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Phage Therapy: Precision Targeting of Pathogens

Shaojie Bonkoungou*

Department of Marine Biology and Fisheries, Hainan University, Haikou 570228, China

Introduction

Phage therapy, the use of bacteriophages (viruses that specifically infect bacteria) to target and eliminate bacterial pathogens, has emerged as a promising alternative to traditional antibiotics, especially in the face of growing antibiotic resistance. Unlike broad-spectrum antibiotics, which can indiscriminately kill both harmful and beneficial bacteria, phages offer precise targeting, attacking only specific bacterial strains while leaving the surrounding micro biome largely unharmed. Discovered in the early 20th century, phage therapy was overshadowed by the advent of antibiotics but has regained attention due to the increasing prevalence of multidrug-resistant infections. With advancements in biotechnology, phage therapy is being revisited as a highly targeted and potentially customizable approach to combating bacterial infections, offering a unique solution in the era of antimicrobial resistance [1].

Description

Phage therapy relies on bacteriophages, which are viruses that infect and kill bacteria by injecting their genetic material into bacterial cells, hijacking the host machinery to produce new phages. This replication process ultimately leads to bacterial cell lysis, releasing new phages that can then infect nearby bacterial cells. Each bacteriophage is specific to a particular bacterial strain, which means that phage therapy can be tailored to target pathogenic bacteria without harming beneficial bacteria in the body. This specificity makes phage therapy an attractive option for precision medicine, especially in treating localized infections or infections caused by multidrug-resistant bacteria like Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli. One of the key advantages of phage therapy is its adaptability. Phages can be isolated from various environments, including soil and water, where they naturally occur. This diversity allows scientists to find phages specific to a wide range of bacterial pathogens, and new phages can be identified and purified to match evolving bacterial strains. Additionally, bacteriophages can evolve alongside bacteria, potentially overcoming resistance mechanisms that bacteria develop against antibiotics. Unlike antibiotics, which have a fixed chemical structure, phages are living entities that can co-evolve with their bacterial hosts, making them a "living drug" that can adapt over time to remain effective. In some cases, phages can even work in synergy with antibiotics, weakening bacterial defenses and allowing antibiotics to work more effectively, which could revitalize the use of existing drugs that had become ineffective on their own. To enhance the precision and effectiveness of phage therapy, modern techniques such as genetic engineering are used to modify bacteriophages. By altering phage genomes, scientists can increase phage specificity, enhance bacterial lysis efficiency, and even engineer phages to deliver genetic elements that disrupt bacterial resistance mechanisms [2].

***Address for Correspondence:** Shaojie Bonkoungou, Department of Marine Biology and Fisheries, Hainan University, Haikou 570228, China; E-mail: shaojie@bonkoungou.cn*

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For example, CRISPR-based gene-editing technology has been used to engineer phages that carry "gene-editing payloads" to disable bacterial genes responsible for resistance, making the bacteria more susceptible to treatment. This approach not only improves phage efficiency but also enables phages to work as gene therapy tools against bacteria, opening new frontiers for phage therapy as a versatile tool for infection management. However, phage therapy is not without its challenges. The specificity of phages, while advantageous, also requires that the correct phage be identified for each infection, a process that can be time-consuming and complex. Additionally, the body's immune system may recognize phages as foreign entities and neutralize them before they reach the infection site. Repeated use of phages can lead to immune responses that limit their effectiveness over time [3].

To overcome these issues, phage cocktails mixtures of multiple phages targeting different bacterial strains are often used to increase the likelihood of successful treatment. Encapsulation techniques, such as using hydrogels or liposomes, have also been developed to protect phages from immune detection and extend their activity within the body. Another challenge is regulatory approval. As biological entities, phages are difficult to standardize and characterize compared to small-molecule drugs, making the path to regulatory acceptance more complex. The unique nature of phage therapy means it must often be customized to individual infections, raising questions about quality control and consistency. Despite these hurdles, clinical trials and compassionate-use cases have shown promising results, with phage therapy successfully treating severe infections that were resistant to all available antibiotics. As regulatory frameworks adapt, phage therapy is moving closer to broader acceptance, supported by collaborations between hospitals, research institutions, and regulatory bodies aiming to establish guidelines for safe and effective use [4].

