'...phages are a potentially very valuable tool for dealing with infections caused by antibiotic-resistant bacteria and, in some cases, they might be the only effective modality currently available for saving patients' lives.'

editorial

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Phage therapy: an attractive option for dealing with antibiotic-resistant bacterial infections

The discovery of 'compound 606' (trade named 'Salvarsan') – the first 'magic bullet' for fighting bacterial infections – by Paul Erlich in 1909 is considered the birth of chemotherapy. The search for new 'magic bullets' increased in subsequent years, and it focused on identifying novel and safe compounds effective against bacterial infections. The discovery of antibiotics during the 1940s was the pinnacle of this process, and it revolutionized medicine from that point forward. Hundreds of antibiotics have been developed by various pharmaceutical companies since Eli Lilly pioneered the production of penicillin more than half a century ago, and many of them are currently available for clinical use. Antibiotics have saved more lives than any other drugs in the history of humankind, and their phenomenal success led the USA's Surgeon General to declare, during the late 1960s, that it was time to close the book on bacterial diseases. Indeed, partially triggered by this type of sentiment and, more importantly, by financial considerations, many large pharmaceutical companies have recently been 'closing the book' on developing new antibiotics, and they have been redirecting much of their R&D activities to more lucrative targets, such as drugs for treating chronic conditions. This trend and the increasing emergence of antibiotic-resistant bacterial pathogens could have very serious public health ramifications. In that regard, a recent report by a special Task Force co-chaired by the CDC, FDA and NIH stated that 'The world may soon be faced with previously treatable diseases that have again become untreatable, as in the pre-antibiotic era' [1].

Although the need for additional antibiotics is becoming increasingly vital, the number of newly developed antibiotics has been on the wane. For example, only nine new antibiotics were approved by the FDA during 1998 to 2003, and only two of them had a novel mode of action – a critical consideration in the battle against antibiotic resistance [2]. Indeed, seeking novel targets that are different from those affected by currently available antibiotics could provide a powerful tool for dealing with infections caused by antibiotic-resistant bacteria. Various sophisticated approaches such as sequencing the human genome, functional genomics, microarray analysis, haplotype mapping and chemical genetics, have been used during studies attempting to achieve that goal. However, as scientifically exciting and impressive as these recent achievements and methods are, their promise has not yet been realized, and it might take many years before we see effective drugs resulting from this type of research. Thus, exploring alternative approaches to develop antibacterial products is also a worthwhile task, and re-examining the

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potential of promising older methods might be of value. Phage therapy could be one such approach.

Lytic bacteriophages (phages, for short) – that is, viruses that infect and kill bacteria – were discovered independently by Frederick Twort and Felix d'Herelle in 1915 and 1917, respectively [3]. In the pre-antibiotic era, the discovery of bacteriophages engendered great enthusiasm and high expectations regarding their potential therapeutic applications. Indeed, after the first published report (in 1921) of successfully using bacteriophages therapeutically in humans, several hundred papers describing phage therapy of humans and agriculturally important animals were published (reviewed in [4,5]). The use of phages in mammals was apparently very safe; however, phage therapy was not always effective and, with the advent of antibiotics active against a broad spectrum of bacteria, it gradually fell out-of-favor in the USA and western Europe. Several factors (reviewed in more detail in [5,6]), including an inadequate understanding of phage biology and imperfections in the diagnostic bacteriology techniques available at the time, contributed to the failure of some early phage therapy studies and to a decline of interest in phage therapy in the West. However, the approach continued to be utilized in the former Soviet Union (FSU) and eastern Europe (EE), and, on a much smaller scale, in France, Switzerland and Egypt [5].

Lytic bacteriophages are very effective in lysing the bacteria that serve as their specific hosts. In addition, because they kill bacteria via mechanisms that are different from those of antibiotics, they fit nicely in the 'novel mode of action' concept desired for all new antibacterial agents. Thus, re-evaluating the potential of phage-based prophylaxis and therapy of antibiotic-resistant bacterial infections might be worthwhile, 'going-back-to-the-future', research. Possible variations of the approach could include using: (1) a classical phage therapy approach, that is, using phages as direct antibacterial agents (which, technologically, could be fairly rapidly adapted for clinical applications in the West); (2) phage-encoded lytic enzymes as antibacterial agents (which may require a longer development period); and (3) phages' lytic mechanisms to identify novel drug targets (the most long-term, but still very intriguing, approach). Current biomedical technology is vastly superior to that available during the early days of phage therapy research, and our understanding of the biological properties of phages and the mechanisms of phage-bacterial host interactions has improved dramatically since that time. Thus, it would seem to be prudent to utilize those advances to develop novel therapeutic phage preparations and to design science-based strategies for integrating phage therapy into our arsenal of tools for preventing and treating bacterial infections. In reality, however, the question of whether phage-based preparations should be developed for therapy and/or prophylaxis still is controversial in the western world [7,8].

