Perspective

Essential data for developing bacteriophage therapeutics

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Introduction

The rise of multidrug-resistant organisms is a significant global health threat, projected to cause up to 10 million deaths annually by 2050, surpassing cancer as the leading cause of mortality [1]. Traditional antibiotic development has not kept pace with this threat, necessitating innovative approaches to combat resistant pathogens. Bacteriophage therapy, which leverages viruses to specifically target and destroy bacteria, has emerged as a promising alternative. This letter outlines the key developments in bacteriophage research, the challenges facing its clinical application, and the steps necessary to integrate phage therapy into mainstream medical practice.

Bacteriophages were first discovered in the early 20th century, with initial studies demonstrating their potential for treating bacterial infections. However, the advent of antibiotics in the 20th century shifted the focus away from phages. The current antimicrobial resistance (AMR) crisis has renewed the interest in phage therapy as a viable therapeutic option. Unlike antibiotics, phages are highly specific and target only their bacterial hosts without harming human cells, which reduces off-target effects and preserves beneficial microbiota [2].

Phages are particularly advantageous for treating biofilm-associated infections that are resistant to antibiotics. These infections often occur in patients with implanted medical devices, such as prosthetic joints or ventricular assist devices, where biofilms protect the bacteria from antibiotic treatment. Phages can penetrate biofilms and lyse the bacteria within them, offering a potential solution for persistent infections.

Recent advancements in genetic engineering have further enhanced the potential of phage therapies. Genetically modified phages have been successfully used in clinical settings to treat otherwise untreatable infections, such as those caused by *Mycobacterium abscessus* [3]. A landmark case in 2017 in which phages were used to save a patient from a deadly antibiotic-resistant infection highlighted the rapid response capability of phage therapy and set the stage for more extensive clinical trials [4].

Challenges in clinical implementation

Despite this promise, the clinical application of phage therapy faces several challenges, particularly in terms of regulatory approval and production. In the United States, phages are classified as biological drugs subject to stringent investigational new drug application processes. This process requires proof of safety, purity, potency, and consistent manufacturing, which is a significant challenge given the unique nature of

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each phage and its production process. Key concerns include the potential for endotoxin contamination, the risk of phages transferring undesirable genes to bacteria, and the need for standardized in vitro phage susceptibility testing [5].

Phage production for clinical use is a significant hurdle. Good Manufacturing Practice (GMP) facilities are essential for producing clinical-grade phages; however, only a few such facilities exist globally. Establishing a GMP-compliant process involves substantial cost and time, with each phage requiring a tailored production approach to ensure safety and efficacy. Moreover, the long-term stability of phage preparations must be validated to ensure that phage activity remains within acceptable limits over extended periods. This process is costly and time-consuming, as well as adding to the complexity of bringing phage therapies to the market.

Innovations in phage therapy development

One of the most promising areas of research in phage therapy is the development of synergistic combinations of phages and antibiotics [6]. Studies have shown that certain phage-antibiotic combinations can significantly enhance treatment efficacy by reducing the minimum inhibitory concentrations of antibiotics by up to 512-fold (unpublished data). These findings suggest that phage therapy could be used as a standalone treatment and as a buster to existing antibiotic regimens, potentially reversing resistance in previously untreatable infections.

Another critical aspect of phage therapy development is the optimization of phage characteristics. The ideal therapeutic phages exhibit high adsorption rates, large burst sizes, and short latency periods [7]. These properties ensure rapid and effective clearance of bacteria. Additionally, phages must be free from antibiotic resistance and toxin genes, as confirmed by comprehensive genome sequencing. Genetic safety is paramount for preventing horizontal gene transfer, which can inadvertently enhance bacterial resistance.

Regulatory and clinical pathways

The path to the broader clinical adoption of phage therapy requires addressing several regulatory challenges. Phages must be rigorously tested to meet the U.S. Food and Drug Administration (FDA) standards for biological drugs, which include demonstrating safety, efficacy, and consistent manufacturing quality. One of the major concerns is the potential for endotoxins to cause immune reactions, such as fever and chills. Therefore, phages must be extensively purified to remove these contaminants. Furthermore, the FDA has emphasized the need for phages to be free of genes that could confer antibiotic resistance or increase bacterial virulence.

Phage therapy is currently being tested in many clinical trials across the United States and Europe, with early results showing promise. A study from San Diego University reported a significant improvement in 11 of 13 patients treated with phage therapy, with minimal side effects [8]. The PhagoBurn trial showed results comparable to those obtained after the use of standard antibiotics for burn wound infections despite early termination due to production challenges [9]. Phage therapy for bone and joint infections demonstrated an 87% success rate across 33 cases, with 24% of patients experiencing mild transient adverse events [10].

These trials are crucial for establishing the safety and efficacy of phage therapy in a controlled environment, and their success will be instrumental in gaining regulatory approval. However, the complex nature of phage therapy, including the need for individualized treatment plans based on the specific bacterial infection, adds another layer of difficulty to the approval process [11].

Clinical applications and future directions

The specificity of phage therapy makes it particularly suitable for treating infections resistant to conventional antibiotics, including those associated with biofilms and implanted medical devices. The ability of phages to target specific bacterial strains without harming human cells or beneficial microbiota makes them valuable tools in the fight against AMR. However, the clinical application of phage therapy is still in its early stages, and further research is needed to fully understand its potential limitations.

