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Molecular Mechanisms and Precision Applications of Bacteriophages Against Multidrug-Resistant Pathogens

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Abstract

The relentless rise of multidrug-resistant (MDR) pathogens, particularly the ESKAPE group, has rendered many conventional antibiotics ineffective, necessitating alternative precision therapies. Bacteriophages (phages), the most abundant and highly specific natural predators of bacteria, have re-emerged as a cornerstone of next-generation antimicrobial strategies. This review elucidates the molecular mechanisms underpinning phage therapy, from receptor-specific adsorption and genome translocation to holin–endolysin-mediated lysis and the sophisticated lysis–lysogeny decision-making process. It details bacterial counter-defenses, including restriction-modification systems and CRISPR-Cas adaptive immunity, alongside phage counter-adaptations such as anti-CRISPR (Acr) proteins and SAM-lyases. Advances in synthetic biology have enabled precision engineering of phages, including tail-fiber reprogramming for expanded host range, CRISPR-armed phages for genotype-specific killing, and fully synthetic genomes with customizable therapeutic payloads. Phage-derived enzymes endolysins for rapid peptidoglycan hydrolysis and depolymerases for biofilm matrix degradation offer enzybiotic alternatives with minimal resistance potential. Clinical evidence from 2024–2025 trials demonstrates successful personalized phage cocktails against MDR S. aureus, P. aeruginosa, K. pneumoniae, and vancomycin-resistant enterococci, often in synergy with antibiotics. Regulatory harmonization (European Pharmacopoeia Chapter 5.31, EMA reflection paper, FDA reforms) and scalable GMP manufacturing platforms now support broader implementation. As AI-driven host-range prediction and phage–microbiome engineering mature, bacteriophage therapy is poised to deliver safe, effective, genotype-specific interventions that preserve the commensal microbiota and combat the global AMR crisis.

Keywords: Bacteriophage Therapy, Multidrug-Resistant Pathogens, ESKAPE Group, Phage Lifecycle, Endolysins, Depolymerases, CRISPR-armed Phages, Anti-CRISPR Proteins, Phage Engineering, Biofilm Disruption, Personalized Phage Cocktails, Precision Antimicrobial Therapy

Introduction

The global escalation of antimicrobial resistance has precipitated a paradigm shift in infectious

disease management, transitioning from a reliance on broad-spectrum chemical agents toward targeted, biological interventions (Baruah et al., 2024). As conventional antibiotics lose efficacy against the "ESKAPE" group comprising *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species bacteriophages have emerged as the vanguard of precision antimicrobial therapy (Konkova et al., 2025). These viruses, the most abundant biological entities on Earth with an estimated population of 10^31 to 10^32 virions, function as natural predators of bacteria, maintaining ecological equilibrium through highly specific predatory-prey dynamics (Sindhushree et al., 2025). The resurgence of phage therapy is not merely a return to historical practices but a sophisticated integration of synthetic biology, CRISPR-Cas engineering, and advanced pharmacogenomics designed to overcome the evolutionary defenses of multidrug-resistant pathogens (Coque et al., 2023).

1. Molecular Architecture and the Infection Lifecycle

The efficacy of bacteriophages as therapeutic agents is rooted in their structural simplicity and functional specialization. Typically composed of a genomic core of DNA or RNA encapsulated within a proteinaceous capsid, phages are obligate parasites that lack independent metabolic machinery (Sanz-Gaitero et al., 2021).

1.1. Host Recognition and Adsorption Kinetics

The first determinant of phage host range is the adsorption process, a three-step sequence involving random diffusion, reversible attachment, and irreversible binding. Random collision, often driven by Brownian motion or fluid flow, brings the phage into proximity with the bacterial cell (Palombi, 2021). Initial reversible binding occurs when receptor-binding proteins located on the phage tail fibers or spikes interact with primary receptors such as lipopolysaccharides (LPS), teichoic acids, or outer membrane proteins. This phase allows the phage to "scan" the bacterial surface for secondary receptors required for stable attachment (Lyu et al., 2023).

