Phage Warfare: Mechanisms of Bacteriophages and Clinical Applications

BY: NORAH HOM

WHEN ANTIBIOTICS FAIL, CAN VIRUSES SAVE US?

Let us say antibiotics no longer work—once-treatable infections turn deadly, and modern medicine becomes powerless against resistant bacteria. Although this scenario may sound ridiculous, given the past successes of antibiotics, this reality is approaching quicker than most would like to believe. In fact, in July 2024, the Center for Disease Control and Prevention (CDC) published new data on antimicrobial resistance threats in the United States from 2021-2022. The report demonstrated that six drug-resistant bacterial infections starting in hospitals increased by a combined 20% during the COVID-19 pandemic compared to the pre-pandemic period, peaking in 2021 and staying above pre-pandemic levels in 2022.[1] Such a trend was likely driven by increased antibiotic use, as critically ill patients were often given antibiotics to treat or prevent secondary bacterial infections (even though COVID-19 itself is caused by a virus). The issue of antibiotic resistance is not confined to the United States. Globally, the World Health Organization (WHO) has warned that antimicrobial resistance is catching speed at an alarming rate. In 2019 alone, drug-resistant infections contributed to nearly 5 million deaths and continue to pose a growing threat to public health worldwide.[2]

One potential solution? It's all around us. Ubiquitous in the environment and the most abundant biological agent on the planet, bacteriophages (phages) are nature's viral assassins. They wield an arsenal of sophisticated infection strategies, acting as microscopic predators with the singular purpose to hunt, hijack, and dismantle bacteria. Phages have been locked in an evolutionary arms race with their bacterial hosts for billions of years, constantly adapting to overcome bacterial defenses. In turn, bacteria evolve their own immune strategies—such as CRISPR-Cas systems (bacterial immune mechanisms that help bacteria defend against viral infections, especially from phages)—to resist phage attacks, driving this ongoing cycle of adaptation.

Phage therapy (the use of phages to control bacterial pathogens and reduce disease) is a promising, yet still developing, approach among various alternatives for combating antibiotic resistance. While some clinical use and trials exist, more research is needed to ensure that broad-spectrum phage treatments are robust against bacterial

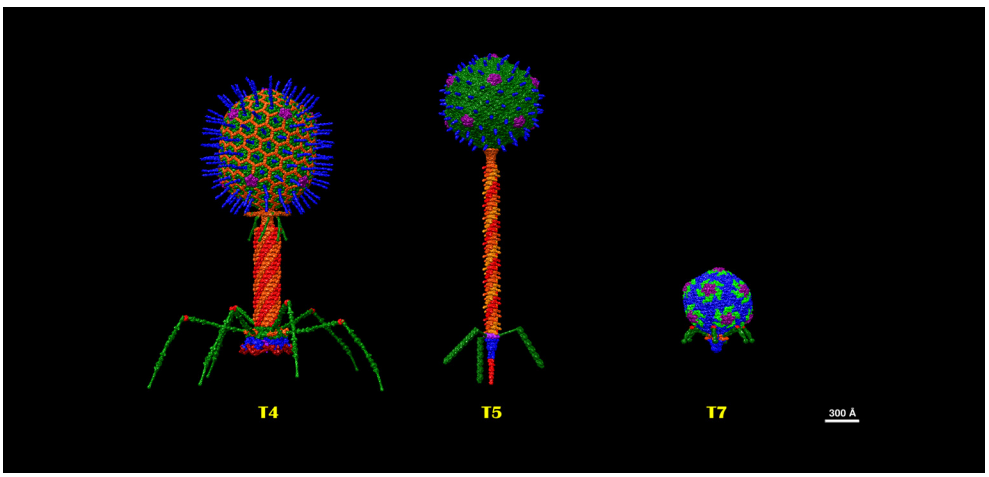

Figure 1: Structures of T Bacteriophages representing seven T types of Escherichia coli: T4 of the Myoviridae family, T5 of the Siphoviridae family, and T7 of the Podoviridae family.

evolution. Today, scientists are harnessing phage power in the fight against superbugs (bacteria that have evolved resistance to several antibiotics), potentially improving life expectancy for those suffering from deadly bacterial infections while revolutionizing the future of medicine—one where phages, not antibiotics, may hold the key to survival.

