Phage therapy

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Phage therapy is the therapeutic use of lytic bacteriophages to treat pathogenic bacterial infections. Bacteriophages, or "phages" are viruses that invade only bacterial cells and, in the case of *lytic* phages, cause the bacterium to burst and die, thus releasing more phages. Phage therapy is a potential alternative to antibiotics. After having been extensively used and developed mainly in former Soviet Union countries for about 90 years, some phage therapies are now becoming tested on an experimental basis in other countries such as USA for a variety of bacterial and poly-microbial biofilm infections. Phage therapy has many potential applications in human medicine as well as dentistry, veterinary science and agriculture. [1]

An important theoretical benefit of phage therapy is that bacteriophages can be much more specific than more common drugs, so can be chosen to be harmless to not only the host organism (human, animal or plant), but also other beneficial bacteria, such as gut flora, reducing the chances of opportunistic infections. They also have few if any side effects as opposed to drugs, and do not stress the liver. Because they replicate *in vivo*, a single, small dose is sometimes sufficient.[*citation needed*] On the other hand this specificity is also a disadvantage, a phage will only kill a bacterium if it is a match to the specific subspecies; thus phage mixtures are often applied to improve the chances of success, or samples can be taken and an appropriate phage identified and grown.

Phages are currently being used therapeutically to treat bacterial infections that do not respond to conventional antibiotics, particularly in the country of Georgia.[2][3][4][5] They tend to be more successful where there is a biofilm covered by a polysaccharide layer, that antibiotics typically cannot penetrate.[*citation needed*]

In the West, no therapies are currently authorised for use on humans, although phages for killing food poisoning bacteria are now in use.[6]

History

Following the discovery of bacteriophages by Frederick Twort and Felix d'Hérelle[7] in 1915 and 1917, phage therapy was immediately recognized by many to be a key way forward for the eradication of bacterial infections. A Georgian, George Eliava, was making similar discoveries. He travelled to the Pasteur Institute in Paris where he met d'Hérelle, and in 1926 he founded the Eliava Institute in Tbilisi, Georgia devoted to the development of phage therapy.

In neighbouring countries including Russia, extensive research and development soon began in this field. In the USA during the 1940s, commercialization of phage therapy was undertaken by the large pharmaceutical company, Eli Lilly.

Whilst knowledge was being accumulated regarding the biology of phages and how to use phage cocktails correctly, early uses of phage therapy were often unreliable. When antibiotics were discovered in 1941 and marketed widely in the USA and Europe, Western scientists mostly lost interest in further use and study of phage therapy for some time.[8]

Isolated from Western advances in antibiotic production in the 1940s, Russian scientists continued to develop already successful phage therapy to treat the wounds of soldiers in field hospitals. During World War II, the Soviet Union used bacteriophages to treat many soldiers infected with various bacterial diseases e.g. dysentery and gangrene. The success rate was as good as, if not better than any antibiotic.[*citation needed*] Russian researchers continued to develop and to refine their treatments and to publish their research and results. However, due to the scientific barriers of the Cold War, this knowledge was not translated and did not proliferate across the world. [9][10]

There is an extensive library and research center at the Eliava Institute in Tbilisi, Georgia. Phage therapy is today a widespread form of treatment in neighbouring countries. For 80 years Georgian doctors have been treating local people including babies and newborns with phages.

As a result of the development of antibiotic resistance since the 1950s and an advancement of scientific knowledge, there is renewed interest worldwide in the ability of phage therapy to eradicate bacterial infections and chronic polymicrobial biofilm, along with other strategies.

Phages have been explored as means to eliminate pathogens like *Campylobacter* in raw food[11] and *Listeria* in fresh food or to reduce food spoilage bacteria.[12] In agricultural practice phages were used to fight pathogens like *Campylobacter*, *Escherichia* and *Salmonella* in farm animals, *Lactococcus* and *Vibrio* pathogens in fish from aquaculture and *Erwinia* and *Xanthomonas* in plants of agricultural importance. The oldest use was, however, in human medicine. Phages were used against diarrheal diseases caused by *E. coli*, *Shigella* or *Vibrio* and against wound infections caused by facultative pathogens of the skin like staphylococci and streptococci. Recently the phage therapy approach has been applied to systemic and even intracellular infections and the addition of non-replicating phage and isolated phage enzymes like lysins to the antimicrobial arsenal. However, definitive proof for the efficiency of these phage approaches in the field or the hospital is only provided in a few cases.[12]

