Future MICROBIOLOGY

EDITORIAL

Re-establishing a place for phage therapy in western medicine



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Use of bacterial viruses as antibacterial agents has a history nearly as long as the now 100-year study of bacteriophages. Therapeutic phages are especially useful in the absence of alternative treatments, as was the case in the preantibiotic era and is again true in the face of declining antibiotic effectiveness and increasing awareness of their often-problematic consequences. As the dilemma of antibiotic resistance grows, new antimicrobial strategies must be found or our healthcare system will revert to a preantibiotic era for many pathogens. This has become a major priority of WHO, as well as politicians and public health systems around the world [1]. Antibacterial agents against which resistance has not yet evolved, ones that are inexpensive and also display low toxicities are needed. Bacteriophages, in particular, exhibit these characteristics and this, the 100th anniversary of their discovery [2], is a good time to consider how phages may be integrated into our antibacterial arsenal. The key issue is how to leverage an extensive history of clinical and experimental safety and efficacy toward re-establishing a place for phage therapy in western medicine. Here we suggest increased emphasis on collaborative compassionate use to lay the groundwork for physician and public acceptance as well as full-blown clinical trials.

There is widespread interest in bacteriophages playing a role in helping to fill the antimicrobial gap [3]. Unlike small-molecule antibiotics, these natural and ubiquitous antibacterials offer clinical advantages [1,4], as well as challenges [5], in that they very precisely target specific bacteria and nothing else [6,7]. Longstanding medical use of phages supports their usefulness [6,8,9] and no reasonable amount of Phase I clinical trials could demonstrate the safety of phage therapy beyond what we can already infer from the large number of people who have been treated using phages in France and Eastern Europe without serious consequence [6,7,10,11]. We are surrounded by phages, including in our food. Phages targeting the foodborne pathogen *Listeria*, in fact, were approved by

KEYWORDS
• clinical phage trials
• compassionate care • MRSA
• phage therapy • *Staphylococcus aureus*

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the US FDA in 2006 for use in packaged meats and cheeses, and have been given the designation Generally Regarded As Safe (GRAS) [12]. Phages are also able to disrupt biofilms [13] as well as self-replicate in conjunction with their antibacterial activity.

Targets for phage treatment include infections caused by *Acinetobacter, Pseudomonas aeruginosa* and *Staphylococcus aureus* (including MRSA), in wounds, burn patients and the lungs of those with cystic fibrosis; foodborne or enteric pathogens such as *Campylobacter*, *Escherichia coli, Klebsiella*, *Listeria*, *Proteus*, *Salmonella, Shigella* and *Vibrio cholerae*; and the potential bioweapons, *Bacillus anthracis* and *Yersinia pestis* [6,7,14]. A number of companies are pursuing phage therapy preclinical research, serve as suppliers of existing products or function as facilitators of phage-therapy services for those individuals who are able and willing to travel [15]. Notwithstanding the extensive need, interest, experience and reported successes of phage therapy, typical western approaches to biomedical research and implementation are poorly adapted to motivate, regulate or assess such nonstandard approaches to antibacterial therapy [5,16].

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Phages have been used clinically for decades, especially in eastern Europe [6,7], but modern phage therapy has been subject to multiple roadblocks in the USA and western Europe. Phage therapy in its first decades suffered from inadequate understanding of phage biology. By the time this issue was resolved, phage therapy in the USA was dealt a double blow of inconsistent clinical results [17] and introduction of the seemingly miraculous antibiotics. In the former Soviet Union, by contrast, phage therapy had been more systematically developed as a standard of care prior to the widespread introduction of antibiotics [6,7] and so was less easily supplanted. Today, in the west, phage therapy suffers from insufficient credibility, patient and physician unfamiliarity and related limited product availability. This ties in with a very challenging regulatory environment that, although in many ways supportive of phage therapy development, is both expensive and poorly suited to harnessing the power of what could be an abundance of relatively inexpensive, diverse and safe antibacterial agents [5,6,16,18].

Here we consider one cause of the delay in getting clinical phage therapy to effectively take root, especially in the USA, and in addressing that issue suggest a solution. As recently outlined by one of us [9], phage therapy is relatively unique among medical therapies in that far more experience and indeed success exists for clinical phage therapy than for corresponding preclinical efforts. This in ways flips the modern model of medical research, which consists of some form of *in vitro* discovery, subsequent animal testing, safety trials in patients and then efficacy trials. Instead, to the extent that this path was followed for phage therapy, it took place many decades ago, with those efforts followed by extensive clinical use such that the vast majority of experience using phages as antibacterial agents has accumulated in the course of medical practice.

