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The Promise of Bacteriophage Antimicrobial Therapeutics

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Abstract

With the end of the antibiotic era looming, alternative antimicrobial agents are desperately needed. Lytic bacteriophage specific for a variety of bacteria have been used for almost 100 years to successfully treat serious infections. Here we make the case for pursuing formal regulatory approvals for the use of bacteriophage as therapeutic antimicrobial agents.

Following Alexander Fleming's discovery of penicillin in 1928, the world experienced an antibiotic renaissance in which previously deadly bacterial infections could be cured by a variety of antimicrobials. However, in the past three decades, bacteria have responded to the onslaught of new antibiotics with a deluge of mutations and gene acquisitions, as well as the means to transmit them to both their own and other bacterial species, such that they are rapidly becoming insensitive to all of the drugs. The U.S. Centers for Disease Control and Prevention (CDC) estimates that antibiotic resistant bacteria cause at least two million illnesses and 23,000 deaths annually in the United States. The speed at which bacteria replicate combined with their ability to transfer antibiotic resistance factors in the microbial community has led to an ever-expanding group of serious infectious threats. For rapidly emerging pathogens like carbapenem-resistant Enterobacteriaceae, the mortality rate can approach that of Ebola virus. This observation was driven home in July of 2011 at the National Institutes of Health Hospital in Bethesda, MD when an outbreak of carbapenem-resistant *Klebsiella pneumonia* infected 18 patients, 11 of whom died. There were simply few therapeutic options for these patients.

Lagging Antibiotic Development

Antibiotic development has lagged far behind the development of resistant organisms. Between 2010 and 2015, the United States Food and Drug Administration only approved 8 new antibiotics. Seven had similar mechanisms of action to currently approved drugs. However, past experience with antibiotics like linezolid, levofloxacin, and ceftaroline should temper optimism, because resistant organisms to each of these drugs appeared within a year or less after their release [1-3].

In addition to the need to avoid resistance, new approaches to antimicrobial therapy must avoid disruption of the gut microbiome. Disruption of the gut microbiome or dysbiosis has been shown to play a role in neurodegenerative disease, obesity, heart disease, diabetes, multiple sclerosis, and tumorigenesis [4-7]. However, the most immediate serious effect of dysbiosis is superinfection with *Clostridium difficile,* an organism that causes approximately a half million infections and 29,000 deaths annually in the U.S. [8]. The most effective new anti-microbial agents will be those that target the pathogenic bacterial species without causing dysbiosis.

Bacteriophages as Anti-microbials

With anti-microbial resistance approaching a critical level, other alternatives are needed. Lytic bacteriophage, bacterial viruses that infect and destroy a narrow range of bacteria, may be effective alternatives to antibiotics. The literature on the use of bacteriophage to treat bacterial infections goes back almost 100 years and has been extensively reviewed [9,10]. In the early 1920s, investigators described the successful intravenous use of phages to treat typhoid fever, cholera, and *Staphylococcus aureus* bacteremia [9-11]. During a 10-year study of the use of bacteriophages to treat typhoid fever at Los Angeles County General Hospital, researchers treated 56 patients with type-specific phages with the result that 53 made complete recoveries [12]. In 1982, a study was conducted in which 48 patients with purulent lung disease and who received intravenous *S. aureus* phages were compared to a control group that received antibiotics. The recovery rate was 95% for the group that received phages versus 64% for the group treated with antibiotics [13].

Bacteriophage possesses all the features of an ideal therapeutic agent in that they can destroy a microbial pathogen yet are harmless to the patient. The safety and efficacy of bacteriophage therapy has been recently reviewed [14]. Yet, although there have been no safety issues reported, the authors cited several potential concerns related to phage therapy. The first is that phages may not remain in circulation long enough to effectively remove the pathogen. Yet Ochs et al. have shown that clearance of bacteriophage φX174 takes several days [15]. Furthermore, researchers have shown that it is possible to select for long-circulating bacteriophage variants [16].