For example, in phages like T5, primary adsorption involves the O-antigen polymannose moiety of lipopolysaccharides, while irreversible binding occurs at the conical portions of the straight tail, which harbor receptor-binding proteins that attach permanently to the ferrichrome outer membrane protein, FhuA (Peng et al., 2025). The specificity is so refined that some phages, like SSU5, isolated from O-antigen-deficient Salmonella mutants, are incapable of infecting wild-type strains because the O-antigen masks the core polysaccharides needed for binding (Leprince & Mahillon, 2023). This high degree of specificity ensures that phages selectively eliminate pathogens while preserving the commensal microbiota, a critical advantage over conventional antibiotics (Beyer, 2025).

1.2. Genome Translocation and Intracellular Replication

Following irreversible attachment, the phage injects its genetic material into the bacterial cytoplasm. This process is often assisted by virion-associated enzymes, such as ectolysins or depolymerases, which locally degrade the peptidoglycan layer or capsular polysaccharides to facilitate the passage of the viral genome (Bołoz et al., 2025). Once the genetic material enters the host, the phage enters either a lytic or lysogenic cycle. Lytic phages immediately hijack the host's transcriptional and translational machinery to synthesize viral proteins and replicate the phage genome (Evstigneeva, 2025).

In the lytic cycle, the phage genome replication is followed by the synthesis of capsid proteins and the assembly of mature virions. Upon reaching a critical mass, the lytic proteins including holins

and endolysins become active (Vendrell-Fernández et al., 2025). Holins insert into the cytoplasmic membrane to create pores, allowing endolysins to access and hydrolyze the peptidoglycan cell wall, releasing novel phage progeny to reinitiate the cycle (Dotto-Maurel et al., 2025). Conversely, temperate phages may integrate their DNA into the host chromosome as a prophage, establishing a stable lysogenic relationship (Guan et al., 2020). Recent research has identified that some phages, such as VP882, utilize the host's quorum-sensing signals to inform this lysis-lysogeny decision, suggesting a level of inter-kingdom communication that allows phages to synchronize their replication with bacterial population density (Santoriello et al., 2026).

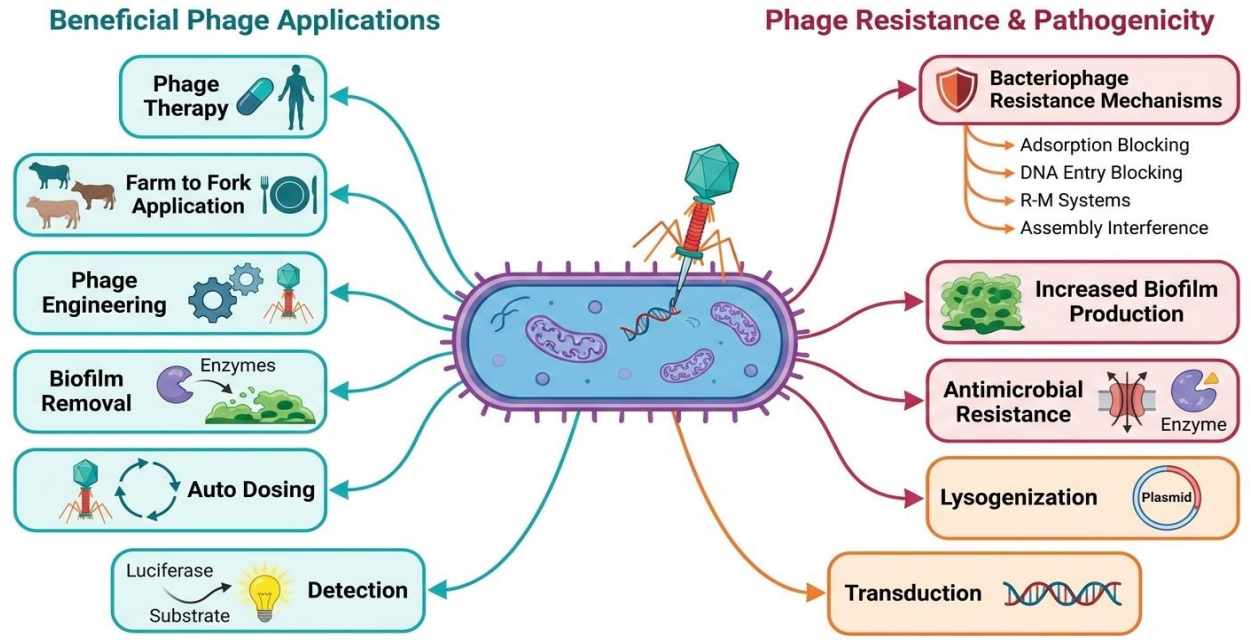
Table 1: Molecular Mediators and Functional Outcomes in the Phage Infection Lifecycle

