CLINICAL MICROBIOLOGY

Treat phage like living antibiotics

Bacteriophage therapeutics has emerged as one of the few potential beacons that represent possible solutions to the growing global crisis of antimicrobial resistance. Bringing science to the bedside (and vice versa) will maximize the potential of this compelling opportunity.

Robert T. Schooley and Steffanie Strathdee

Robert Redfield, Director of the US Center for Disease Control and Prevention, stated in 2019 that we should "stop referring to a coming post-antibiotic era. It's already here". Bacteriophages (phages) have been parasitizing and shaping evolution of their bacterial prey for 300,000,000 years[1,2]. The primary battlefield for the estimated 10^{31} unique phages and 10^{12} microbial species has been the natural environment, but skirmishes occur continuously within and on surfaces of all animal and plant species[3,4]. In the century during which these 'eaters of bacteria' became known to science, enthusiasm about phages as bona fide antimicrobial therapeutics has fluctuated widely[5]. Phages have been administered for decades in the former Soviet Union and Eastern Europe — generally as crude lysates but rarely parenterally. In this issue of *Nature Microbiology*, Jonathan Iredell's Westmeade Hospital group contributes to a growing consensus that it is time to rigorously evaluate phages in the urgent effort to develop novel approaches to the global crisis of multidrug-resistant bacterial infections[6].

The manuscript reports their experience using adjunctive phage therapy to treat 13 patients with persistent *Staphylococcus aureus* sepsis. As they note, the study design precluded any serious assessment of efficacy. However, it is one of the first efforts to parenterally administer a well-characterized fixed combination of phages to a prospectively defined patient population with a serious bacterial infection. This represents an important step forward from the growing number of isolated case reports of parenterally administered phage therapy in western literature over the past three years. With all of the caveats of missing signal in a severely ill patient population, the investigators add to the knowledge base about the safety of parenterally administering phages prepared under rigorous GMP-like conditions and meticulously scrubbed of bacterial endotoxin. Furthermore, efforts to systematically collect useful information about pharmacokinetics, pharmacodynamics and resistance kinetics were an important addition and illustrate the best in investigator-initiated research.

So, what's next?

It is time to reframe the discussion about phage therapeutics from being fringe to a novel antimicrobial approach that should follow the same clinical development pathways we've successfully applied to traditional antimicrobials for over 70 years. The most important caveat is that phages are living antimicrobials that evolve with their bacterial targets. The guiding conceptual framework of clinical development thus requires working at the interface between bacteriology and virology — developing the clinical and translational research agenda with both disciplines in mind.

The process for developing an understanding of absorption, distribution, metabolism and excretion characteristics of antibiotics is well established and relies heavily on preclinical animal studies in uninfected animals[7]. Many antibiotics have failed simply because they cannot be delivered to their sites of infection or because rapid metabolism and excretion make clinical administration impractical. One of the major advantages of phage therapeutics may well be that replication within their bacterial hosts at the site of infection will make them much more forgiving than antibiotics in terms of delivery. However, phage therapeutics will require the introduction of new considerations, such as multiplicity of infection, physical contiguity and size of the bacterial target population, and the rate of bacterial evolution in the setting of selective pressure by one (or likely more than one) phages during treatment. These investigations should be aided by the

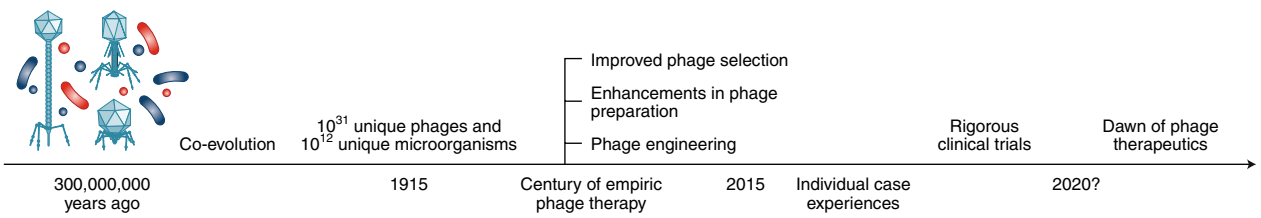

Fig. 1 | Phage evolution: from sideshow to centre stage. In the 300,000,000 years since phages and bacteria began their evolutionary dance, they have continuously shaped each other. Efforts to harness their bactericidal potential to treat serious bacterial infections began shortly after their discovery just over 100 years ago. These efforts were abandoned in the 1940s in the west with the advent of modern antibiotics. As microbial evolution has outpaced antibiotic development, there has been an increasing interest in developing novel solutions to the multidrug antibiotic resistance crisis. Advances in the understanding of phage biology and in technologies that enable the production of large quantities of highly purified phages have rekindled an interest in phage therapeutics. At this inflection point, from anecdotal, single-patient experiences to rigorous clinical trials, the stage is set to determine the true potential of phages in human medicine.

construction of carefully characterized and annotated phage libraries.

Mathematical modelling was critical to the expeditious development of antiretroviral therapeutics, and it will be even more important in phage development[8]. Methodologies that enable clinical laboratories to both exploit phage diversity but accurately and rapidly identify phages with the greatest likelihood of clinical efficacy against a unique bacterial isolate are not yet developed, but will prove vital. Despite pressures for rapid financial returns when new technologies first reach the clinic, in the case of phage therapeutics, it would be a mistake to launch a large number of 'simple' clinical endpoint trials that are not based on a solid understanding of pharmacokinetics and pharmacodynamics. Doing so is fraught with risk for trial participants and for the field of phage therapeutics.

We may not yet be in a 'post-antibiotic' era, but we should use everything we learned about drug development in the antibiotic era to get there. Phage therapeutics has been characterized by some as 'high risk, high gain' research. A more compelling argument can be made that phage development is actually rather low risk but still high gain.

Phage have been killing bacteria since life emerged on the planet. Despite hand wringing within some corners of the investment and commercial worlds, regulatory agencies (especially those in the US) have a much clearer understanding of clinical development issues than given credit for. Clinical development that proceeds through the traditional framework with carefully considered clinical development plans and rigorously defined and prepared therapeutic products rather than haphazard clinical studies with heterogenous, semi-characterized materials is much more likely to yield what is most needed: namely, the ability to work in concert with these ancient organisms to address the growing scourge of multidrug resistance.

As we embark on these studies, we should also consider whether there are features of phage biology that can be exploited with modern molecular tools to create 'next generation' phages that transcend potential shortcomings of environmentally sourced phages. These could include broadened host range, increased lytic or biofilm disruptive capacity, or removal of genetic material that might promote bacterial pathogenicity or lysogeny. Phage development will require creativity, patience and rigor, but the need is great enough that the chance for ultimate success is very high (Fig. 1). ❐

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Competing interests

R. T. S. serves as a consultant to CytoDyn and has stock options in CytoDyn and Antiva Biosciences. He is a member of the Gilead Sciences Scientific Advisory Board and previously served as an uncompensated member of the AmpliPhi Scientific Advisory Board. S. S. holds stock in Adaptive Phage Therapeutics and is an uncompensated scientific advisor to NextBiotics.