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Review Article

Revitalizing Phage Therapy in Combating Multi-Drug Resistant Bacteria

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Abstract: Bacterial infections are one of the most dangerous infections that threaten the existence and continuity of life. Despite the discovery and manufacturing of effective antibiotics to tackle these menaces, bacteria have developed resistance against such treatments and transformed into new mutant resistant strains. Bacteriophages, or phages, are regarded as effective alternative antibacterial agents. Recently, scientists have been taking a closer look at the variety of different phages that attack bacteria. This review primarily focuses on the potential of phage therapy as an alternative treatment to overcome a wide spectrum of resistant bacterial infections, as well as current phage therapy advancement. It also proposes the idea of engineering "broad-spectrum phage" to overcome a wide range of resistant bacterial infections, and its advantages over antibiotics, individual phage, and phage cocktails.

Keywords: Phage therapy, broad-spectrum phage, phage cocktails, bacteriophages, antibiotics, multi-drug resistant bacteria.

INTRODUCTION

It is obvious that our health is endangered by many serious infectious diseases. Some are curable, others are resistant to treatment, and some have no cure yet. Many infectious diseases such as cholera, plague, anthrax, and tuberculosis are caused by bacteria. Some of these diseases have prophylactic protection by vaccination and suitable treatment, while some others do not have neither vaccine nor specific treatment [1]. Antibiotics are used to treat various bacterial infections. However, the misuse and overuse of antibiotics have increased the emergence of pathogenic bacteria resistant to most, if not all. This has become a critical problem in modern medicine, particularly because of the concomitant increase in immunosuppressed patients. Antibiotic resistance is a main health concern because it increases health care costs, causes people to stay longer in hospitals, results in treatment failures, and sometimes leads to death. Currently, rigorous research activities are being conducted around the globe to develop alternative methods of treatment for infectious diseases caused by multi-drug resistant (MDR) bacteria. Revitalizing phage therapy may be a good alternative for solving this problem.

Phage therapy is not a new treatment for treating bacterial infections, in fact, bacteriophages have been in use since the 1920s for addressing a wide range of infections [2]. With the advent of antibiotics (for example, the discovery of penicillin) and other commercial antibiotics, phage therapy fell out of favor and the practice has only persisted in some European countries as an experimental treatment [3]. Due to the looming spectra of antibiotic resistance, researchers (especially in the West) are giving phages a serious look. Recently, the US National Institute of Allergy and Infectious Diseases listed phage therapy as one of the seven plans to combat antibiotic resistance. Furthermore, a recent American Society for Microbiology (ASM) meeting had presented phage therapy plans for Phagoburn; the first large, multi-center clinical trial of phage therapy for human infections funded by the European Commission [4].

Phage therapy has many advantages compared to conventional antibiotic treatment. Phages are highly specific and easy to obtain; thus, it may be used in cases of dangerous bacterial disease outbreaks. Moreover, they do not have chemical side effects like antibiotics [5]. However, phage therapy is still facing many problems and challenges [6]. One of the main challenges is bacteriophage host range. Currently, each phage has a limited spectrum of infectivity against its bacterial targets. To overcome this problem, a cocktail phage therapy has been developed. Nevertheless, until today, cocktail phage therapy is still facing some difficulties. One of the major problems is to find suitable cocktails for the targeted bacteria. The idea of modifying phage using genetic engineering tools to construct a new phage against a wide range of multi-

drug resistant pathogenic bacteria might offer valuable therapy. Furthermore, this idea may overcome the major problem that is associated with phage therapy cocktails. Additionally, if it is successful and approved, the engineered broad-spectrum phage would have an economical benefit where it may save money spent on extensive antibiotics research and development.

This review discusses the recent approaches of phage therapy as an alternative antibacterial treatment. It also examines the possible properties of the proposed broad-spectrum phage that make it distinctive from the currently presented antibacterial treatments of antibiotics, individual phage, and phage cocktails.

Potential therapy of phages against bacterial infections

Development and mass production of antibiotics to treat various bacterial infections was one of the brightest scientific efforts in the last century. They gained their importance and reliability from their effectiveness. Over the past sixty years, clinicians have been depending on them to treat bacterial infections. Due to their frequent and uncontrolled usage, bacteria have developed resistance against them; thus, transforming such drugs to less effective agents [7]. In the last decade, antibiotic resistance has grown from a concern to a crisis. For example, bacteria isolated from patients who suffered *Klebsiella* infections were reported to be resistant to most known antibiotics [8]. In 2011, a multidrug-resistant form of methicillin-resistant *Staphylococcus aureus* (MRSA) in a UK neonatal unit infected 12 babies [9].