Phase of Infection	Molecular Mediators	Functional Outcome
Adsorption	Receptor-Binding Proteins (RBPs), LPS, Teichoic Acids	Host recognition and surface attachment
Penetration	Ectolysins, Tail Sheath Contraction	Localized peptidoglycan degradation and DNA injection
Biosynthesis	Host RNA Polymerase, Viral DNA Polymerase	Replication of viral genome and capsid proteins
Assembly	Terminases, Scaffolding Proteins	Encapsidation of viral DNA into mature virions
Lysis	Holins, Endolysins, Spanins	Enzymatic breakdown of cell wall and progeny release

2. Bacterial Defense Systems and Phage Counter-Adaptations

The co-evolutionary struggle between bacteria and phages has yielded a diverse array of immune mechanisms and counter-measures. Bacteria employ several layers of defense, including restriction-modification systems, abortive infection, and the adaptive CRISPR-Cas system, to neutralize viral threats (Scholthof, 2026).

Figure 1. The Dual Nature of Bacteriophage Interactions: Beneficial Clinical Applications vs. Bacterial Counter-Defense Mechanisms.



2.1. Restriction-Modification and Methylation Dynamics

Restriction-modification (RM) systems act as an innate immune system by distinguishing between "self" and "non-self" DNA. These systems typically consist of a methyltransferase (MT) that methylates specific sequences in the host genome and a restriction endonuclease (RE) that cleaves unmethylated foreign DNA (Dimitriu et al., 2020). Phages have evolved various strategies to bypass RM systems. For instance, phages like T3 encode SAM-lyases (SAMase) that degrade the S-adenosylmethionine pool, a necessary metabolite required for DNA methylation (Liu et al., 2024). By degrading SAM and inhibiting host methylase production, phages prevent the host from protecting its own DNA, potentially leading to autoimmunity and cell death while ensuring the phage's own genome remains unmolested (Hampton et al., 2020).

2.2. CRISPR-Cas Adaptive Immunity and Anti-CRISPR Proteins

The CRISPR-Cas system provides bacteria with a form of acquired immunity. During the adaptation phase, a Cas protein complex (often Cas1-Cas2) recognizes short DNA fragments, known as protospacers, from the invading viral genome and integrates them as spacers into the bacterial CRISPR array (Mosterd et al., 2021). These spacers are later transcribed into guide RNAs that lead Cas nucleases to recognize and cleave complementary phage DNA upon subsequent infection (Watson et al., 2021).

To counter this, many phages encode anti-CRISPR (Acr) proteins. These small, diverse proteins, generally containing 80–150 amino acids, inhibit the CRISPR-Cas complex through various mechanisms (Ilyina, 2022). For example, AcrVIA1, encoded by Listeria phage LS46, inactivates the type VI-A CRISPR system by preventing the binding of targeted RNA and subsequent conformational changes of Cas13a (Meeske et al., 2020). Other phages utilize AcrIII-1, which rapidly degrades cyclic tetraadenylate (cA4) signaling molecules required to activate the type III CRISPR defense system (Hayes et al., 2025). Furthermore, phages may deploy "fast on-fast off" transcriptional bursts of Acr proteins to suppress immunity during the initial stages of infection. Interestingly, a community of acr-carrying phages may cooperate to suppress bacterial immunity, as a single phage might be destroyed while depositing enough Acr proteins to immunosuppress the cell for subsequent infections (Pons et al., 2023).

3. Precision Engineering of Therapeutic Bacteriophages

The limitations of naturally occurring phages, such as narrow host range and the risk of lysogeny, have driven the development of engineered phages using synthetic biology and nanotechnology. CRISPR-Cas technology itself has been repurposed as a tool for editing phage genomes, allowing for the precise insertion of antimicrobial payloads and the removal of undesirable genes (Onyeyili et al., 2025).

