# Bacteriophage therapy: what is needed for success?

Juan José Valdez Alarcón, PhD

**Juan José Valdez Alarcón. Bacteriophage therapy: what is needed for success? J Microbiol Biotechnol Rep. 2017;1(1):6-7.**

## EDITORIAL

Since the description of bacteriophage activity by Twort in 1915 and D'Herelle in 1917 (1), the implementation of bacteriophage therapy as a successful approach for the control of infectious diseases has been elusive. Although bacteriophage activity was discovered more than a decade before penicillin, pharmaceutical industry found a huge business in producing and synthesizing antibiotics for the control of infectious diseases because of its wider spectrum of action and their easy handling than a viral biological system. Unfortunately, in short time periods as short as five years or less, reports on bacteria resistant to the antibiotic were published. Chemical modification of naturally available antibiotics provided a transitional alternative, until multirrestistant bacteria harbouring long mobile genetic elements, mainly plasmids and transposons, with a variety of resistance genetic determinants came to the scenario. In May 2015, the World Health Organization Assembly established a global action plan to fight against antibiotic resistance in which, besides increasing knowledge about antibiotic resistance mechanisms, improving diagnostic and surveillance and optimizing use of antibiotics, they established the need of generating new alternatives for the control of infectious diseases. Many strategies have been addressed since then that include search for new antibiotics, use of antimicrobial peptides and the use of nanotechnology among others. Bacteriophage therapy research gained a new boost as one of this strategies and the industry got involved. It seemed a good alternative because it's a form of biological control, specific, environmentally friendly, auto-limitative and it was predicted that due to its abundance in nature, little or no rejection or immune response will be induced by its application in the human body. Now several bacteriophage-based products have been developed to reduce microbial loads of important food-borne pathogens such as *Escherichia coli*, *Listeria monocytogenes*, *Salmonella* spp., *Campylobacter jejuni*, *Cronobacter sakazakii*, *Shigella* spp., and *Staphylococcus aureus* (2). Bacteriophage therapy for human and animal use has not been so lucky. Industrial bacteriophage-based products pipelines for infectious diseases caused by *Escherichia coli*, *Salmonella* spp., *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Acinetobacter baumannii*, *Clostridium difficile* and *Shigella* spp. among others are still under laboratory tests, pre-clinical or clinical trials, so they may take a long time to get into the market (3).

By mid-august of this year, the first report of a successful clinical trial against *A. baumannii* in a patient, required a personalized design of bacteriophage therapy. After the administration of a first bacteriophage a resistant subpopulation with modified surface properties and decreased virulence emerged; a second bacteriophage was necessary to attack this resistant subpopulation (4). This report evidenced the need of individualized surveillance of the bacteriophage therapy due to the narrow host range of bacteriophages and the emergence of the resistant subpopulation due to host adaptation. With animal infections and particularly with pathogens showing a zoonotic potential, there are different challenges. By taking the example of *Staphylococcus aureus*, it is evident that its success as a pathogen in several hosts causing diverse pathologies (hospital- and community-acquired infections, human and animal mastitis and dermatitis, toxic shock syndrome and food-borne intoxications) is related to its genetic diversity. Molecular epidemiology approaches have demonstrated that specific *S. aureus* genotypes may be associated with different hosts or pathologies, and that these apparently specific genotypes have been interchanging genetic elements that lead to an increase in its host range. This evolving genetic diversity suggests the need of an intense epidemiological surveillance in order to establish the kind of bacteriophages needed against each genotype of the bacterial species and for each particular event of bacteriophage control of a pathogen (5). A very detailed study on mycobacteriophages suggested that bacteriophage specificity is due mainly to mutations in genes encoding tail proteins, and the rate of mutation is a direct function of bacterial host genetic diversity at the site of collection (6). An alternative to bacteriophage therapy is the use of endolysins and virion-associated peptidoglycan hydrolases (VAPH). Both are bacteriophage's lytic enzymes, the first responsible of bacterial cell wall destruction and bacterial lysis, the second responsible of bacteriophage infection. Endolysins and VAPHs structure is composed by one or more active domains with hydrolytic activity against the different chemical bonds established in the structure of peptidoglycan and a recognition/regulatory domain (7,8). Genetic engineering of endolysins or VAPHs have been designed to contain quimeric activities combining active domains of several endolysins or VAPHs or some other kind of lytic enzymes, such as lysozyme.