BACTERIOPHAGES AND THEIR MECHANISMS

Bacteriophages, or phages, are viruses that specifically infect and replicate within bacterial hosts. They are the most abundant biological agents on Earth, vastly outnumbering bacteria, and hold significant roles in microbial ecology, bacterial evolution, population dynamics, and even global biogeochemical cycles. Structurally, phages exhibit remarkable diversity but generally share common features. A typical bacteriophage consists of a protein capsid encasing its genetic material (DNA or RNA), along with a tail well-armed with receptor-binding proteins for host recognition. Moreover, bacteriophages share a common life cycle enabling them to infect, reproduce, and, in many cases, lyse (rupture and disintegrate) their bacterial hosts—making them extremely valuable tools when battling antibiotic-resistant illnesses.[3]

The general process of phage mechanics begins with encountering a suitable bacterium host. The phage then clutches onto the bacteria's specific surface receptors and injects its genetic poison into the cell. Depending on the type, phages undergo either a lytic or lysogenic cycle. For the lytic process, the phage hijacks the bacterial machinery, forcing it to produce new viral particles until the cell bursts (lysis), while colonizing the bacteria with its viral army. In contrast, the lysogenic cycle integrates the phage genome into the bacterial DNA, allowing it to replicate indefinitely along with the bacterium until the next round of excision and lysis is triggered, often by environmental stress.

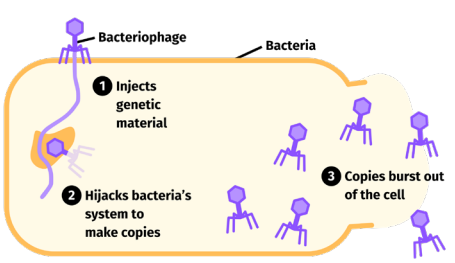

Figure 2: Diagram showing the lytic life cycle of a bacteriophage.

Antibiotic resistance occurs when bacteria evolve mechanisms to withstand exposure to antibiotics that would normally kill them or inhibit their growth. Such bacterial defenses decrease the efficacy of standard treatments, leading to persistent infections and an increased risk of transmission—particularly in hospital and high-density community settings. On this front, phages offer a promising alternative strategy to combat these resistant bacteria, as their unique talent in specifically targeting and lysing bacterial cells can be leveraged to fight infections that can no longer respond to conventional antibiotics. By examining the dynamics of this predator-prey relationship between phages and bacteria, researchers are investigating phage therapy as a means to bypass resistance mechanisms while restoring the efficacy of our typical bacterial infection treatments.[4]

ANTIBIOTIC RESISTANCE MECHANISMS

Bacteria employ several methods to achieve resistance, including limiting drug uptake through alterations in membrane permeability, modifying drug binding sites by changing protein structure, deactivating antibiotics by producing new enzymes, and actively pumping out the drugs using efflux systems (which expel antibiotics).

These developments may be intrinsic to a bacterium or acquired through a process called horizontal gene transfer (HGT), by which some bacteria incorporate genetic material from another organism.The specific type of HGT most relevant to phages is transduction, in which DNA is transferred from one bacterial cell to another and is phage-mediated—a phage is used as an intermediate in the transfer process.[5] Transduction raises important questions: if bacteriophages contribute to the spread of human-induced antibiotic resistance in this way, then how are they able to counteract their own actions to battle antibiotic resistance simultaneously? And how might scientists make the latter process outweigh the destructive impacts of the former?

PHAGES OVERCOMING ANTIBIOTIC RESISTANCE

Phages counteract antibiotic resistance by exploiting their natural ability to recognize and infect bacteria through receptors on bacteria that are often conserved, even among resistant strains. For instance, they can deploy enzymes such as depolymerases to degrade biofilms, which are structured communities of bacteria that accumulate on surfaces and secrete a self-produced extracellular polymeric substance that protects against antibiotics. Also, phages can be engineered or naturally evolved to deliver CRISPR-Cas systems that target and disable resistance genes, thereby effectively reversing resistance mechanisms such as drug efflux, target modification, and enzymatic inactivation.[6]

Most simply, phages take advantage of their inherent lytic cycle to directly eliminate antibiotic-resistant bacteria, and some even target the very efflux pumps that confer this resistance.[7] Upon attaching to bacteria, phages inject their genome and take command of the bacterial host's cellular machinery to produce offspring phages, ultimately leading to bacteria lysis. This replicative burst of new phages accomplishes two significant things: reducing the population of resistant bacteria and propagating further infection. So, how can the therapeutic impact be maximally amplified?