3.1. Tail Fiber Reprogramming and Host Range Expansion

One of the most promising applications of phage engineering is the modification of receptor-binding proteins to alter or broaden host specificity. By swapping tail fiber domains or utilizing de novo protein design, researchers can create phages capable of infecting multiple strains of a pathogen or even crossing species boundaries (Dams et al., 2019). Recombinant tail proteins, such as TF2 and TF6, have been derived from specific phages to recognize clinical isolates like *A. baumannii*. These engineered proteins can be immobilized onto substrates like alumina-coated magnetic nanoparticles to serve as affinity probes, enabling the rapid detection and trapping of specific bacteria from complex clinical samples like serum (Nekounam et al., 2022).

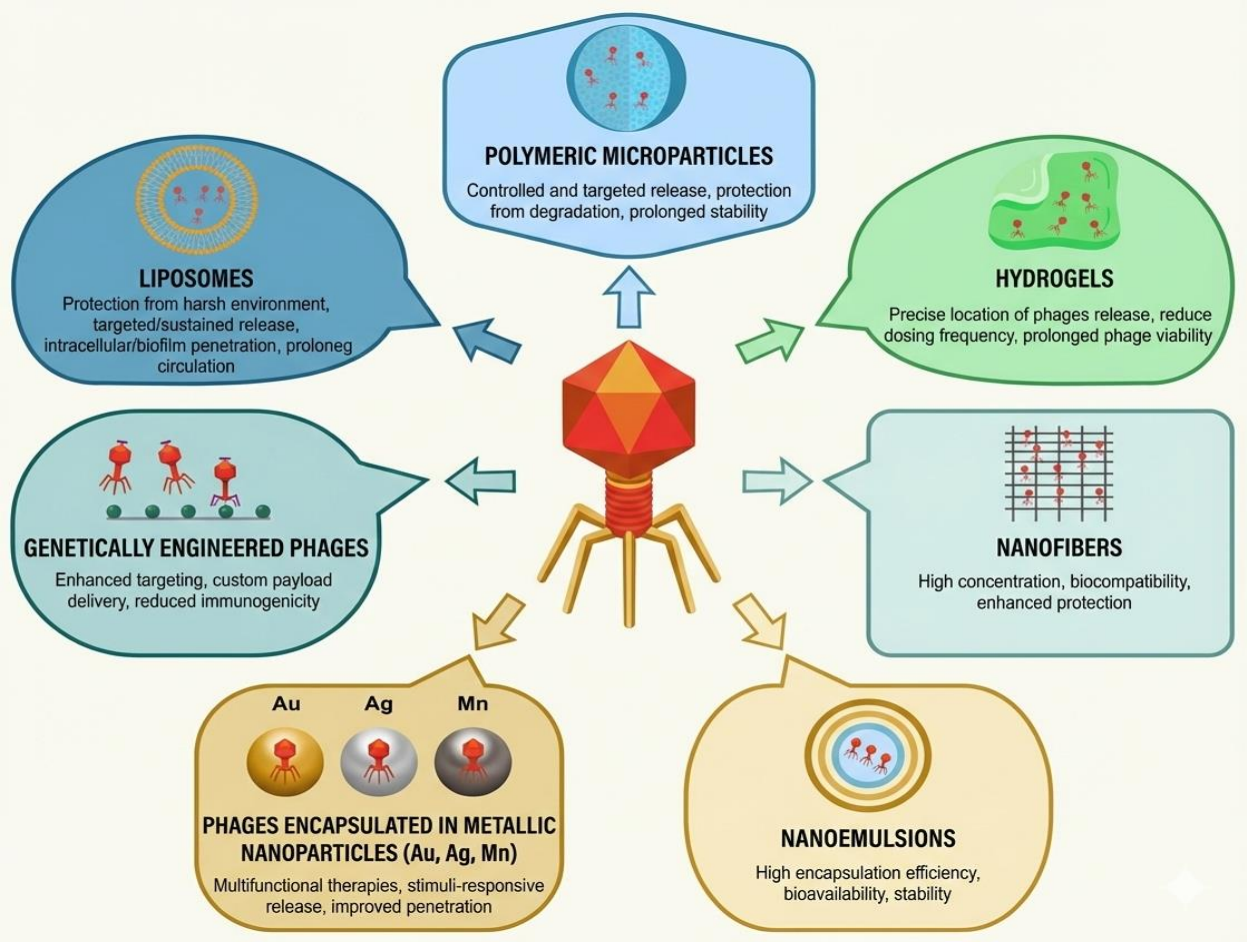
3.2. CRISPR-Armed Phages as Genotype-Specific Antimicrobials