Collaboration between academic institutions and industry is vital for overcoming the challenges associated with phage therapy. Partnerships with phage treatment centers have been instrumental in advancing phage therapy through clinical trials and expanding the understanding of phage-bacteria interactions. These collaborations will continue to play crucial roles in bringing phage therapy into mainstream clinical practice.

Although phage therapy shows great promise, similar to other treatments, some challenges still need to be overcome [12,13]. For example, although bacterial resistance to phages can occur, strategies such as the use of phage cocktails can help maintain their effectiveness. Adverse reactions are rare, and most studies have reported favorable safety profiles. The long-term stability of phage preparations is achievable with proper storage and formulation, ensuring that their therapeutic potential remains unchanged. These considerations reflect the ongoing refinements aimed at making phage therapy a reliable tool for combating bacterial infections.

As research advances and clinical trials yield positive results, phage therapy may soon become a critical component of the medical arsenal against AMR. However, its successful integration into clinical practice requires continued collaboration, innovation, and rigorous regulatory supervision.

Technological advancements in phage therapy include significant progress in phage engineering, such as designing phages with enhanced antibacterial activity using genetic modification tools, such as CRISPR-Cas systems [12]. Novel delivery methods, including encapsulation and site-specific targeting, improve treatment effectiveness, particularly for difficult-to-reach infections. Integration with other treatments, such as antibiotics or immune modifiers, has shown synergistic effects [14]. Phage cocktails have also expanded the range of the bacteria that can be targeted. With the evolution of phage-production techniques, phage therapy is becoming more cost-effective and may represent a promising alternative to antibiotics.

Conclusion

Bacteriophage therapy is a promising frontier in the battle against multidrug-resistant infections. As research advances and clinical trials yield positive results, phage therapy may soon become a critical component of the medical arsenal against AMR. The future of phage therapy is promising, with the

potential to significantly affect the treatment of infectious diseases and save millions of lives by providing an innovative and effective approach to combating antibiotic-resistant pathogens.

Ethics statement

This was not a human population study; therefore, approval by the institutional review board and informed consent were not required.

Conflict of interest

Dongeun Yong serves as the Chief Executive Officer (CEO) of Microbiotix Inc., Korea. He is currently an editorial board member of the *Annals of Clinical Microbiology*. However, he was not involved in reviewing this article.

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References

1. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. 2016. https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf [Online] (last visited on 28 August 2024).
2. Jędrusiak A, Fortuna W, Majewska J, Górski A, Jończyk-Matysiak E. Phage interactions with the nervous system in health and disease. Cells 2023;12:1720.
3. Dedrick RM, Guerrero-Bustamante CA, Garlena RA, Russell DA, Ford K, Harris K, et al. Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*. Nat Med 2019;25:730-3.
4. Schooley RT, Biswas B, Gill JJ, Hernandez-Morales A, Lancaster J, Lessor L, et al. Development and use of personalized bacteriophage-based therapeutic cocktails to treat a patient with a disseminated resistant *Acinetobacter baumannii* infection. Antimicrob Agents Chemother 2017;61:10-1128.
5. Suh GA, Lodise TP, Tamma PD, Knisely JM, Alexander J, Aslam S, et al. Considerations for the use of phage therapy in clinical practice. Antimicrob Agents Chemother 2022;66:e02071-21.
6. Łusiak-Szelachowska M, Międzybrodzki R, Drulis-Kawa Z. Cater K, Knežević P, Winogradow C, et al. Bacteriophages and antibiotic interactions in clinical practice: what we have learned so far. J Biomed Sci 2022;29:23.
7. Chae D. Phage-host-immune system dynamics in bacteriophage therapy: basic principles and mathematical models. Transl Clin Pharmacol 2023;31:167-90.
8. Aslam S, Lampley E, Wooten D, Karris M, Benson C, Strathdee S, et al. Lessons learned from the first 10 consecutive cases of intravenous bacteriophage therapy to treat multidrug-resistant bacterial infections at a single center in the United States. Open Forum Infect Dis 2020;27:ofaa389.

9. Jault P, Leclerc T, Jennes S, Pirnay JP, Que YA, Resch G, et al. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial. Lancet Infect Dis 2019;19:35-45.
10. Suh GA, Ferry T, Abdel MP. Phage therapy as a novel therapeutic for the treatment of bone and joint infections. Clin Infect Dis 2023;77(Suppl 5):S407-15.
11. Furfaro LL, Payne MS, Chang BJ. Bacteriophage therapy: clinical trials and regulatory hurdles. Front Cell Infect Microbiol 2018;8:376.
12. Pires DP, Costa AR, Pinto G, Meneses L, Azredo J. Current challenges and future opportunities of phage therapy. FEMS Microbiol Rev 2020;44:684-700.
13. Fabijan AP, Iredell J, Danis-Wlodarczyk K, Kebriaei R, Abedon ST. Translating phage therapy into the clinic: recent accomplishments but continuing challenges. PLoS Biol 2023;21:e3002119.
14. Karn SL, Gangwar M, Kumar R, Bhartiya SK, Nath G. Phage therapy: a revolutionary shift in the management of bacterial infections, pioneering new horizons in clinical practice, and reimagining the arsenal against microbial pathogens. Front Med 2023;10:1209782.