Bacteriophages (phages) are viruses capable of infecting and multiplying only in bacterial cells. They are not able to infect eukaryotic cells (human, animal, fungus, plants, and insects). Phages are widely distributed in soils, water, food, or the intestines of animals where bacterial hosts are abundantly located. Up to 9×10^8 virions per milliliter of phages and other viruses have been found in microbial mats at the surface of the sea water [10]. It is known that up to 70% of marine bacteria may be infected by phages [10]. Due to these qualities, it is usually relatively easy to isolate phages against important bacterial pathogens such as *Escherichia coli* O157: H 7, *Salmonella*, *Campylobacte*r, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Like all viruses, phages hijack the energy and cellular machinery provided by a host cell to replicate and make viral copies since they do not have their own metabolism. During the phage lytic cycle, endolysin enzyme encoded in the bacteriophage genome lyse the peptidoglycan of the bacterial cell wall, releasing dozens or hundreds of new phages [11]. The cycle continues until there are no bacteria left to attack. Since phages only attack specific types of bacteria, they are unlikely to harm any human cells. In addition, it seems that bacteria resistance may unlikely occur or is difficult to occur because phages are known to coevolve with their bacterial victims in about 1000 years [12].

Phage therapy is defined as the application of lytic bacteriophages to reduce densities of specific pathogenic bacteria in human. Phage therapy treatment can consist of a single phage, natural phage cocktails, and lytic phage enzymes lysins and holins. These enzymes are molecules that have the ability to destroy bacterial cell wall, especially in cases for resistant pathogenic bacteria. Phages become more potent toward the target bacteria (host) when they use both of their lytic activity along with the use of lytic enzymes [13]. A comparison of the prophylactic and/or therapeutic use of phages and antibiotics were listed in Table 1. The fast reproduction of lytic phages makes them suitable for phage therapy in which each parent phage can produce about 200 phages per lytic cycle [14]. Phage's bacteria-killing activity is quite easy to evaluate in the lab; for example, a confluent lawn of microbes is grown in a petri dish, then a known phage is added to the confluent microbes, and the resulting killing zone (clear zone) is then measured [15]. Pizzorno et al. [16] stated that phages exert a natural friendly character; they do not disrupt normal body flora and they do not exert chemical side effects like those of antibiotics, therefore, they can be used for patients who suffer from allergic reactions to chemical drugs. Phage cocktails for treating bacteria infecting crops have also been produced [17] but were not discussed in this review.

Development of phage resistant bacteria in patients treated with phage

Theoretically, phage resistant bacteria can be developed under a direct individual phage therapy approach *via* evolution. Since phages can be easily found living together with bacteria in numerous environments, the idea of using phage cocktails seems encouraging compared to individual phage for targeting specific bacterial infections *in situ.* Phage cocktails use different modes of action to reduce the occurrence of resistance. Normal flora in the human body are conserved with phage cocktail therapy due to their bacterial specificity. Development of phage resistant bacteria in patients treated with phage cocktails seems to be difficult due to the very competitive environment where the human microbiota is balanced. This is the most significant advantage compared to the broad-spectrum antibiotics where it blindly kills all bacteria. Furthermore, if phage resistant bacteria occur, a fitness cost is needed for acquiring the resistance; as a result, the resistant strain becomes less virulent and can be easily destroyed by the human innate system [22]. According to Keen [23], like bacteria, phages can mutate, therefore, they can also develop their own resistance to counter phage-resistant bacteria. Maxwell [24] demonstrated that phages readily mutate to defeat the bacteria's defense system and is in a consistent

evolutionary battle between phages and the bacteria they infect.

