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Phaging out antibiotics

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During the First World War (WWI), more soldiers died of infection than they died of enemy gunfire. Mortality was high. Army camps all across the world were breeding grounds for infections and 57 000 American soldiers died due to infection, while 50 000 died in combat.[1] The race was on to find the cure for this deadly disease. It was around WWI that a virus named bacteriophage had been discovered. However, the world was then split between the viral and self-perpetuating enzymatic theory of bacteriophages.[2] It was not until 1940, after the invention of the electron microscope that this debate was put to an end.[3]

In 1917, Felix D'Herelle at the Pasteur Institute in Paris, a pioneer in phage therapy, isolated bacteriophages in the faeces of patients with dysentery and started using it immediately to treat his patients.[4] During this time, he also collaborated with George Eliava who started the Eliava Institute of Bacteriophage Microbiology and Virology in Georgia (erstwhile USSR) dedicated to bacteriophage therapy. However, due to WWII and the cold war that ensued, scientific literature from the 'Eastern Bloc' was labelled 'communist' and ostracized (another example of McCarthyism). Simultaneously, due to the discovery of highly efficacious antibiotics (sulpha drugs and penicillin) which provided great results on patients suffering from infectious diseases and the ability to produce them *en masse* side-lined phage therapy for decades. However, by the late 2000s, the same pharmaceutical boom had resulted in reckless antibiotic prescription, and bacteria, much like the sword of Gryffindor, became stronger and harder to destroy[5] as they evolved mechanisms of resistance to conventional antibiotics. Since bacteria have inherent mechanisms that allow them to evolve at a faster pace than the pharmaceutical industry, soon many antibiotics were rendered useless (at least temporarily) due to rampant resistance. I understood how severe the problem was in my third year as a medical student while participating in the clinical rounds of the medicine ward, when I read the prescription chart for one of the patients. On the chart was an astounding cocktail of vancomycin, linezolide and quinpristin, which I had learnt were end-of-the-line drugs and that if bacteria became resistant to these, prayer was the only available solution.

It was not until recently that I had read an article on the applications of phage therapy, where 'viruses that ate bacteria' were being used as bactericidal agents, the way nature intended the world to be. In this battle royale between the bacteriophage and antibiotic therapies, phage therapy draws first blood due to its unique physiology. Bacteria are notorious for undermining antibiotics through their CRISPR/Cas (Clustered regularly interspaced short palindromic repeats) pathway as is evident from the emergence of 'extremely' drug-resistant bacteria (superbugs).[6] Phages can counter these mechanisms through their anti-CRISPR chemistry.[7] Bacteriophages have enzymes that degrade extracellular polymeric substances (EPSs) through EPS depolymerase. This helps them penetrate biofilms and thus making them effective against biofilms,[8] which have often been proven to be resistant even against most kinds of sterilization procedures. The pharmacodynamic properties of phages allow them to multiply inside the host and in fact increase their concentration over time and engage in bactericidal activity only where required, whereas the concentration–time graphs of all antibiotics point downward, and the antibiotics often end up causing immense collateral damage.

Preparation of phages is an interesting process as most phages are isolated from the sewage of the nearby locality and purified for clinical use. Preparation of phage therapy usually follows one of two different models. The first is a 'fixed-formulation approach' (pret a porter), where the causative agent is identified, and the corresponding virulent phage synthesized. Such an approach is highly personalized but extremely rigid as the entire process needs to be repeated in case a phage-resistant bacterium develops. The second is the 'phage bank approach' (sur-measure), where multiple phages (usually about 10) are synthesized into a 'phage cocktail'; its spectrum being broad its synthesis is labour-intensive and expensive (one course of phage therapy at Eliava Institute costs €8000–€20 000).[9] A phage bank that is customisable for an individual seems to be a middle ground between these two extremes.[10] Phage therapy is extremely versatile in its modes of administration. Phage-impregnated polymer (PhageBioDerm) has been used to treat infected skin ulcers.[11] Normal saline with phages has been used as an irrigation fluid that provides prophylaxis against wound/surgical site infections.[12] Phage therapy can be even directly administered to the site of infection for increased efficacy, such as up the urethra into the bladder for urinary tract infections, intraperitoneally for systemic infections, by nebulization for pneumonia, into the middle ear cavity for otitis media and applied topically on burns and infected wounds.[13] A crucial aspect of biological antibacterials is their applicability on living tissue, i.e. their selective toxicity and less potency to cause harm to commensal microbiota.[14]

Globally, there are two major challenges that prevent mass acceptance and widespread prescription of phage therapy among the medical community. The first is the paucity of randomized controlled trials (RCTs) due to an inherent inability to constitute a control arm which is not prescribed antibiotics, as it would be ethically wrong to not provide the participants with the best therapy available. Hence, the RCTs even if conducted, with a control arm (antibiotics only) and the test arm (antibiotics+phage therapy), could only measure the incremental

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benefit that phage therapy provides and not its independent efficacy over antibiotics. However, since most newly discovered chemically synthesized antibiotics also face the same problem, conducting RCTs and generating evidence should not be the main obstacle going forward. Indeed, a landmark phase 1 and 2 trial conducted by Wright *et al*. in 2009 provides a concept of proof for others to emulate.[15] In addition, phages are biotherapies, similar to maggots, larvae and the faecal microbiota transplant (FMT) used to treat pseudomembranous colitis, which due to their highly specific and evolvable nature fall into the category of personalized medicine and make conduction of RCTs theoretically difficult if not impossible.

Second, the regulation surrounding phage therapy in India is non-existent. However, since 2011, phages have been considered by the European Union and the United States Food and Drug Administration (USFDA) as a 'medicinal product' or 'drug' subject to strict rules and regulations.[16] According to the USFDA guidelines, they must be produced according to good manufacturing practices, must demonstrate their safety and efficacy in RCTs (phase 1, 2, 3 and 4) and must obtain marketing authorization. Even though such regulations have their own pitfalls (phage therapies are personalized and cannot be manufactured *en masse* industrially), they are a good starting point towards recognizing the problem of antimicrobial resistance and attracting industrial and academic funding, which is crucial for establishing the expensive infrastructure needed to isolate, purify and manufacture phages on an industrial scale. To translate phages from the raw material (sewage, nearby river bodies) to the final product (pill, capsule, lotion, skin patch), the following steps are key. The isolation of phages from the raw material using a bacterial host which requires state-of-the-art bacterial culture facilities with the appropriate Bio-Safety Levels according to the virulence of the host bacteria (BSL-2 for *Pseudomonas aeruginosa*). Phage identification and phage enumeration, which require state-of-the-art polymerase chain reaction (PCR) and whole-genome sequencing techniques to rule out phages that increase the toxicity of the bacteria, following a lysogenic cycle, or confer anti-phage resistance to the bacteria itself. Ultimately, numerous quality control and safety tests need to be performed on the resultant preparation to check for identity, quantity, bioburden, bacterial endotoxin levels, pH, water content, etc. All these costs are incurred even before the first dose of phage therapy is administered and are usually prohibitive for new companies to establish without major funding. Naturally, there is only one government institution in India that performs research on phage therapy, the Central Research Institute in Kasauli, Himachal Pradesh (especially against *Salmonella*),[17] and few entrepreneurial ventures such as 'Phage Shift'[18] have started in India that are trying to bring phage therapy into existence.

In the past few decades, in modern medicine, we have concerned ourselves more with short-term gains and conveniences over long-term consequences. It seems poetic to me that the ultimate solutions to all our problems lie within nature. Phage therapy is a sobering reminder of humankind's place as an integral part of the ecosystem and not as its master.

Conflicts of interest. None declared

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