Engineering phages to carry CRISPR-Cas constructs allows for a novel mechanism of action: killing bacteria based on their genotype rather than their phenotype. These "CRISPR-armed" phages deliver guide RNAs targeting specific antibiotic resistance genes, such as blaNDM-1, mecA, or carbapenemases (Ye et al., 2025). When the phage injects the CRISPR payload, the Cas nuclease cleaves the bacterial genome at the resistance locus, leading to cell death or resensitization to conventional antibiotics. Phagemid systems carrying these arrays have successfully reduced multidrug-resistant populations in vitro and in animal models (Moghadam et al., 2025).

3.3. Synthetic Genomes and Modular Assembly

Advances in de novo genome synthesis and rebooting techniques such as the use of L-form bacteria as hosts for assembly enable the creation of entirely synthetic phages with optimized therapeutic profiles (Kilcher et al., 2018). These phages can be designed to express high levels of biofilm-degrading enzymes or to include "off-switches" that prevent their persistence in the environment once the target pathogen has been eradicated (Fernbach et al., 2023). Furthermore, filamentous phages have been engineered to act as targeted nanomedicines, displaying targeting moieties while carrying large payloads of cytotoxic drugs like chloramphenicol, linked via branched molecules like neomycin to enhance potency by a factor of 20,000 compared to free drugs (Alessa et al., 2025).

Figure 2. Advanced Delivery Platforms and Engineering Strategies for Enhanced Phage Bioavailability and Targeting



4. Phage-Derived Enzymes: Endolysins and Depolymerases

Beyond the use of intact virions, phage-derived enzymes represent a potent class of "enzybiotics" capable of direct bacterial lysis and biofilm disruption (Husain et al., 2025).

4.1. Molecular Mechanisms of Endolysins

Endolysins are peptidoglycan hydrolases produced at the end of the lytic cycle to rupture the bacterial cell wall. In Gram-positive bacteria, endolysins possess a modular structure consisting of an enzymatically active domain (EAD) at the N-terminus and a cell-binding domain (CBD) at the C-terminus, the latter providing high substrate specificity (Gouveia, 2026). These enzymes cleave critical bonds in the peptidoglycan matrix, such as the beta-1,4-glycosidic bonds (glycosidases) or the amide bonds in the peptide cross-links (amidases), leading to immediate osmotic lysis (Bhagwat et al., 2020).

The application of endolysins against Gram-negative bacteria is more challenging due to the protective outer membrane. However, innovative strategies have emerged:

- **Artesian Endolysins (Innolysins)**: Fusing endolysins with antimicrobial peptides (AMPs) or hydrophobic motifs allows the enzyme to penetrate the outer membrane and access the peptidoglycan layer (Wojciechowska, 2025).
- **Intrinsic Cationic Domains**: Some endolysins possess positively charged C-termini that naturally destabilize the outer membrane (Sisson et al., 2024).
- **Outer Membrane Permeabilizers (OMPs)**: Combining endolysins with chemical OMPs like EDTA or citric acid destabilizes the lipopolysaccharide layer, facilitating enzymatic action (Murray et al., 2021).
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Table 2: Functional Characteristics and Therapeutic Utility of Phage-Derived Enzymes