Table 1: Differences of therapeutic usage of phages and antibiotics as antibacterial agents

Bacteriophages	Antibiotics	Remarks
Highly specific. Only infects the targeted bacterial species. Chances to develop secondary infections and dysbiosis can be avoided.	Not specific. Target pathogenic bacteria and normal microflora in humans. This creates imbalance in patients, thus, increases the development of secondary infections.	Highly specific, can be considered as a disadvantage for phage because bacteria that causes diseases must be identified before phage therapy treatment. When the infectious agent is not identified, antibiotics might be the best choice for treatment.
To date, no serious side effects have been observed [18]. Phages may be considered as good alternative for patients allergic to antibiotics.	Various side effects such as intestinal disorders, allergies, and secondary infections (such as yeast) have been described [19].	Release of endotoxins *in vivo* due to bacteria lysis by phages have been reported to cause minor side effects [18-20]. Antibiotics treatment may also exhibit this effect [21].
Phages can be found throughout nature; thus, rationally, the process to find active phages against every antibiotic-resistant or phage-resistant bacterium is more rapid and can be accomplished in days or weeks.	Identifying and developing new antibiotics against antibiotic-resistant bacteria is complicated and time consuming, which may even take several years.	A strong evidence to support the idea that active phages can be identified against every antibiotic-resistant or phage-resistant bacterium is from the evolutionary perspective; the natural selection theory.
Phages are very specific, therefore, phage-resistant bacteria remain susceptible to other phages that possess a similar range of target.	Resistance to antibiotics is not limited to targeted bacteria. Once resistance develops, antibiotics with similar mechanism of action will become ineffective.	Antibiotics possess a broad spectrum of activity. This means that antibiotics can cause resistance in many bacterial species, not only in targeted bacteria.
Phages themselves exhibit auto "dosing" to establish phage dosage. In such cases, there is no need to repeatedly administer phages for optimal treatment.	Repeated doses of antibiotics are required to cure bacterial disease.	Phages replicate at the site of infection, thus, directly targeting the site where the infection occurs; whereas, antibiotics are metabolized and disposed from the body and may not necessarily target the site of infection.

Phage interactions with mammalian systems

Although the question on how therapeutic viruses interact with the human immune system and whether they might cause side effects is not yet clearly defined, some phage therapy products that proved to work have been developed in the 60s. Coliphagine, Intestiphagine, Pyophagine, and Staphagine were officially approved phage products available in drinkable and injectable forms. Salves and sprays were developed by a small pharmaceutical firm, Saphal, from Switzerland in the 60s [25]. Coliphagine was used for *E. coli*, Intestiphagine for diarrhoeal diseases, Pyophagine for purulent skin infections, and Staphagine for *staphylococci.* Dabrowska *et al.* [26] showed that some phages, including T4, have a direct effect on mammalian cells. Earlier, they thought that a gpHoc protein of T4 does not have an important function for phages' particle structure or even for phages' antibacterial activity. However, from an evolutionary viewpoint, it is impossible that gpHoc protein does not have an important function since it resembles eukaryotic immunoglobulin-like proteins. When T4 gpHoc and a mutant that lacks gpHOC were compared, substantial differences in biological activity were observed in mammalian cells. This study concluded that T4 gpHoc proteins seem to be one of the molecules predicted to modulate the interactions of T4 with mammalian organisms and/or actually interact with mammalian organisms. Later, Barr *et al.* [27] revealed that the interaction of the mucus layer on various animal tissues with the phage head is mediated by the Hoc protein. This interaction provides a position for the phage tails to stick out, thus, ready to interact with incoming bacteria.

In 2009, Zimecki *et al.* [28] speculated that the adaptive immune response resulting in anti-phage antibodies could be triggered if the same phage or cocktails are repeatedly exposed to the same strain of bacteria. The antibody responses may be higher when using cocktails of phage compared to a single viral strain. However, it is not clearly understood whether phage therapy is hindered or helped by such antibodies. A retrospective analysis of immune responses in 153 people treated with phages between 2008 and 2010 indicated that the therapies were well-tolerated in 80%

of patients. Adverse reactions like nausea or pain in response to gut treatments, or local reactions to topical phage applications, were only observed in a small number of patients [29]. Several patients produced anti-phage antibodies from the 122 patients that received phage orally or in local applications. However, the presence of anti-phage antibodies in the patients does not mean that the therapy was unsuccessful [30].