DEVELOPMENTS IN PHAGE THERAPY

"Today, scientists are harnessing phage power in the fight against superbugs (bacteria that have evolved resistance to several antibiotics), potentially improving life expectancy for those suffering from deadly bacterial infections while revolutionizing the future of medicine—one where phages, not antibiotics, may hold the key to survival. "

Recent developments in phage therapy have focused on improving both the precision and efficacy of phage treatments, steering the field closer to safe, routine clinical use. For example, some involve sophisticated genetic engineering techniques, such as CRISPR-Cas systems (natural bacterial immune system mechanisms that can be adapted to target specific genetic sequences, including antibiotic resistance genes), are aimed at enhancing therapeutic potential. These can be integrated into phages, allowing researchers to target and disable antibiotic resistance genes. On the other hand, engineered phage cocktails (blends of various kinds of phages designed to target a broader range of bacterial strains) have been employed to resensitize bacteria to conventional antibiotics.[8]

Promising outcomes have been witnessed clinically; for example, phage therapy has been successfully used to treat multidrug-resistant infections in patients, including those with urinary and respiratory tract infections (UTIs and RTIs, respectively), supported by multiple Phase I and II trials. Furthermore, companies like Locus Biosciences have innovated CRISPR-enhanced phage formulations that have demonstrated notable efficacy in early trials against infections, including UTIs.[9]

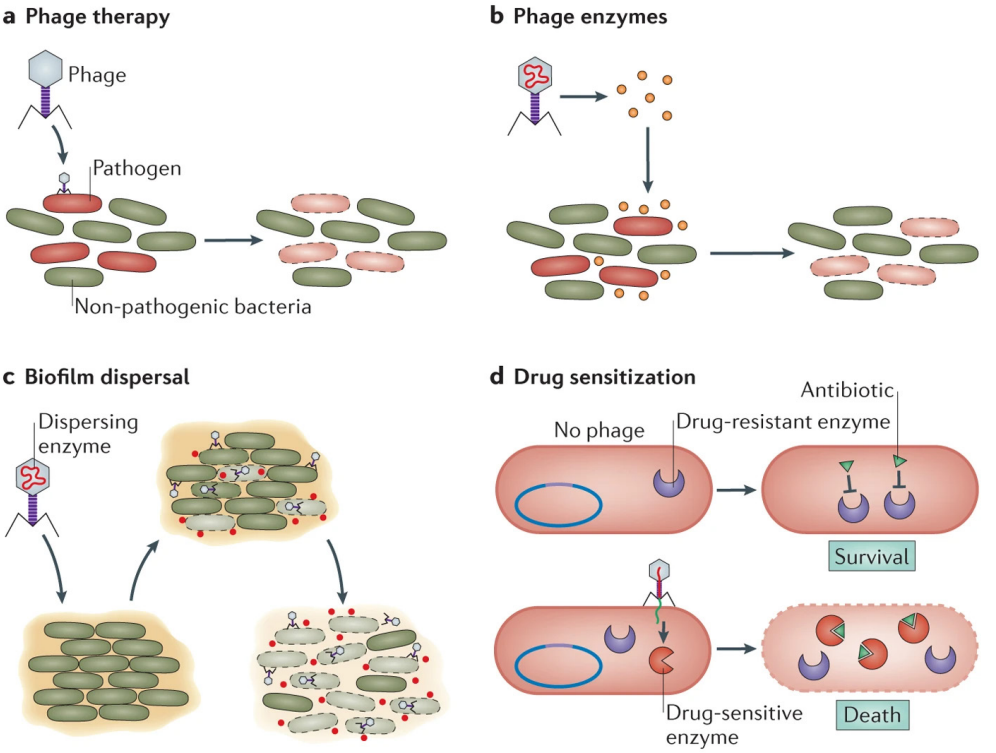

Figure 3: Strategies by which bacteriophages combat antibiotic resistance. (A) Phage therapy directly targets and eliminates pathogenic bacteria while sparing non-pathogenic species. (B) Phage enzymes, such as lysins, degrade bacterial cell walls, leading to cell lysis. (C) Biofilm dispersal is facilitated by phage-derived enzymes that break down the protective extracellular polymeric substance, making bacteria more susceptible to antibiotics. (D) Drug sensitization occurs when phages disable bacterial resistance mechanisms, such as drug-resistant enzymes, thereby restoring antibiotic efficacy and leading to bacterial cell death.