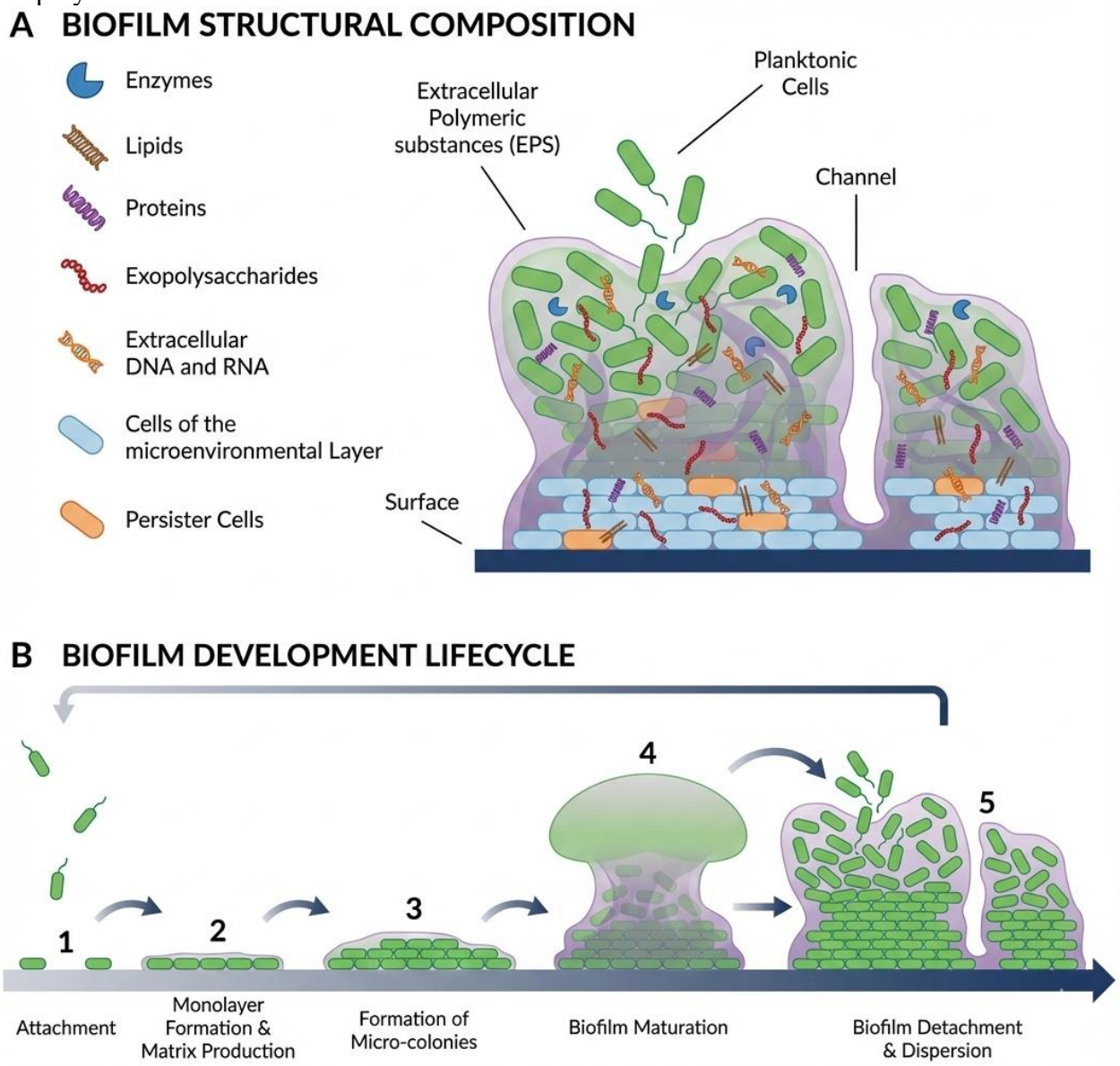
Enzyme Type	Substrate	Bond Targeted	Therapeutic Utility
Endolysin	Peptidoglycan	Amide, Glycosidic	Rapid bactericidal action; low resistance
Depolymerase	EPS, CPS, LPS	1,4-glycosidic linkage	Biofilm disruption; immune resensitization
Holin	Inner Membrane	Pore formation	Facilitates endolysin egress
Spanin	Outer Membrane	Fuses membranes	Final step in Gram-negative lysis

4.2. Biofilm Disruption via Phage Depolymerases

Biofilms represent a major hurdle in treating chronic infections, as they shield bacteria from the immune system and increase antibiotic resistance by up to 1,000-fold. Phage depolymerases are specialized enzymes that degrade the extracellular polymeric substances (EPS) or capsular polysaccharides (CPS) of the biofilm matrix (Osman et al., 2025). Classified as either hydrolases (e.g., sialidases, levanases) or lyases, these enzymes cleave the carbohydrate polymers that form the structural backbone of the biofilm. Hydrolases catalyze the cleavage of glycosidic bonds, while lyases introduce a double bond via a beta-elimination mechanism (Topka-Bielecka et al., 2021).