Some of the interest in the West can be traced back to 1994, when Soothill demonstrated (in an animal model) that the use of phages could improve the success of skin grafts by reducing the underlying *Pseudomonas aeruginosa* infection. [13] Recent studies have provided additional support for these findings.[14]

Recently, the use of phages as delivery mechanisms for traditional antibiotics has been proposed.[15][16]

Benefits

A clear benefit of phage therapy is that it does not have the potentially very severe adverse effects of antibiotics. Also it can be fast-acting, once the exact bacteria are identified and the phages administered. Another benefit of phage therapy is that although bacteria are able to develop resistance to phages the resistance is much easier to overcome. The reason behind this is that phages replicate and undergo natural selection and have probably been infecting bacteria since the beginning of life on this planet. Although bacteria evolve at a fast rate, so too will phages. Being smaller, they can mutate faster. Bacteria are most likely to modify the molecule that the phage targets, such as a cell surface glycoprotein, which is usually a bacterial receptor. In response to this modification, phages will evolve in such a way that counteracts this change, thus allowing them to continue targeting bacteria and causing cell lysis. As a consequence phage therapy is devoid of problems similar to antibiotic resistance.

Bacteriophages are often very specific, targeting only one or a few strains of bacteria.[17] Traditional antibiotics usually have more wide-ranging effect, killing both harmful bacteria and useful bacteria such as those facilitating food digestion. The specificity of bacteriophages reduces the chance that useful bacteria are killed when fighting an infection.

Increasing evidence shows the ability of phages to travel to a required site — including the brain, where the blood brain barrier can be crossed — and multiply in the presence of an appropriate bacterial host, to combat infections such as meningitis. However the patient's immune system can, in some cases mount an immune response to the phage (2 out of 44 patients in a Polish trial [18]).

Development and production is faster than antibiotics, on condition that the required recognition molecules are known.

Research groups in the West are engineering a broader spectrum phage and also target MRSA treatments in a variety of forms - including impregnated wound dressings, preventative treatment for burn victims, phage-impregnated sutures. Enzobiotics are a new development at Rockefeller University that create enzymes from phage. These show potential for preventing secondary bacterial infections e.g. pneumonia developing with patients suffering from flu, otitis etc..

Application

Collection

In its simplest form, phage treatment works by collecting local samples of water likely to contain high quantities of bacteria and bacteriophages, for example effluent outlets, sewage and other sources. They can also be extracted from corpses. The samples are

taken and applied to the bacteria that are to be destroyed which have been cultured on growth medium.

The bacteria usually die, and the mixture is centrifuged. The phages collect on the top of the mixture and can be drawn off.

The phage solutions are then tested to see which ones show growth suppression effects (lysogeny) and/or destruction (lysis) of the target bacteria. The phage showing lysis are then amplified on cultures of the target bacteria, passed through a filter to remove all but the phages, then distributed.

[edit] Treatment

Phages are "bacterium specific" and it is therefore necessary in many cases to take a swab from the patient and culture it prior to treatment. Occasionally, isolation of therapeutic phages can typically require a few months to complete, but clinics generally keep supplies of phage cocktails for the most common bacterial strains in a geographical area.

Phages in practice are applied orally, topically on infected wounds or spread onto surfaces, or used during surgical procedures. Injection is rarely used, avoiding any risks of trace chemical contaminants that may be present from the bacteria amplification stage,and recognizing that the immune system naturally fights against viruses introduced into the bloodstream or lymphatic system.

In August 2006, the United States Food and Drug Administration approved spraying meat with phages. Although this initially raised concerns since without mandatory labeling consumers won't be aware that meat and poultry products have been treated with the spray,[1] it confirms to the public that, for example, phages against *Listeria* are generally recognized as safe (GRAS status) within the worldwide scientific community and opens the way for other phages to also be recognized as having GRAS status.