A second concern is the possibility of anaphylactic reactions to injected phage. There are no reports of this occurring. Some of the early researchers noted shock-like responses to phage injections; however this was due to contaminants from the media in which the phage were grown [14]. Today, therapeutic phages are highly purified from media components and residual endotoxin from their bacterial hosts [14].

A third concern is that rapid phage-mediated lysis of bacteria could cause a catastrophic release of bacterial exo- and endotoxins. However, many antibiotics rapidly lyse bacteria, and the adverse effects are both minimal and manageable from a clinical standpoint.

Advantages of Phage as Anti-Microbial Therapeutics

Bacteriophage therapy has several distinct advantages over antibiotics, especially for drug resistant pathogens. Antibiotic classes generally target processes common to many bacterial species, a property that allows them to be used against a number of microbial pathogens. However, as noted above, this can be a double-edged sword. Therapy with a broad-spectrum antibiotic can cause dysbiosis, resulting pathologies such *C. difficile* colitis. In contrast, most phages have narrow host ranges, which limit their effect on the normal flora and the side effects that result from dysbiosis [17].

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Phage therapy is particularly suited to treating skin, wound, and purulent infections as well as deep tissue and bone infections. The Eliava Institute in Tbilisi, Georgia has been a pioneer in the area of commercial phage therapeutic products. Their PhagoBioDerm product is a polymer bandage containing phages against *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus*, *Streptococcus*, and *Proteus,* species frequently associated with suppurative skin infections. In one study, patients who had failed to respond to traditional treatments for skin ulcers, showed complete healing after application of the PhagoBioDerm polymer [18]. The product has also been successful in treating furunculosis and surgical abscesses [1].

To avoid resistance, phage cocktails can be used in a manner similar to HAART therapy for HIV. HAART therapy consists of at least 3 different antiviral drugs each targeting a different step in the viral life cycle, which mitigates the development of drug resistance. Similarly, the phages in a cocktail directed against a particular pathogen may target different receptor molecules, making it highly unlikely that the bacterium would develop resistance.

In order for an antibiotic to be effective, it must achieve a certain level in the blood or tissues in order to reach the minimum bactericidal concentration for a given organism. This is especially difficult for deep tissue and bone infections where drug penetration levels may fall below that needed to treat the infection. In contrast, when a single phage finds it target, it amplifies its ability to kill through replication and release of millions of progeny that can spread and infect other bacteria in the area.

Respiratory infections have also been successfully treated with bacteriophage. In 2011 researchers from the Eliava Institute reported the successful treatment of a 7-year-old female cystic fibrosis patient who showed chronic colonization of her lungs with *P. aeruginosa* and *S. aureus* [19]. Several other researchers have validated the efficacy of bacteriophage therapy for treating respiratory infections [20-22]. More recently, at this year's Centennial Celebration of Bacteriophage Research at the Institute Pasteur in Paris, Dr. Robert Schooley of the Division of Infectious Diseases at the University of California San Diego School of Medicine described a case where an intravenous application of a bacteriophage was able to save the life of a patient terminally ill from multi-drug resistant *Acinetobacter baumannii* [23].

Conclusions

Before single phage or phage cocktails can become standard therapeutics for bacterial infections they will need to go through carefully crafted clinical trials in order to gain regulatory approval. While the literature is replete with reports of the clinical applications of phage therapy, to date the research has been piecemeal and lacking in both careful controls and the number of patients required to demonstrate its efficacy for a given application. After 95 years of small-scale studies and discussions of its promise, it is time to focus on providing the proof necessary to bring phage therapy into clinical practice. The age of antibiotics is coming to an end, and if the scientific community does not make a concerted effort to find alternative therapies, simple urinary tract infections could soon prove routinely fatal. However, nature may have already provided the answer in the form of lytic bacteriophage. Understanding and developing phage technology may provide the weapons to allow us to survive antibiotic resistant organisms.

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