Depolymerases "strip" the protective polysaccharide layers, exposing pathogens to phagocytosis and allowing antibiotics to penetrate deeper into the biofilm. Clinical studies have shown that phages expressing depolymerases are highly effective against encapsulated *K. pneumoniae*, *P. aeruginosa*, and *Proteus mirabilis* (Guo et al., 2023).

Figure 3. Biofilm Structural Architecture and Lifecycle Dynamics: Targets for Phage-Derived Depolymerases.



5. Clinical Applications and Trial Outcomes (2024–2025)

The clinical landscape for phage therapy has shifted from small-scale compassionate use to structured interventional trials, particularly focusing on the ESKAPE group. As of February 2025, over 60 interventional phage studies are registered on ClinicalTrials.gov (König, 2025).

5.1. ESKAPE Pathogen Targeting

The WHO Bacterial Priority Pathogens List (2024 update) underscores the urgency of targeting carbapenem-resistant strains. Recent clinical reports have highlighted successes in treating these recalcitrant infections:

- **Staphylococcus aureus**: Single-arm safety studies confirmed that intravenous phage cocktails are well-tolerated. Combinations of endolysins and antibiotics like vancomycin or daptomycin have significantly reduced mortality in bacteremia cases (Konkova et al., 2025).

- **Enterococcus faecium**: In 2024, a case of vancomycin-resistant enterococci (VRE) bacteremia documented rapid clearance and a relapse-free interval following combined intravenous phage and antibiotic therapy (Konkova et al., 2025).
- **Pseudomonas aeruginosa**: Phages have shown efficacy in reducing bacterial load in the lungs of patients with chronic airway disease (Beyer, 2025).
- **Klebsiella pneumoniae**: The use of phage KpJH46φ2 in patients with prosthetic reinfections resulted in significantly decreased biofilm biomass, facilitating recovery where conventional antibiotics failed (Sindhushree et al., 2025).

5.2. Personalized Phage Cocktails and Rapid Diagnostics

One of the defining features of 21st-century phage therapy is the shift toward personalized medicine. Centers are increasingly adopting a "magistral" approach, where phages are selected based on their specific activity against the patient's isolate (Hampton et al., 2020). Rapid diagnostic tools are critical: optical density dynamics analysis can detect effective phages in approximately 3.5 hours, and flow cytometry is being used for early detection of phage infection by identifying cells with low-density cell walls (Baruah et al., 2024). These tools allow for the formulation of "precision cocktails" tailored to the patient's unique bacterial population, minimizing off-target effects on the microbiome (Coque et al., 2023).

5.3. Phage-Antibiotic Synergy (PAS)

The combination of phages and antibiotics often yields outcomes superior to either treatment alone. This synergy can be attributed to several factors:

- **Evolutionary Trade-offs**: Bacteria developing resistance to phages often mutate surface receptors, which can simultaneously increase susceptibility to antibiotics or reduce virulence (Guan et al., 2020).
- **Enhanced Replication**: Sub-lethal concentrations of certain ribosome-targeting antibiotics can stress bacteria in ways that accelerate phage replication (Dimitriu et al., 2020).
- **Matrix Breakdown**: Depolymerases facilitate antibiotic penetration into biofilms. Clinical studies of 100 patients demonstrated 70% superior eradication rates with combination therapy compared to phage monotherapy (Meeske et al., 2020).

6. Manufacturing Challenges and Regulatory Evolution (2025)

The transition from laboratory-scale production to Good Manufacturing Practice (GMP) compliance is a primary focus for the 2025-2026 period (Dams et al., 2019).