Beyond human health, phage therapy has applications in agriculture, aquaculture, and food safety. In agriculture, bacteriophages can be used to control bacterial diseases in crops and livestock, reducing the need for antibiotics and lowering the risk of antibiotic resistance. In aquaculture, phages can help control bacterial infections in fish farms, improving yield and reducing losses due to disease. In the food industry, phages are applied to food surfaces to control bacterial contamination, providing an extra layer of safety and extending shelf life. These applications not only help address bacterial threats but also contribute to a more sustainable and resistance-free approach to bacterial management across sectors.

One of the advantages of phage therapy is its adaptability. Bacteriophages can be sourced from diverse environments like soil, sewage, and water, where they naturally occur in large numbers and varieties. This diversity allows for extensive phage "libraries" that can be curated to address various bacterial pathogens, including those that are resistant to multiple antibiotics. Furthermore, the evolutionary adaptability of phages enables them to counteract bacterial resistance mechanisms. Whereas bacteria can develop resistance to antibiotics through genetic mutations, phages are equally capable of evolving new ways to infect resistant bacteria. This "arms race" between phages and bacteria makes phage therapy a dynamic treatment option that can be modified and adapted to counter bacterial resistance, offering potential solutions even against bacteria that have become resistant to all known antibiotics.

The precision of phage therapy is enhanced by genetic engineering, which allows researchers to modify phages to increase their effectiveness and expand their range of action. Engineered phages can be designed to carry genes that specifically target bacterial resistance mechanisms or enhance the lysis process, making them more potent against stubborn

infections. Techniques like CRISPR-Cas9, originally developed for gene editing, have been adapted to create "CRISPR-enhanced" phages that can specifically disrupt bacterial genes responsible for resistance or virulence. These engineered phages can be used as both a treatment and a tool to reverse bacterial resistance, making the bacteria more susceptible to existing antibiotics and providing a synergistic effect when used in combination with other antimicrobial therapies. For example, phages engineered to disarm bacterial defense mechanisms can weaken bacteria enough to allow lower doses of antibiotics to be effective, reducing the potential side effects and toxicity of conventional antibiotic therapy.

Despite the advantages, implementing phage therapy in clinical settings presents several challenges. One major hurdle is the immune system's response to phages, which may recognize and neutralize phages before they reach the infection site, especially if repeated doses are needed. To address this, researchers are exploring phage encapsulation methods, such as encapsulating phages in biocompatible materials like hydrogels or liposomes, which can protect them from immune attack and allow for controlled, sustained release. Another approach is to develop phage cocktails a combination of different phages targeting the same or related bacterial strains which not only increases the likelihood of effective bacterial elimination but also reduces the probability of bacteria developing resistance to any single phage [5].

Regulatory approval for phage therapy has been challenging due to the unique nature of phages as biological entities. Unlike standardized small-molecule drugs, phages are living organisms that may vary from batch to batch, making it difficult to establish consistent quality control. Additionally, phage therapy often requires customization for individual patients or infections, as specific phages must be matched to the causative bacterial strain. This individualized approach complicates the process of regulatory approval, as traditional models of drug testing and approval may not apply to such tailored therapies. Nonetheless, successful compassionate-use cases and clinical trials have demonstrated the potential of phage therapy, spurring regulatory agencies to consider frameworks that can accommodate personalized phage treatments.

Conclusion

Phage therapy presents an innovative approach to tackling bacterial infections through precision targeting, offering hope in the fight against multidrug-resistant bacteria. By specifically attacking pathogenic strains while sparing beneficial bacteria, phages enable a more targeted and potentially safer alternative to antibiotics. Although challenges remain, including immune response management, regulatory hurdles, and the need for rapid phage selection, advancements in genetic engineering and biotechnology are enhancing the versatility and effectiveness of phage therapy. As research and clinical evidence continue to demonstrate its potential, phage therapy is emerging as a viable component of precision medicine, contributing to more sustainable, adaptive strategies for combating bacterial infections in both healthcare and non-medical fields.

Acknowledgement

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Conflict of Interest

No potential conflict of interest was reported by the authors.

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