Bacteriophages as a New Drug
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Introduction

Over the years, we have become increasingly dependent on antibiotics to fight bacterial infections, but now more and more bacteria have developed resistance to these drugs. We need a new way to fight bacterial infections, and one way could be through bacteriophages. The use of bacteriophages as a new drug was first demonstrated in an experiment by Carl Merril and Richard Carlton, where mice were injected with *Escherichia coli* and then treated with bacteriophages that target the bacteria. The mice that did not receive any bacteriophage treatment died, while those that did had much higher survival rates. This is proof that bacteriophages could be and are becoming a legitimate form of anti-bacterial treatment (Travis, 2002).

Despite the promise of bacteriophages, little research has been done on them in the United States; the center of phage research and therapy is located in Eastern Europe. This paper therefore proposes that to encourage bacteriophage research in order to eventually lessen our dependence on antibiotics, we need to offer more monetary incentives in the form of governmental grants. Bacteriophages should also be fast tracked (a process that speeds up the review of a drug for serious medical conditions and that meets an unmet medical need) and submitted to priority review (drug proposal is reviewed within 6 months) (FDA, 2010).

Background

*How bacteriophages work:*

Bacteriophages (phages) are viruses that infect bacteria. They have a single type nucleic acid, a protein coat which surrounds the nucleic acid, a tail to inject the DNA or RNA into the host, and tail fibers to help attach to the host. Bacteriophages are specific – each one recognizes a different receptor that allows it to bind. They cannot bind and infect eukaryotic cells, therefore they only affect bacteria (Tortura, 2010).

Bacteriophages used for phage therapy replicate using a lytic cycle. In this form, the bacteriophage first attaches to a specific receptor site on a bacterial cell. It then injects its DNA or RNA into the host by releasing phage lysozyme through its tail, which degrades a portion of
the cell wall. The tail sheath contracts, making the tail core drive through the cell wall and into the plasma membrane, where the nucleic acid is released. Biosynthesis of the viral nucleic acid then begins. The host DNA is degraded and protein synthesis is stopped as the phage DNA or RNA takes over the cell, using the host nucleotides and enzymes to replicate the phage’s DNA/RNA. After this, the phage uses the machinery of the cell to make viral proteins, which happens exactly the same way as if the bacterial cell were making its own proteins, except viral RNA is now transcribed, not bacterial. The phage DNA/RNA and capsids assemble, lysozyme is synthesized within the cell to break down the cell wall again, and the new viruses are released. The bacteria cell is dead, while the newly made viruses can move on to infect other cells (Tortura, 2010).

Pros of Bacteriophages:
A review of a study by Levin and Bull (1995) found that not only do bacteriophages work to fight bacterial infections, but that they can work better than antibiotics. Once administered, antibiotics degrade over time, while phages (if given before the bacteria reach a lethal level) have the ability to reproduce. This means that while antibiotics may become less effective over time, bacteriophages remain consistently effective and can therefore better clear bacteria (Levin and Bull, 1995).

Besides outlasting antibiotics, bacteriophages can be easily engineered to target specific bacteria (Barnum, 2005). For example, Collins and Lu did a study to find the most effective enzyme against *Escherichia coli*, which worked by degrading a polymer. Once they found this enzyme, Collins and Lu inserted the gene that codes for the enzyme into the DNA of a bacteriophage. The genetically modified bacteriophages were dropped on to biofilms of *E. coli*, which disappeared after only a few days. This worked because in addition to continuously killing the bacteria, the engineered bacteriophages also excreted an enzyme that helped break up the biofilm. (Castelvecchi, 2007).

In addition to being easily modified, bacteriophages can be radioactively or fluorescently tagged to identify tumors or infections that might otherwise go unnoticed. Phages also evolve along with the bacteria that they infect. This means that when the host evolves to protect itself against the virus, the virus responds by evolving so that it can still attack the host. Antibiotics cannot do this – if bacteria is resistant to it, there is no way for the antibiotic to change unless we modify it in the lab, which can take many months or years (phagetherapycenter.com)
Current use of bacteriophages:

Scientists have known about bacteriophages and their potential to fight bacteria since the early 1900’s. With the discovery of antibiotics, however, the focus changed and the only ongoing research is in Eastern Europe, in former Soviet Union territories (Levin and Bull, 1995). Today, the main center of phage therapy and research is the Phage Therapy Center in the Republic of Georgia. The Phage Therapy Center treats patients with bacterial infections that are unresponsive to antibiotics and specializes in acute and chronic infections like laryngitis and acne, infections where circulation is poor (in diabetes patients, for example), and infections with bacteria that are highly resistant such as methicillin resistant *Staphylococcus aureus* (MRSA) (phagetherapycenter.com). In order to treat patients, scientists at the Phage Therapy Center first collect a bacterial sample to determine the strain of bacteria and to characterize it. They then develop a phage mixture that is specific to the bacterial infection and work with other doctors and surgeons to successful treat the disease. This treatment works well against these bacterial infections, especially those that are highly resistant to antibiotics. For example, from the years 1987 to 1999, the center treated 1307 people and had an 85% success rate and 10% improvement rate (the rest had no effect). Success rates for specific diseases ranged from 61% (varicose ulcers of lower extremities) to 100% (purulent meningitis), with most diseases having success rates in the 80 and 90 percents (phagetherapycenter.com).

