from publicly available sources. No new experimental data were generated during this research. All cited sources are referenced in the reference list.

AUTHORS' CONTRIBUTIONS

KSO: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. The author has read and approved the final manuscript.

ETHICS STATEMENT

Not applicable. This is a narrative literature review based entirely on previously published data; no new data involving human participants, animals, or primary clinical material were collected or analyzed.

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