

Leveraging Artificial Intelligence (AI) to Optimize Phage Therapy: A Perspective.

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Phage therapy originated around 100 years ago, when phages were used to treat various infections. However, improper storage, purification methods, and the treatment of bacterial infections not specific to the therapeutic phage led to its downfall in the West, except in Eastern European countries, where it is still practiced. With the emergence of antimicrobial resistance, phage therapy once again has attracted the attention of scientists as a promising strategy. According to the 2024 Lancet analysis estimates, antimicrobial resistance (AMR) will be responsible for approx. 1.91 million deaths annually by 2050, with a total of 39 million deaths projected between 2025 and 2050 if the current trend continues [1]. This observation further rekindles interest in phages, as their specificity to particular bacterial strains is well known, making them an attractive alternative over antibiotics for treating multidrug-resistant bacteria. Traditionally, phage therapy involves isolating or selecting lytic phages active against clinical bacterial isolates, followed by genomic screening, host-range testing, evaluation of the emergence of resistance, and product-quality assessment. In recent years, phage therapy has primarily focused on phage stability, novel formulations, and biocompatibility. Various animal models have been used to assess disease treatment, antibiotic synergy, and biomaterial modification. Nanocarriers, hydrogels, liposomes, polymeric particles, and other biomaterial-based systems have also been investigated to further improve phage delivery and stability under biologically relevant conditions [2,3]. Despite substantial progress in the field, further technological refinement is required to achieve successful therapeutic outcomes.

In 2020, a commentary published by Jean Pirnay in journal "*Frontiers of Microbiology*" described the use of AI-based algorithms to design novel phages using their corresponding host bacterial genetic sequences. This AI-based new generation approach may help to combat AMR more effectively through sequence-informed phage selection, synthetic biology, and AI-enabled design [4]. A recent proof-of-concept study by investigators at Stanford University and the Arc Institute showed that use of genome-scale generative models can lead to the design of functional bacteriophage genomes. Investigators used genome-scale generative models to produce candidate genomes; nearly 300 were

selected and chemically synthesized. Sixteen candidate designs produced functional phages; phage cocktails derived from these designs overcame resistance to phage ΦX174 in three evolved *E. coli* strains. The scientists used Evo 1 and Evo 2 genome-scale generative models to generate candidate phage genomes related to ΦX174. It showed AI can assist in producing functional viral genomes [5]. In the last few years, AI-driven tools have been extensively used to identify phage genome annotation, identification of phage sequences in bacterial hosts, host prediction, and selection of phages from large genomic banks. These novel phage gene sequences are used to design and engineer therapeutic phages. The AI algorithms can identify the most suitable therapeutic phages from the vast phage library, enabling rapid phage selection. The AI driven physics-informed neural networks (PINNs) have been explored as models for phage-bacteria-host dynamics thereby optimizing personalized dose for efficient therapeutic outcome [6]. Further, bacterial resistance can be overcome by designing optimum phage cocktail formulation by using AI algorithms [7]. Phages have been combined with antibiotics to increase the efficiency of treatment. These phage-antibiotic interactions could be synergistic, neutral or antagonistic. AI-based machine learning systems enable phage-antibiotic optimization using pharmacokinetic and pharmacodynamic, bacterial growth, host-range, and interaction datasets to prioritize phages and antibiotics for experimental validation [8]. However, cocktail selection still relies heavily on empirical host-range resistance and interaction testing. To prevent therapeutic failure due to AMR, AI-assisted CRISPR phages have been designed to deliver the CRISPR-Cas system into host bacteria, specifically targeting AMR genes. Although not an inherent requirement for CRISPR-phage development, this could eliminate multidrug-resistant pathogens more effectively. Another use of AI is in developing phage libraries for rapid phage selection. Computational triage may shorten candidate selection, but it still requires wet-lab and clinical testing. Algorithms like natural language processing (NLP) can be used to cluster phages based on genetic homology and host specificity. In this way, large datasets of available phage genomes have been extracted using AI/ML, and the therapeutic potential of phages has been evaluated.

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AI could significantly reduce the candidate prioritization process; however, culture recovery from patients, bacterial identification, antibiotic and phage susceptibility testing, phage amplification, quality-control release testing, and regulatory processes may still require days to weeks.

Despite its potential advantages, certain limitations of AI in phage therapy are being considered. Many regulatory, ethical, and practical barriers encompass the AI-driven phage therapy. Bacteria can evolve resistance to both naturally isolated and AI-designed phages through receptor modification, CRISPR-Cas, and other anti-phage defense mechanisms. Another issue is phage standardization for dosing, which is limited by batch-to-batch consistency and quality control of preparations, since phages are strain-specific, biologically active entities. The AI-designed phages may be rapidly neutralized in the host compared to their “*in vitro*” stability, thereby reducing therapeutic efficacy. In addition, AI-assisted phage systems increase the complexity of the ethical and legal framework. Any computational error in the algorithm could lead to a false positive host outcome, particularly in patients with multidrug-resistant infections. It is said that governance systems for operating AI-based phage therapy should rigorously rely on data use agreements, accountabilities, and responsibilities shared among clinicians, microbiologists, legal experts, data analysts, and patients. Progress in this area should be accompanied by proportionate progress with increasing safeguards in AI systems, DNA synthesis, laboratories, and biosafety in institutions.

In conclusion, AI-driven phage therapy could empower phage discovery, selection, engineering, manufacturing, and treatment design if supported by efficient validation and appropriate regulatory guidelines, and it has a promising future in the management of increasingly prevalent AMR. The development of phage therapy guided by AI and coupled with increased funding and clinical trials could help prevent deaths due to AMR. AI-driven phage therapy is the next generation of therapeutics to address the global AMR concern in the 21st century.

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Not applicable

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Availability of data and materials

All information used is available in the cited literature, & Data will be made available on request.

AI declaration

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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