Phage therapy is used for the treatment of a variety of bacterial infections including: laryngitis, skin infections, dysentery, conjunctivitis, periodontitis, gingivitis, sinusitis, urinary tract infections and intestinal infections, burns, boils, etc. - also poly-microbial biofilms on chronic wounds, ulcers and infected surgical sites.[*citation needed*]

In 2007, Phase 2 clinical trials are nearing completion at Great Ormond Street Hospital for *Pseudomonas aeruginosa* infections (otitis). [19][20]

Phase 1 clinical trials are underway in the South West Regional Wound Care Center, Lubbock, Texas for an approved cocktail of phages against bacteria, including *P. aeruginosa*, *Staphylococcus aureus* and *Escherichia coli* (better known as E. coli).[*citation needed*]

Reviews of phage therapy indicate that more clinical and microbiological research is needed to meet current standards. [21]

Distribution

Phages can usually be freeze dried and turned into pills without materially impacting efficacy. In pill form temperature stability up to 55C, and shelf lives of 14 months have been shown.[*citation needed*]

Other forms of administration can include application in liquid form. These vials are usually best kept refrigerated.[*citation needed*]

Oral administration works better when an antacid is included, as this increases the number of phages surviving passage through the stomach.[*citation needed*]

Topical administration often involves application to gauzes that are laid on the area to be treated.[*citation needed*]

Obstacles

General

The host specificity of phage therapy may make it necessary for clinics to make different cocktails for treatment of the same infection or disease because the bacterial components of such diseases may differ from region to region or even person to person. Such a process would make it difficult for large scale production of phage therapy. Additionally, patent issues (specifically on living organisms) may complicate distribution for pharmaceutical companies wishing to have exclusive rights over their "invention"; making it unlikely that a for-profit corporation will invest capital in the widespread application of this technology.

In addition, due to the specificity of individual phages, for a high chance of success, a mixture of phages is often applied. This means that 'banks' containing many different phages are needed to be kept and regularly updated with new phages, which makes regulatory testing for safety harder and more expensive.

Some bacteria, for example clostridium and mycobacterium, have no known therapeutic phages available as yet.

To work, the virus has to reach the site of the bacteria, and unlike antibiotics, viruses do not necessarily reach the *same* places that antibiotics can reach. [22]

Funding for phage therapy research and clinical trials is generally insufficient and difficult to obtain, since it is a lengthy and complex process to patent bacteriophage products. Scientists comment that 'the biggest hurdle is regulatory', whereas an official view is that individual phages would need proof individually because it would be too complicated to do as a combination, with many variables. Due to the specificity of phages, phage therapy would be most effect with a cocktail injection, generally which is rejected by the FDA. Researchers and observers predict that for phage therapy to be

successful the FDA must change its high regulatory stance on drug cocktails. [23] Public awareness and education about phage therapy are generally limited to scientific or independent research rather than mainstream media. [24]

The negative public perception of viruses may also play a role in the reluctance to embrace phage therapy.[25] (The term probiotic is not usually applied to viruses.)

Safety

Phage therapy is generally considered safe. As with antibiotic therapy and other methods of countering bacterial infections, endotoxins are released by the bacteria as they are destroyed within the patient (Herxheimer reaction). This can cause symptoms of fever, or in extreme cases toxic shock (a problem also seen with antibiotics) is possible.[26] Ramachandran argues that this complication can be avoided in those types of infection where this reaction is likely to occur by using genetically engineered bacteriophages; which have had their gene responsible for producing endolysin removed. Without this gene the host bacterium still dies but remains intact because apoptosis is disabled. [5] Eventually these dead cells are consumed by the normal house cleaning duties of the phagocytes, which utilise enzymes to break the whole bacterium and its contents down into to its harmless sub-units of proteins, polysaccharides and lipids. [27]

Care has to be taken in manufacture that the phage medium is free of bacterial fragments and endotoxins from the production process.

Lysogenic bacteriophages are not generally used therapeutically. This group can act as a way for bacteria to exchange DNA, and this can help spread antibiotic resistance or even, theoretically, can make the bacteria pathogenic (see Cholera).

The lytic bacteriophages available for phage therapy are best kept refrigerated but discarded if the pale yellow clear liquid goes cloudy.

Cultural references

- The novel *Arrowsmith* used phage therapy as a plot point.[28][29][30]

See also

- Phage meetings
- Phage monographs

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