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Mycobacteriophages as a Modern Medicine to Treat Tuberculosis: Hope or Illusion?

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Editorial

The upsurge of Antimicrobial Resistance (AMR) has reignited interest in bacteriophages as an alternative to antibiotics. *M. tuberculosis* is genetically not diverse, and standard phages do not yet target it. The genome of human-adapted *M. tuberculosis* is substantially smaller than that of its environmental progenitors [1]. Also, it was previously speculated that intracellular life had hindered the defence mechanisms of active phage. It is now known that *M. tuberculosis* has the "direct repeat" regions on its genome, used for decades to genotype *M. tuberculosis*. These repeats constitute a defunct Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) system to defend against phages. Contemporary *M. tuberculosis* may not be prepared to resist the attack bacteriophages, especially in the face of various genetically modified bacteriophages. Table 1 shows the criteria for identifying infectious disorders eligible for phage treatment, as proposed by Harper [2].

Thus to investigate the potential of phages against Tuberculosis (TB), the bacterium from the active TB patient sputum and aerosol is an appealing target for proof-of-concept for trials. These tests should include pharmacokinetic/dynamic analyses to determine the best concentration, dosage interval, and treatment duration, as well as tests for a putative host immune response or phage resistance [3].

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Removing latent TB would be an intriguing long-term aim for phage, but it would likely depend on the location dormancy of the organism in the host if the phage can penetrate that environment. Following the availability of a lytic phage cocktail, the next stage is to scale up manufacturing to an acceptable purity level for clinical trials, which can begin after consultation with regulatory and ethics organizations.

To conduct safe clinical trials, it is necessary to carefully study the frequency of administration, the appropriate dosage method, and the interaction of available anti-tuberculosis drugs. Patients with Extremely Drug-Resistant Tuberculosis (XDR-TB) have the highest demand for alternative treatment options. They should first receive phage therapy to obtain therapeutic benefits in response to the global appeal to tackle AMR. The majority of *M. tuberculosis* observed in sputum is extracellular; hence the effect of phage treatment should be measured by a decrease in the number of live mycobacterial sputum bacteria. The penetration and activity within granulomas and phagocytes, where some mycobacteria are thought to live, will be more difficult to achieve [4,5].

Phages have been found to penetrate biofilms and kill persisted-type bacteria. However, this has not been demonstrated with *M. tuberculosis* [5]. Using phage-infected non-pathogenic mycobacterial cells to deliver phages to granulomas and phagocytes [6] is an intriguing concept for tackling the issue of phage transportation into granulomas and phagocytes. Small proteins can be successfully transported to phagocytes by coating them in liposomes, which would also protect the phages from circulating antibodies, according to a recent experience with new mRNA vaccines for Coronavirus Disease 2019 (COVID-19) prevention [7,8,9]. However, it can be assumed that on extracellular level, phage treatment maybe safe and effective, but phage penetration into intracellular and granulomatous settings, as well as synergistic effects with antibiotics, are key concerns to investigate further.

Table 1: Suitability of pulmonary tuberculosis for mycobacteriophage therapy, the table adopted from Harper [2].

Is there unmet need?		
Confirmed bacterial pathology	Pros	• *M. tuberculosis*
Need is sufficient to support planned development work	Pros	• Global significance • Millions of cases yearly • Rising resistance rates • Few new antibiotics
	Cons	• Not attractive for profit-oriented investment at this time
Is the disease suitable for phage therapy?		
A single or limited number of bacterial species responsible for pathology	Pros	• Low strain diversity of *M. tuberculosis* facilitates a “one cocktail for all” approach
Quantitative assay for target bacteria	Pros	• Sputum counts and culture conversion as done in antibiotic studies
Suitable model systems available	Pros	• Hollow fiber and animal models
	Cons	• Models imperfect for human disease
Accessible site of infection	Pros	• Per inhalation or intravenously
Bacterial density to support amplification	Pros	• Extracellular *M. tuberculosis* implicated in pulmonary TB and expelled sputum and as droplets
	Cons	• The intracellular nature of *M. tuberculosis* and granuloma formation limit phage access
Patient group suitable for trials	Pros	• In high prevalence areas
Are suitable bacteriophages available?		
Mycobacteriophages	Pros	• Effective 5-phage cocktail • Obligate lytic • No transduction potential • Genetically diverse • Active against all lineages of *M. tuberculosis* • Beneficial resistance profiles
High levels of growth in suitable bacterial hosts	Pros	• Dual infection of fast-growing *M. smegmatis* and *M. tuberculosis*
Stability and purity of the product	Pros	• Manufacture to GMP standard as explored in other therapeutic areas

Conflict of Interest

The authors declare no conflict of interest.

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