Table 2: Phage products targeting various bacterial infections and colonization developed by SMEs

Companies	Country	Description	Web
Viridax Inc.	USA	Develops specific phage products against *Staphylococcal* infections.	www.viridax.com
New Horizons Diagnostics Corporation	USA	Phage Associated Enzymes (PAE) are enzymes that act as antibiotics.	http://www.nhdiag.com/phage.shtml
Intralytix, Inc	USA	Phage preparation for controlling foodborne bacterial pathogen of *Listeria monocytogenes*, *Escherichia coli* O157:H7, and *Salmonella* serotypes.	www.intralytix.com
OmniLytics, Inc	USA	Products are made using bacteriophage mixtures. Development of bacteriophage for pathogen control in agricultural, food & water, and industrial sectors.	www.phage.com
Biocontrol	UK	Develops bacteriophage to treat *pseudomonas aeruginosa*, ear infections, cystic fibrosis, hospital-acquired infections, and burns.	www.biocontrol.ltd.com
Phico Therapeutics	UK	Develops bacteriophages for several bacteria: *Listeria monocytogenes*, *M. tuberculosis*, and *Staphylococcus aureus* (MRSA, MSSA).	www.phicotherapeutics.co.uk
Novolytics	UK	Focuses on using phages to treat *Staphylococcus aureus* (MRSA) infectious disease.	http://www.novolytics.co.uk/
AmpliPhi BioSciences Corporation	Australia	*Clinical trials against infections caused by* Staphylococcus aureus *in chronic rhinosinusitis (CRS),* S. aureus *(including MRSA),* Pseudomonas aeruginosa *lung infections in cystic fibrosis (CF) patients,* Clostridium difficile *infections, and* C. difficile-*associated diarrhea.*	http://www.ampliphibio.com
CheilJedang Corp.	South Korea	Using phages to protect from *Salmonella gallinarum* and *pullorum* in chicken feed.	http://www.cj.co.kr/cj-en/index
Micreos Food Safety	Netherlands	Using phages to protect food preparation against *Listeria sp* and *Salmonella sp*.	http://www.phageguard.com/about-us/
Gangagen Inc.	India	Late preclinical development of phage products against *S. aureus* (MRSA) and *Pseudomonas aeruginosa* in burns & wounds	www.gangagen.com
Pherecydes Pharma	France	Development of phage therapies for human health. PHAGOBURN clinical trial funded by the EU.	www.pherecydes-pharma.com
Biophage Pharma Inc	Canada	Development of simple, accurate, highly sensitive biosensors based on phages.	http://www.biophagepharma.net/index.php/en/

Current phage therapy in clinical trials

Most pathogenic bacteria phages are not studied very well compared to *E. coli* phages such as T4, λ (lambda), P1, and M13. Despite lacking the basic biology of phages infecting the pathogenic bacteria and the challenges with phage cocktails therapy, numerous companies are currently bringing the phage therapy technology into clinics. Various small and medium enterprises (SMEs) such as Intralytix, Ampliphi Biosciences, Novolytics, Technophage, Micreos, and Pherecydes Pharma, in collaboration with public research institutions, use modern techniques (microbiology, electronic microscopy, molecular biology; including phage genome sequencing and annotation) to look into phages. Several phage products against bacterial infections were developed by SMEs such as *Pseudomonas aeruginosa*, *Stapphylococcus aureus*, *Escherichia coli*, *Acinetobacter baumani*, and *Clostridium difficile* which target the respiratory tract, intestinal tract, post-surgical regions, as well as skin infections including burn wounds [31] (Table 2). A problem that hampered the phage therapy progress is the issue of intellectual property (IP). Phage therapy as a therapeutic has dated a hundred years old, so the concept of using it as therapeutics is unpatentable. This means it is quite difficult for entrepreneurs to get

funding. However, theoretically engineered phage with new characteristics is patentable.

Phage cocktails must become a professionalized therapy with approved manufacturing and clinical evaluation processes before it can be used as the alternative treatment against multidrug resistant bacteria. In the early days, preparation and clinical applications of phage therapy in Eastern Europe were not standardized. Each hospital prepared its own formulation and gave cocktails to particularly tough infections. However, due to strict Western regulatory agencies, the use of phage therapy in USA and Western European were hampered [32]. Good Manufacturing Product (GMP) standards of these new live biological agents are currently being developed. In order to strengthen the historical data developed by Eastern European countries, a clinical assessment of phage cocktails within international, randomized, and multicentric trials is currently on the way [31]. To date, two phage cocktails, PP0121 and PP1131, are now in phases I-II in clinical trials conducted by Phagoburn and in accordance to modern Western standards. These cocktails are against *Escherichia coli* and *Pseudomonas aeruginosa* which cause infections in burn wounds. This is the first of phage therapy treatment being assessed on a worldwide scale.