An enormous problem exists – antibiotic resistance – but also there have been decades of apparent phage therapy clinical success in addressing the problem [6,7,9–11,14]. The root of that success, however, dates back to before the widespread introduction of double-blind efficacy trials as the gold standard of medical research, much of the experience is observed in distant lands, and clinical results have been published mostly, although not entirely, in languages other than English. Modern, western phage therapy researchers, following established pharmaceutical development protocols, therefore have been compelled to proceed through a process of emulating existing phage therapy clinical experience via extensive preclinical, proof-of-principle research. In principle, these preclinical efforts are followed, resources allowing, by formal clinical trials, all before western physicians might be encouraged to use phages to relieve the very real suffering of countless patients affected by antibiotic-resistant infections. In practice, however, 20-plus years after the 'rediscovery' of phage therapy by western scientists, not a single Phase III disease-treatment clinical trial has taken place [6,11].

From the perspective of phage therapy research and development, an important lesson from these observations is that there is much to be learned from past and present phage treatment of bacterial infections in actual patients [9]. From the perspective of bringing phages into more common use in western medical practice, we feel that physician-initiated trials are needed that join historical knowledge with modern, molecularly characterized phage products. Physicians are in the best position to bring the benefits of phage therapy to their patients, especially in

treating chronic or otherwise antibiotic-resistant bacterial infections. This clinical experience needs to then be tested in formal clinical trials, an important step that has been stymied at least in part by legitimate commercial concerns in combination with the extremely high costs of formal clinical development of pharmaceuticals. It should be noted that this is a problem that has had a hindering effect not just on phage therapy, but on antibacterial clinical development more generally.

In our opinion, timely phage therapy clinical development will require greatly increased coordination of input from interested parties. To help jump-start the process we therefore strongly encourage the formation of collaborative public–private and academic–patient–practitioner endeavors aimed toward clinical adoption of phages, particularly for treatment of widespread health problems that are challenging in terms of standard antibiotic treatments. To be successful, the chosen targets should be clearly defined and widespread, with substantial socioeconomic impact, yet still permit continuation of existing, standard treatments during phage administration. Furthermore, these should be applications where appropriate phages are already identified, well studied and readily available.

By these criteria, *S. aureus* is an ideal target. It is a ubiquitous inhabitant of our skin, yet also a major component in many wound infections, postsurgical complications, pressure ulcers, diabetic ulcers, pneumonias and competitive sports injuries, among others, and is increasingly multidrug resistant [8]. *S. aureus* surface properties are sufficiently homogeneous that, in contrast to phages targeting Gram-negative pathogens, most purely lytic *Staphylococcus* phages are active against most species members, including MRSA [8,19]. *Staphylococcus* phages also have been widely used in French, Belgian, US, Russian and Georgian phage formulations [6,7] ("Georgian" refers to the former Soviet Republic and now the country of Georgia). Broad safety data also can be derived from decades-long human use in the USA of Staphage Lysate (Delmont Laboratory, Swarthmore, PA, USA) [8], which has phage concentrations as high as Georgian commercial phage cocktails [Bennett M, Kutter EM, Unpublished Data], [Kuhl SJ, Kearney G, Unpublished Data].

We suggest compassionate use of *S. aureus* phages in combination with standard *Staphylococcus* treatment protocols, in collaboration with academic phage researchers and suppliers of existing phage products, moving as appropriate toward clinical trials of topical phage applications. Much pertinent clinical data [6–8] underlies this proposal, from the first phage therapy paper [20] to MacNeal *et al.*'s 1930s–1940s work with hundreds of patients in NY, USA [21], to extensive French, Polish and Georgian published clinical work extending up until current times [6–8,10]. The influential 1930s Eaton and Bayne-Jones *JAMA* report [17], exploring over 100 English-language articles, concluded that phage therapy of *Staphylococcus* infections was the one area where there was sufficient evidence to say that these phages clearly work: "A great many of the reported favorable results of bacteriophage therapy have come from the use of this agent in staphylococcal infections." One also sees far less bacterial resistance to *Staphylococcus* phages than to other phages, or antibiotics, that are used clinically [7,8,11].

In many applications, introducing anti-*Staphylococcus* phage therapy into western clinical practice in a collaborative, compassionate-use fashion would not require further deviation from the current standard of care beyond careful record keeping as well as blinding for clinical trials. We predict that successes would facilitate progress toward large-scale clinical trials of a range of external phage applications. Such accomplishment would increase confidence and interest in the potential of phage therapy, encouraging commitment of both private and public funds to its further western development.

Acknowledgements

The authors would like to thank Bob Blasdel, Randy Fish and Gordon Wheat for helpful discussions.

Financial & competing interests disclosure

EM Kutter serves as Chairman of the Board of the nonprofit Phagebiotics Research Foundation (phagebiotics.org), which she founded. ST Abedon has consulted and served on advisory boards for various companies with regard to phage therapy issues and is the founder of the website, phage.org, as well as the related, phage-therapy.org. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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