HARNESSING PHAGES: A NEW ERA IN BACTERIAL DEFENSE

As antibiotic resistance threatens to undermine modern medicine, phages can give ushope. These naturally occurring bacterial predators, endowed with the remarkable ability to infect, dismantle, and kill bacteria, offer a promising alternative to traditional antibiotics. Ongoing advancements in genetic engineering, personalized phage therapies, and regulatory frameworks propel the future of bacteriophage research toward more targeted, effective, and widely accessible treatments for bacterial infections. In turn, the relentless fight against drug-resistant bacteria becomes a less daunting task.

ACKNOWLEDGMENTS

A huge thank you to Professor Britt Koskella from the Integrative Biology department of UC Berkeley for carefully reviewing my manuscript for accuracy while sharing valuable feedback for improvement.

REFERENCES

1. Antimicrobial resistance facts and stats. (2025, February 4). Antimicrobial Resistance. https://www.cdc.gov/antimicrobial-resistance/data-research/facts-stats/index.html#:~:text=In%20July%202024%2C%20CDC%20published,period%2C%20peaking%20in%202021%2C%20and
2. World Health Organization: WHO. (2023, November 21). Antimicrobial resistance. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
3. Kasman, L. M., & Porter, L. D. (2022, September 26). Bacteriophages. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK493185/
4. Egido, J. E., Costa, A. R., Aparicio-Maldonado, C., Haas, P., & Brouns, S. J. J. (2021). Mechanisms and clinical importance of bacteriophage resistance. FEMS Microbiology Reviews, 46(1). https://doi.org/10.1093/femsre/fuab048
5. Reygaert, W. C. (2018). An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiology, 4(3), 482–501. https://doi.org/10.3934/microbiol.2018.3.482
6. Moghadam, M. T., Amirmozafari, N., Shariati, A., Hallajzadeh, M., Mirkalantari, S., Khoshbayan, A., & Jazi, F. M. (2020). How Phages Overcome the Challenges of Drug Resistant Bacteria in Clinical Infections Infection and Drug Resistance, Volume 13,ZZ 45–61. https://doi.org/10.2147/idr.s234353
7. Chan, B. K., Sistrom, M., Wertz, J. E., Kortright, K. E., Narayan, D., & Turner, P. E. (2016). Phage selection restores antibiotic sensitivity in MDR Pseudomonas aeruginosa. Scientific reports, 6(1), 26717.
8. Sahoo, K., & Meshram, S. (2024). The Evolution of Phage Therapy: A Comprehensive review of current applications and future innovations. Cureus. https://doi.org/10.7759/cureus.70414
9. Łusiak-Szelachowska, M., Międzybrodzki, R., Drulis-Kawa, Z., Cater, K., Knežević, P., Winogradow, C., Amaro, K., Jończyk-Matysiak, E., Weber-Dąbrowska, B., Rękas, J., & Górski, A. (2022). Bacteriophages and antibiotic interactions in clinical practice: what we

have learned so far. Journal of Biomedical Science, 29(1). https://doi.org/10.1186/s12929-022-00806-1

IMAGE REFERENCES

1. Header Image: File:Bacteriophages at work.jpg. (2023, October 24). Wikimedia Commons. Retrieved 16:46, March 26, 2025 from https://commons.wikimedia.org/w/index.php?title=File:Bacteriophages_at_work.jpg&oldid=814752622.
2. Figure 1: File:T Bacteriophages 2024.tif. (2024, April 6). Wikimedia Commons. Retrieved 15:40, March 26, 2025 from https://commons.wikimedia.org/w/index.php?title=File:T_Bacteriophages_2024.tif&oldid=866211779.
3. Figure 2: File:Bacteriophage lifecycle.svg. (2024, August 11). Wikimedia Commons. Retrieved 15:40, March 26, 2025 from https://commons.wikimedia.org/w/index.php?title=File:Bacteriophage_lifecycle.svg&oldid=908658857.
4. Figure 3: Salmond, G. P. C., & Fineran, P. C. (2015). A century of the phage: past, present and future. Nature Reviews Microbiology, 13(12), 777–786. https://doi.org/10.1038/nrmicro3564