Development of engineered phage for phage therapy

Phages as antibacterial agents exhibit two major potential disadvantages, despite exhibiting several advantages over antibiotics [33]. The two major disadvantages are phage selection and phage host-range limitations. Phages must be selected based on the capability of lysis or obligate lytic, they should be stable under normal storage conditions and temperatures, have appropriate efficacy, as well as the absence of undesirable genes such as toxins. Minimally, temperate phages should be avoided and, ideally, full genome sequencing should be carried out to identify the virulence factor. Fortunately, nowadays, it should be feasible to engineer phages due to the increasingly cost-effective genome sequencing and synthetic biology technologies, which include large-scale DNA synthesis and the refactoring of phage genomes [34-35]. Another major disadvantage of phage is its narrow host range which limits the usage of phage therapy as antibacterial. Although the application of phage cocktails increases the broader lytic phage spectrum products compared to individual phage, phage cocktails possess one major challenge where it is quite difficult to find the right combination with the appropriate pharmacokinetics [36-38].

Studies on engineered phages to combat antibiotic-resistant bacteria are currently available [39-41]. Phage genome can be engineered in a way that its natural host can be extended. For example, engineered T7 phage that expresses K1-5 endosialidase is able to infect and lyse *E. coli* that is usually resistant to infections by T7 phage due to the K1 polysaccharide capsule [42]. Lu and Collins [43] demonstrated that a modified phage that expresses the extracellular polymeric substances (EPS)-degrading enzymes can efficiently kill the bacteria. EPS is the material that makes up the biofilms during bacteria colonization. The motivation behind this design is that most antibiotics are resistant to biofilms. Secondly, the possibility of obtaining phages that are both specific to the target bacteria and capable of producing EPS-degrading enzymes are likely to be low in nature [44]. Lu and Collins of Boston University [45] had proposed a way of combating antibiotic-resistant bacteria. Their idea was to weaken the bacteria to make them more susceptible to antibiotics. According to Kohanski *et al.* [46], by knocking out the *recA* gene and disabling the SOS response, the bacterial killing by bactericidal antibiotics is enhanced. Based on this knowledge, Lu and Collins attacked the gene networks that are involved in the bacterial SOS response using overexpress proteins produced by the engineered phage. They engineered the M13 phage to overexpress the Lex A bacterial protein. Lex A bacterial protein is a repressor of the SOS response [47]. When the engineered M13 phage infects the *Escherichia coli*, the Lex A protein is overexpressed, thus causing the bacteria to be more accessible to DNA damaging drugs such as ofloxacin. The engineered phage will then increase the capability of ofloxacin to kill *E. coli* resistant to antibiotics. In this case, the engineered phage acts as an adjuvant for antibiotics therapy and revives antibiotics that are no longer effective.

The latest advancement of phage engineering is the construction of a phage that delivers a specific DNA-editing system, the clustered regularly interspaced short palindromic repeats (CRISPRs) and CRISPRs-associated (cas) genes into the antibiotic-resistant bacteria and kills it. This system involves the recognition of the target sequence by the CRISPR RNA which then guides the Cas9 nuclease to the target sequence, thus creating double stranded breaks in the DNA. Yosef et al. [40] used this approach to kill the antibiotic resistant strain by making the bacteria susceptible to antibiotics. Another example is where phages are engineered to deliver CRISPR-Cas system into the bacteria, as shown by Citorik et al. [39]. They demonstrated how the bacteria are killed if the antibiotic-resistance gene is located at the bacterial chromosome. However, if it is located on an episome, the bacterium will retain its sensitivity to antibiotics. Bikard et al. [48] showed that a mouse model injected with engineered phage of CRISPR-Cas system possessed antibacterial activity, as indicated from the reduction of skin colonization by the virulent *S. aureus.* However, CRISPR-Cas system has one potential drawback where it is based on the sequence recognition of the DNA target sequence by the CRISPR-Cas complex [49].

To date, most studies are conducted using the *E. coli* strain and *E. coli* phages as an example. Despite all these efforts, a phage has limited host range, and it is not relatively easy to obtain the right phage for each of the resistant strain bacteria.

