Bacteriophages as Therapeutics for Managing Drug-Resistant Tuberculosis?

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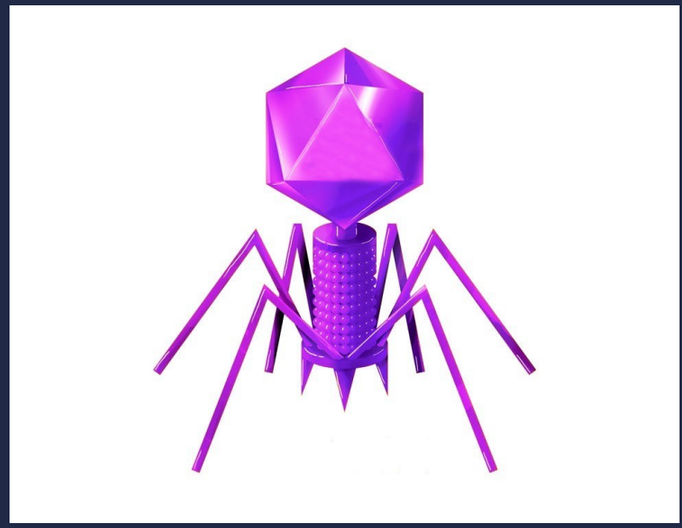
The world health organization has predicted high mortality rates due to infection by drug-resistant pathogens and has called for taking urgent measures to mitigate the crisis (WHO Report, 2019). While several national and international bodies have taken initiatives for finding new antibiotics, a less enthusiastic R&D by pharmaceutical companies towards antimicrobial drug discovery has aggravated the crisis globally. The alarming rate of occurrence of multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) therefore mandates pacing up the efforts to discover new drugs as well as explore alternative options with open mind.



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The world health organization has predicted high mortality rates due to infection by drug-resistant *Mycobacterium tuberculosis* and has called for taking urgent measures to mitigate the crisis (WHO Report, 2019). While several national and international bodies have taken initiatives for finding new antibiotics, a less enthusiastic R&D by pharmaceutical companies towards antimicrobial drug discovery has aggravated the crisis globally. The alarming rate of occurrence of multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) therefore mandates pacing up the efforts to discover new drugs as well as explore alternative options with open mind.

In this piece, am aiming to highlight the role bacteriophages (phages for short) can play as potential alternative or adjunct to antibiotics and why higher participation by the research and the medical community is required to examine them as effective anti-mycobacterial agents. Phages are virus of bacteria and are estimated to be the most abundant biological entity (1031) on the planet. They are highly specific predators to their bacterial hosts and have a benign presence in the environment. These simple facts make them a useful and inexpensive resource for developing new antibacterial solutions, especially against drug-resistant chronic infections. Also, the phage-encoded lytic enzymes such as endolysins, ectolysins, depolymerases are gaining attention as potential alternate/complement to antibiotics (Hatfull et al., 2012; Fischetti 2018). Bacteriophage therapy is already being practised in Poland, Georgia, Russia since about a century (A. Sulakvelidze*et al.,*2001; LL Furfaro*et al.,*2018; T Parfitt*et al.,*2005). Recently, a successful case study from United States (Schooley et al., 2017) where a terminally ill patient, suffering from a chronic multi-drug resistant *Acinetobacter baumanii*infection was rescued by phage therapy, has catalysed the research on clinical applications of bacteriophages.

Phage/lysin therapy for treating tuberculosis (TB) doesn't exist so far. The challenging part of using phages for treating TB is the intracellular location of *M.tuberculosis*(Mtb), which impedes the targeted delivery of phages. Also, only limited Mtb-specific lytic phages have been discovered so far. However, these are not intractable impediments; a greater number of Mtb-specific phages should be discovered and their variants can be created by genetic engineering to expand their host range or to meet the other therapeutic requirements. A major impetus to the cause came from a recent successful case of phage therapy against a non-tuberculous mycobacterial infection (*M.abcessus*) in a young patient of cystic fibrosis who had undertaken lung transplant and had developed chronic infection and the prognosis was poor (Dedrick et al., 2019). This case has served as a convincing proof of concept and drawn world's notice to the therapeutic potential of phages in treating mycobacterial infections. This was also the first instance, where a cocktail of genetically engineered mycobacteriophages (lysogenic genes were edited) were used in human therapy.

From L to R: Doctor Helen Spencer, Prof. Gram Hatfull, the patient Isabelle who undertook phage therapy for mycobacterial infection and hermother. https://www.sciencemag.org/news/2019/05/viruses-genetically-engineered-kill-bacteria-rescue-girl-antibiotic-resistant-infection

Besides using the whole virulent phages, the phage-derived lytic enzymes such as lysins can also be effectively used in the treatment of bacterial infections. Unlike standard-of-care antibiotics which are broad spectrum, endolysins are specific and hence are safe for the commensal microflora. Lysins can target drug-resistant strains with same specificity and sensitivity. Also, the occurrence of bacterial resistance against these enzymes is less probable since bacteria are less likely to modify peptidoglycan, which is one of the most essential components of the bacterial cell wall. For these reasons, a spurt in interest in phage derived endolysins, also called as enzybiotics, is being witnessed and several of them have been scaled up for commercial purpose (Fischetti, 2018). For example, Staphefekt™ is an endolysin-based aseptic solution (Schmelcher, Mathias, et al., 2015), manufactured by Micreos company (Netherlands) and Ecto-LysinTMP128 is an ectolysin (Shankaramurthy C. et al., 2017) from Ganagen Inc.Both the enzymes target skin infections caused by methicillin resistant*Staphylococcus aureus*(MRSA) Another successful example of a lysin effective against *S. aureus*infections is CF-301 developed by ContraFect Corporation (NY, USA)(Schuch*et al.*, 2017).

Mycobacterial cells have a complex cell wall (envelop) consisting of a cytoplasmic membrane and peptidoglycan layer, which is covalently linked to the arabinogalactan- peptidoglycan (mAGP) complex and mycolic acids (Chatterjee 1997). Mycobacteriophages usually encode two endolysins, Lysin A and Lysin B, which act on the peptidoglycan layer and the mycolic acid–arabinogalactan layer, respectively and help phages lyse the mycobacterium for the release of viral progeny. Phages and the endolysins can also be used synergistically with antibiotics. The combination can help to treat late-stage, drug-resistant infection by reducing the MIC (minimum inhibitory concentration) and delaying the occurrence of antibiotic resistance (Kalapala et al., 2020).

Hence, in the grim state of growing antimicrobial resistance, the natural killers of bacteria need to be brought in centre-stage and studied extensively to utilize their antibacterial potential. By using the modern tools for culture techniques, phage purification, high throughput screening, for genome & proteome analysis and understanding their pharmacokinetic/pharmacodynamics, the century-old therapy can meet the rigours of modern-day medicine. There is a vast reservoir of untapped bacteriophages and their derived lytic enzymes. What is required is to build repositories of well-characterized lytic mycobacteriophages and endolysin (natural and/or engineered) specific to drug-sensitive and resistant Mtb strains, devise efficient phage delivery mechanisms and develop procedures for effective phage therapy against tuberculosis. For this to happen, the scientists, clinicians and regulatory authorities need to work in tandem. Ultimately, framing guidelines for compassionate use of phages/phage-encoded lysins in treating drug-resistant infections and clinical trials should not be far-fetched to our imagination!

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