

Phage therapy—advantages over antibiotics?

As antibiotic-resistant bacteria continue to threaten standard therapies against bacterial infections, a new breed of antimicrobials may be on the horizon. Many researchers believe that bacteriophages—viruses that only infect bacteria—are a promising potential therapy for bacterial disease treatment.

Phage therapy boasts several advantages over traditional antibiotics. "Yeast infection and diarrhoea are frequent side effects of antibacterial therapy because the beneficial bacteria of the genital tract and intestines are also killed, disrupting the ecology and enabling other pathogens to grow out and cause disease", explains Paul Gulig (University of Florida, Gainesville, FL, USA). However bacteriophages target specific bacterial strains, thus sparing patients from the side effects caused by destroying natural flora.

Another positive aspect of phages is their capacity for exponential growth. Essentially, phages closely follow the course of bacterial growth and presence, multiplying alongside bacteria, and disappearing once the bacteria has gone. Even though bacterial resistance is a concern, unlike antibiotics, phages can mutate in step with evolving bacteria. Also if bacteria become resistant to one phage, there is a natural abundance of phage species, which could attack even new resistant strains.

Richard Carlton, president of Exponential Biotherapies (Port Washington, NY, USA), explains, "one great thing about phages is that mutations that enable bacteria to resist antibiotics do not enable the bacteria to resist the phage, and vice versa". That's because each form of treatment acts on a different part of the bacteria to disarm and destroy it, says Carlton.

Phage therapy has been deemed a success in parts of eastern Europe for decades. In Tbilisi, Georgia, home of the Eliava Institute of Bacteriophage, Microbiology, and Virology, where phages have been studied since 1934, researchers report that phage therapy has an 80% success rate against enterococcus infections. In Poland, doctors have had a 90% success rate against cases of *Staphylococcus aureus*,

Pseudomonas aeruginosa, *Klebsiella pneumoniae*, and *Escherichia coli*.

However phage therapy has not been well received by the wider medical community. Why is, for example, the USA so reluctant to accept a therapy that has been deemed successful in eastern Europe? Inadequate scientific methodologies used by early scientists have contributed to the perception of phage therapy as a failed approach, explains Carlton. These poor methodologies have included "the failure to conduct placebo-controlled studies, to remove endotoxins from the preparations,



Phage attack a bacterium

and to reconfirm phage viability after adding sterilising agents to the preparations", he says. Such oversights have produced mixed and allegedly fatal results—in fairness to pioneering phage scientists, their era predated the discovery of phenomena such as lysogeny, which helps identify pure phage strains, and could have enhanced their research efforts.

The new generation of phage scientists have had to overcome this bad publicity and resolve some scientific issues. For example, phages' particular taste for a specific bacterial target increases pressure to have a precise diagnosis. Rapid progressive and fatal infections shorten the timeframe in which to culture and identify a strain to select the suitable phage. Scientists have addressed these points by combining different phages into one therapy. "The down side to the specificity", says Gulig, "is that all strains of a given bacterial species may not be killed by every phage. However, this can be compensated for by using a mixture of phage that collectively covers the majority, if not all, of the known strains of a disease-causing species".

Another shortcoming was that, being foreign proteins, phages were cleared from the body too quickly. "Many drugs have clearance problems", says Carlton, "and that was the case with phages". This problem was addressed by a collaborative research project that involved Exponential Biotherapies, the National Institute of Health (NIH), and the National Cancer Institute in

1996. Led by Carl Merrill, NIH chief of the laboratory of biochemical genetics, researchers developed the "serial passage" method for isolating long-circulating strains of phages (*Proc Natl Acad Sci-USA* 1996; 93: 3188-92).

These long-circulating phages, produced by serial passage, were significantly more effective than the wild-type phages from which they were derived, in terms of curing animals of an otherwise fatal bacteraemia. "Long-circulating phages are important as therapeutic agents", suggests Carlton, "because the wild-type strains tend to be cleared so rapidly that they do not have time to reach and kill the infecting bacteria."

Such research breakthroughs, and more recently, data from several clinical trials presented at this year's annual meeting of the American Society for Microbiology, (Los Angeles, CA, USA; May 21-25) have won phage therapy acceptance by suggesting that it could tackle various antibiotic-resistant bacteria. For example, University of Florida researchers examined bacteriophages isolated from seawater, which could infect *Vibrio vulnificus*, which can cause serious septicemia. When they treated mice with iron overload and infected them with *V vulnificus*, the untreated rodents died within 24h compared with the phage treated mice, which recovered.

Research will continue in the hope of undoing phages therapy's poor reputation and of perfecting natural phages to make them more potent and adaptive. Although phage injections or a prescription for phage pills may still be a long way off, hospitals may be ready to benefit from this antimicrobial aid. Phages could be used in hospitals as a prophylactic to decolonise immunocompromised patients or patients waiting for surgery.

Mike DuBow (McGill University, Montreal, Canada) suggests that "phage therapy won't be a total replacement of the antibiotic arsenal but a supplement to it. But antibiotics remain too important, too successful, and too necessary to completely do without". The next stage, he believes, is more regulatory than science. "What we think we know about phages has to be verified and then deemed reproducible safe and effective", says DuBow.

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