Table 3: Comparison of antibiotics, individual phages, cocktail phages, and the proposed broad-spectrum phage as antibacterial agents

Characteristics	**Antibacterial**			
	Broad-spectrum antibiotics	**Individual phages**	**Cocktail phages**	**Proposed broad-spectrum phage**
Spectrum activity	Broad. This can be a major advantage since there is no need to identify the infecting pathogen before initiating treatment.	Very narrow. Similar to narrow-spectrum antibiotics.	Mixture of phages with different mechanisms, thus, the spectrum activity is wide.	A phage is designed to possess wide mechanisms, thus, the spectrum activity is expected to be broad.
Dosing	Repeated dosing is needed.	Auto-dosing. No repeated dosing required.	Auto-dosing. No repeated dosing required.	Auto-dosing. No repeated dosing required.
Development of bacterial resistance	Yes	Theoretically yes	Theoretically difficult but possible	Theoretically difficult but Possible
Ability of antibacterial to develop mutation	No	Possible. A good trait to counter the development of resistant bacteria.	Possible, although the probability is lower than individual phages. A good trait to counter the development of resistant bacteria.	Similar to cocktail phages
Specificity	Not specific	Very specific	Specific	Specific
Penetration and circulation area reaching	Bad	Good and effective	Good and effective	Theoretically, it should be effective like the natural phages.
Side effects	Yes	To date, no significant side effects have been reported.	To date, no significant side effects have been Reported.	Design without toxic proteins, thus, predicted to have no side effect.
Prophylactic use	A very strict usage with well-accepted approval to avoid excess cost, toxicity, and antimicrobial resistance.	Yes	Yes	Expected to be yes.
Environment friendliness	No	Yes	Yes	Expected to be yes.
Effect against biofilm	No	Yes	Yes	Engineered to be able to breakdown the biofilm.
Action mechanism	Bacteriostatic and bacteriolytic	Bacteriolytic	Bacteriolytic	Engineered to be bacteriolytic.
Administration routes	By all routes	By all routes	By all routes	By all routes

Developing process -Research & Development	Difficult to develop. Currently, no new class of antibiotics has been discovered.	Easy and naturally present everywhere in nature, with some difficulties in properly selecting the right phage for every pathogenic bacterial strain.	Difficult since we need to find the right combination of phages to make the cocktails for every group of bacterial strain.	Difficult to successfully engineer or construct phages with wide spectrum activity against resistant-pathogenic bacteria, as well as the wild type pathogenic bacteria.

Proposed synthetic broad-spectrum phage for phage therapy

With the recent progress in sequencing technologies and synthetic biology, we propose the engineering of broad spectrum phage as a complementary or alternative therapy to current antibacterial treatment. We defined broad-spectrum phage as an engineered phage that can effectively recognize a wide range of antibiotic-resistant bacteria, as well as the wild type bacteria, and kills them by lysis. The ideal engineered broad-spectrum phage should possess the characteristics as in Table 3. To date, the idea of engineered broad-spectrum phage has never been proposed in any literature related to phage therapy. Technical difficulties and time constraints are the two major factors that influence the strategy of constructing the broad-spectrum phage. A phage needs to recognize the surface adherence factors of the bacteria and attach to it before it can enter a bacterial cell [50]. Since most pathogenic bacteria produces biofilm, the specific enzymes degrading EPS and the synthetic receptor that recognizes the surface adherence factors of the bacteria should be constructed in the phage genome. Ideally, the broad-spectrum phage must possess two mechanisms for destroying the bacteria cells. First, it degrades the EPS that is masking a bacteria's surface adherence factors, and secondly, the phage can infect the bacteria by recognizing its surface molecules *via* synthetic phage receptors, and finally, kill the bacteria by lysis.

CONCLUSION

In future, phage is a promising alternative therapy, or can be used together with antibiotics to kill wild type pathogenic and antibiotic-resistant bacteria. Since the phage is a biological agent, there is always the possibility of inducing the production of phage resistant bacteria; although, it might be difficult compared to the emergence of antibiotic-resistant bacteria. However, with the advancement in the field of synthetic biology and the accumulating knowledge on phage infecting pathogenic bacteria, the chances of finding solutions to overcome the phage resistant bacteria problem is higher, if it exists. In the years to come, with antibiotic resistant bacteria on the rise, phage therapy's merits may prove its potential.

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