6.1. Scalability, Purity, and Endotoxin Removal

A critical challenge in phage production is the release of endotoxins during the bacterial lysis process. These contaminants are "critical quality attributes" that must be strictly controlled (Onyeyili et al., 2025). Progress has been made with the 2024 European Pharmacopoeia quality criteria, which specifies standards for bacterial and phage banks, purification steps, and potency determination using plaque assays (Scholthof, 2026). In 2025, modern bioreactor platforms like the CellMaker have identified single-use airlift systems as a solution to reduce the complexity and cost of cleaning and sterilization (Evstigneeva, 2025).

6.2. Global Regulatory Landscapes: The 2025 Update

The regulatory environment is undergoing rapid harmonization. The European Pharmacopoeia

General Chapter 5.31 on Phage Therapy Medicinal Products, effective January 1, 2025, establishes the first unified quality and safety framework in Europe (Beyer, 2025).

- **European Union**: In April 2025, the EMA published a draft reflection paper signaling a shift toward prioritizing advanced analytical characterization and pharmacokinetic (PK) data over large-scale clinical trials for well-characterized molecules (Peng et al., 2025).
- **United States**: The FDA unveiled reforms in October 2025 aimed at halving development timelines from 5-8 years to 2-4 years by focusing on PK evidence and eliminating redundant switching studies for interchangeable status (Sanz-Gaitero et al., 2021).
- **Germany**: The Medical Research Act introduced in 2025 provides flexible manufacturing frameworks to address non-industrial, decentralized production in hospital pharmacies (Mosterd et al., 2021).

Table 3: Global Regulatory Milestones for Bacteriophage Therapy (2025)

Regulatory Milestone	Organization	Date	Impact
General Chapter 5.31	European Pharmacopoeia	Jan 2025	Harmonized standards for quality and safety
Draft Reflection Paper	EMA	April 2025	Reduced reliance on large-scale efficacy trials
Medical Research Act	Germany (MFG)	2025	Flexible frameworks for personalized phages
CDER Strategic Reform	FDA	Oct 2025	Accelerated approval timelines (2-4 years)
Phage Potency Chapter 2.7.38	European Pharmacopoeia	2025 (Draft)	Standardization of plaque assay validation

7. Future Perspectives: AI and Interdisciplinary Integration

As the field approaches 2030, AI and machine learning are expected to revolutionize phage therapy. AI models predict phage-host pairings and the likelihood of resistance development (Konkova et al., 2025). Furthermore, phages are being explored for:

- **Precision Oncology**: Engineered phages as gene delivery vectors for solid tumors (Dams et al., 2019).
- **Microbiome Engineering**: Targeted elimination of strains associated with inflammatory bowel disease or colorectal cancer (Nisar et al., 2025).
- **Biosensing**: Recombinant tail fibers used as sensitive affinity probes for pathogen detection in food and environmental samples (Sindhushree et al., 2025).

The ongoing shift toward personalized, genotype-specific therapies, supported by robust diagnostic platforms and harmonized regulatory standards, heralds a new era of sustainable and effective infectious disease management (König, 2025).

Conclusion

Bacteriophages represent one of the most promising and evolutionarily refined solutions to the escalating global crisis of antimicrobial resistance. Their exquisite host specificity, self-amplifying nature at the infection site, and capacity for biofilm penetration through depolymerases and endolysins provide therapeutic advantages that conventional antibiotics cannot match. The convergence of synthetic biology, CRISPR-based genome editing, and advanced pharmacogenomics has transformed phages from naturally occurring agents into precisely

engineered “smart weapons” capable of targeting specific resistance genes, expanding host ranges, and minimizing off-target effects on the beneficial microbiome. Recent clinical successes against ESKAPE pathogens, combined with 2025 regulatory milestones that streamline approval pathways and establish standardized quality frameworks, have moved phage therapy from compassionate-use cases to structured, reproducible medicinal products. Nevertheless, challenges in scalable GMP manufacturing, endotoxin control, and long-term ecological monitoring remain. The integration of artificial intelligence for rapid phage–host matching, the development of synthetic phage libraries, and the exploration of phage-based vectors for microbiome engineering and oncology will define the next decade of innovation. With sustained investment in interdisciplinary research, robust regulatory support, and equitable global access programs, bacteriophage therapy has the potential to restore the efficacy of our antimicrobial arsenal and usher in a new era of sustainable, precision medicine against multidrug-resistant infections.

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