The extensive, currently available phage therapy literature demonstrates that the administration of bacteriophages is efficacious in preventing and/or treating bacterial infections in at least some settings. However, most phage therapy research was performed in non-English speaking countries after antibiotics became widely available, and most of the data were published in non-English journals. This situation has led to an 'information vacuum' and the general perception that phage therapy studies in the FSU and EE are of low scientific value, with the lack of placebo controls considered to be one of their major shortcomings. Indeed, because of phage therapy's wide acceptance in the FSU and EE, some of the studies performed there did not include placebo-treated control groups. However, there are also numerous papers in which results obtained with control patients not treated with phages (i.e. placebo-treated controls) or treated with an antibiotic (i.e. comparative controls) were compared with those of phage-treated patients. A few recent publications [5,9] have reviewed and discussed translations of several phage therapy studies performed in the FSU and EE. The availability of full-length translations of additional papers on the subject will help western scientists better understand the potential and limitations of the approach.

At the present time, surprisingly little effort is being directed to developing and testing therapeutic phage preparations in the USA and western Europe. Small companies involved with therapeutic phage research do not have sufficient resources to pursue product development and regulatory approvals aggressively, which impacts the speed with which their phage-based products can be developed and brought to market. Large pharmaceutical companies do have the necessary resources, but they seem to be reluctant to deviate from the traditional 'small molecule therapeutics' approach and to get involved with therapeutic phage research, particularly because of the regulatory novelty of the approach and the uncertainty about the acceptance of the idea of phage therapy in the west. Additional research in academic laboratories could play a significant role in breaking this barrier, but such research appears to be hindered by the tendency of funding agencies to support 'basic-science' research, whereas more-applied approaches (e.g. phage therapy) might appear, to many scientists who often constitute the majority of review committees, to be too low tech for grant support. Even special programs specifically established to fund research with a high potential for relatively rapid commercial success (e.g. the Small Business Innovation Research programs, or the Challenge Grants for Joint Ventures in Biomedicine program, which has solicited phage therapy proposals) appear to have this problem. Thus, carefully selecting reviewers who can objectively and critically evaluate the pros and cons of phage therapy research proposals will be very important for supporting research groups interested in rigorously examining the value of the approach in various model systems. Therapeutic phages are not likely to be another 'magic bullet' and to solve totally the problem of antibiotic resistance (as, indeed, no single modality

can). Thus, any attempt to present them as a panacea is unjustified, and it is not the intent of this editorial to do so. However, I believe that phages are a potentially very valuable tool for dealing with infections caused by antibiotic-resistant bacteria and that, in some cases, they might be the only effective modality currently available for saving patients' lives. Therefore, it seems short-sighted not to examine this approach with greater effort.

Phage-based therapeutics have their own specific limitations [7,8], and they also are likely to suffer from many of the same problems as antibiotics, including the emergence of phage-resistance. However, the resistance mechanisms to phages and antibiotics are different, and having both modalities available could provide a much-needed safety net in the battle against antibiotic-resistant bacterial pathogens. Also, phage-based therapeutic preparations offer unprecedented flexibility for keeping up with the emergence of phage-resistance in bacterial populations. Phages have been co-evolving with their host bacteria for >3.5 billion years, and they outnumber bacteria in the environment by >tenfold [10]. Thus, it should be possible to isolate, fairly rapidly from the environment, new phages that are lytic for phage-resistant bacterial mutants. From a practical standpoint, this will require that the phage-susceptibility of the targeted bacteria be continuously monitored, and that the phage preparations are updated as needed. The first approach is not novel or particularly difficult; e.g. bacterial isolation and antibiotic-susceptibility testing is a routine practice in all major hospitals. However, the second approach (phage substitution) might be more challenging.

Updating phage preparations by replacing old phages with new, more effective phages has been commonly and successfully used in the FSU and EE. However, this practice may be novel for the USA's regulatory agencies that are accustomed to approving defined chemicals and require that each change in the preparation be the subject of a new regulatory application. Having similar requirements for preparations containing naturally-occurring phages that target a single or only a handful of bacterial pathogens might prevent, or severely delay, the development of new phage-based therapeutics. Another limiting factor could be possible insistence of regulatory agencies that a single phage-containing preparation, instead of a phage cocktail, be used for therapy [1]. That approach might work in a specific *in vitro* or *in vivo* system. However, based on the currently available literature, the long-term therapeutic efficacy of a single monophage-containing preparation is questionable, and it might not result in a commercially viable product. Thus, gaining a better appreciation of the potential and limitations of phage therapy, and establishing an appropriate strategy for regulating phage-based products, are of critical importance for the future of phage therapeutics. The task might be challenging, but given the ever-increasing problem with drug-resistant bacteria, and the potential of phages to reduce the impact of that problem, it seems very much worth pursuing.

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