These recombinant endolysins have increased host specificity as compared to the bacteriophage where they were isolated. So, where are the challenges and the approaches that should be taken for a successful adoption of bacteriophage therapy in the control of infectious diseases? 1) Knowledge on bacteriophage biology: It is still necessary to know bacteriophage infection mechanisms (receptors, regulation of viral reproductive cycle and lysogeny, genetic diversity) in order to propose strategies to improve infection. Genetic diversity studies of bacteriophages and host specificity will also allow to construct bacteriophage collections from which specific bacteriophages may be selected for specific bacterial host genotypes. Whole genome sequencing of bacteriophage genomes or of phageomes will also be useful in increasing the information of bacteriophage genetic backgrounds. 2) Knowledge of the bacterial pathogen biology. Little is known on how genetic diversity of both bacteriophage and its host bacteria determine host specificity and adaptation of bacteriophage. In developing countries, epidemiological surveillance of infectious diseases does not include a routine molecular typing scheme of the bacterial pathogen, but in the best of the cases, only molecular identification. This will difficult the selection of genotype specific bacteriophages and reduce the possibility of a successful bacteriophage therapy. An alternative may be to generate large collections of bacteriophages available to be tested against emerging pathogen genotypes. The *A. baumannii* experience also suggests that a closer surveillance must be executed at the individual level during the therapy (4), at least until bacteriophage – bacterial host – patient interactions are fully understood. 3) Endolysin-based therapy studies. Two major issues on endolysin/VAPH therapy are the stability of the enzyme in a commercial product and the possibility to generate an immune response that affect to the patient or neutralize the activity of the enzyme. An increase in the research of chemical modifications of endolysins/VAPHs and in the inclusion of these enzymes in nanoparticles may contribute to solve this issue. The expression of endolysins/VAPHs in probiotic vectors will also contribute to the delivery of these enzymes to the target site. Studies on structure – function relationships of endolysins/VAPHs will also help to improve the recombinant technology approaches for the expression of these enzymes. Also, the establishment of

*Faculty of Veterinary Medicine and Animal Production, Multidisciplinary Center of Biotechnology Studies, Michoacana University of Saint Nicolás of Hidalgo, México, Tarímbaro, Michoacán, México*

*Correspondence: Dr Juan José Valdez Alarcón , PhD, Faculty of Veterinary Medicine and Animal Production, Multidisciplinary Center of Biotechnology Studies, Michoacana University of Saint Nicolás of Hidalgo, México. Telephone +52-443-295 8029, e-mail jjvaldezalarcon@gmail.com*

*Received: September 14, 2017, Accepted: September 16, 2017, Published: September 16, 2017*

OPEN ACCESS This open-access article is distributed under the terms of the Creative Commons Attribution Non-Commercial License (CC BY-NC) (http://creativecommons.org/licenses/by-nc/4.0/), which permits reuse, distribution and reproduction of the article, provided that the original work is properly cited and the reuse is restricted to noncommercial purposes. For commercial reuse, contact reprints@pulsus.com

large collections of expressed endolysins/VAPHs will help to the selection of the best activity against particular bacteria. 4) Bacteriophage therapy and the One Health Initiative. This initiative began in the year of 2006 and pretends to integrate multidisciplinary efforts related with human, animal and environmental health to understand and attack or prevent infectious diseases. As bacteriophages are the most abundant biological systems in nature, they are widespread and highly diverse. A One Health approach will contribute to the understanding of bacteriophages ecology and evolution, and thus to improve the search of bacteriophages useful for therapy.

## REFERENCES


1. Duckworth DH. Who discovered bacteriophages? Bacteriol Rev. 1976;40:793-802.
2. Sulakvelidze A. Using lytic bacteriophages to eliminate or significantly reduce contamination of foodborne bacterial pathogens. J Sci Food Agric 2013;93:3137-46.
3. Vandenheuvel D, Lavigne R, Brüssow H. Bacteriophage therapy: advances in formulation strategies and human clinical trials. Annu Rev Virol 2015;2:599-618.
4. Schooley RT, Biswas B, Gill JJ, et al. Development and use of bacteriophage-based personalized cocktails to treat a patient with a disseminated resistant *Acinetobacter baumanni* infection. Antimicrob Agents Chemother 2017.
5. Barrera-Rivas CI, Valle-Hurtado NA, González-Lugo GM, et al. Bacteriophage therapy: an alternative for the treatment of *Staphylococcus aureus* infections in animals and animal models. In: Enany S, Crotty-Alexander LE. (eds.) Frontiers in *Staphylococcus aureus* 2017;179-201.
6. Jacob-Sera D, Marinell LJ, Bowman C, et al. On the nature of mycobacteriophage diversity and host preference. Virology 2012;434:187-201.
7. Barrera-Rivas CI, Cajero-Juárez M, Oviedo-Boyso J, et al. Advances in the use of endolysins: general remarks, structure, applications, genetic modifications and perspectives. In: Mendez-Vilas A. The battle against microbial pathogens: basic science technological advances and educational programs. Formatex Research Center 2015;1:259-68.
8. Rodríguez-Rubio L, Gutiérrez D, Donovan DM, et al. Phage lytic proteins: biotechnological applications beyond clinical antimicrobials. Crit Rev Biotechnol 2016;36:542-52.