While there is nothing like the Phage Therapy Center in Georgia located in the United States, there are American companies that are working with bacteriophages. Intralytic, Inc. is probably one of the closest to developing a product, as it has recently obtained a grant from the US Army to develop a probiotic derived from phages to fight against *Shigella*, called ShigActive. They also have two products in development that target *Staphylococcus aureus* and *Acineobacter baumannii*, along with several other products to help prevent contamination in food processing plants and to reduce bacteria in animals, such as chicken and cattle (intralytix.com). Another company, Epitopix, has developed similar products to reduce bacteria in cattle, specifically *E. coli*, and has obtained a license from the United States to market its phage derived product. Products such as these intend to reduce the risk of food poisoning in humans by diminishing the amount of bacteria in the animals themselves (Byrne, 2009). While these companies have made developments with bacteriophages, these developments are still little in comparison to the
success of the Phage Therapy Center in Georgia on treating human infections.

Cons of Bacteriophages:

The Phage Therapy Center in Georgia reports that there are fewer side effects with their treatment than with antibiotics, since phages are more specific and do not disrupt the natural bacteria in the body. As with antibiotics though, there is still the possibility that phages could kill too many bacteria too fast, causing the bacteria to release dangerous levels of endotoxins which then make the patient sick. One of the main problems with phage therapy, however, is the cost. While it is easier to develop a new phage than it is a new antibiotic, treatment at the Phage Therapy Center in Georgia ranges from $2,500 US dollars for outpatient care to $20,000 for inpatient treatment, in addition to travel costs. In addition, if the bacteria that the patient has is resistant to the phages the center has, there is an extra charge to develop a specific, unique phage for that person. This brings up another problem with bacteriophages – bacteria can become resistant to them just like antibiotics. The difference, however, is that even if a bacteria is resistant to one phage, the phage can respond to the bacteria’s resistance and evolve to infect it again in a new way (phagetherapycenter.com).

Another problem with bacteriophages is the way they are administered, at least in places like the Phage Therapy Center. Patients are given a “cocktail” of phages that may vary between regions and hospitals, and the FDA is not set up to handle such a system but to monitor one specific drug that is not constantly changing (Kantor, 2006). In addition, many pharmaceutical companies are not interested in developing new drugs that will treat a onetime infection – they are more interested in treatments that are needed long-term for chronic diseases like diabetes, as this means more profit for them (Tortora, 2010).

Legislation

There is no current legislation that specifically controls bacteriophage therapy. The only relevant laws include the development of new drugs, which is monitored by the FDA. The development of bacteriophages to fight against infections is the development of a new drug and must therefore go through the FDA. It does not matter if the bacteriophages are genetically engineered or not, the process is still the same. Under section 21 of the Federal Food, Drug, and Cosmetic Act, a person wishing to submit a new drug for the FDA’s approval must send five
things to the Center for Drug Evaluation and Research (drug review department of the FDA): 1) a report which shows if the drug is safe and effective, 2) a list of all the ingredients and their composition in the drug, 3) a description of how the drug is manufactured, processed, and packaged, 4) actual samples of the drug, and 5) a sample of the proposed label for the drug. There is, however, an option for a new drug to be a fast track product (Section 312, Subpart E of the Food, Drug, and Cosmetic Act). This option is for drugs that treat life threatening illnesses, or for drugs that have had a “minor manufacturing changes,” such as changing the formula of the drug or how the drug is made. In addition, fast tracked products can be submitted for priority review under Section 314, Subpart H, where potential new drugs are reviewed within 6 months. The manufacturer of a drug can do this by submitting an additional application to the Secretary for approval, instead of repeating the entire process for a “new” drug (FDA).

Policy Proposal:

Using bacteriophages to fight bacterial infections means that any such product will be treated as a new drug, therefore falling under the FDA’s jurisdiction. So far, the FDA seems to have reasonable guidelines for developing new drugs, but the only problem is the length of time it takes to get approval, especially since this is a way to treat serious diseases for which there is no current effective therapy. Therefore, bacteriophage therapy should be fast tracked and submitted to priority review. In addition, the government should provide more incentives to motivate scientists and especially pharmaceutical companies to invest in developing these products.

Pros and Cons:

Pros:

This policy proposal does not require any new legislation. The drug discovery approval pathway of the FDA has seemed to work, and the approval time can be shortened to 6 months if the drug is submitted under priority review. Monetary incentives to motivate scientists and pharmaceutical companies to invest in developing bacteriophage products could help stimulate more research in the area in our country, since there few companies in the United States working on bacteriophages. Cost of treatments might also be lower if incentives were provided –
companies would not have to charge so much for products in order to make a profit, since the government will have already given them monetary incentives. Most importantly, with more research and development of bacteriophage therapies, we can become less dependent on antibiotics. This is especially important as many bacteria are developing resistance to antibiotics – even to antibiotics considered as a last resort for bacterial diseases that have not responded to any other therapies.

**Cons:**

Companies have apparently not been motivated so far to invest in bacteriophage research, since Eastern Europe has developed most of the new bacteriophage technology, leaving us far behind. Therefore, there is no guarantee that money will motivate these pharmaceutical companies to do more research. In addition, a monetary incentive might cause too much competition between companies, creating secrecy which would inhibit the availability of new information on bacteriophages. There is also the chance that too many people might start working in this field, and neglect other important fields. For example, new antibiotics still need to be developed, as phages do not work on all bacteria (specifically *Mycobacterium, Citrobacter,* and a few others) (phagetherapycenter.com).

Problems still remain with bacteriophage treatments as well. For example, more research needs to be done to see how long these bacteriophages stay in the body, and if it matters that they are still present even after the disease causing bacteria has been destroyed. Also, there has been little research to see how the immune system responds to bacteriophages – have there been problems with bacteriophage therapies being ineffective due to destruction by the immune system, or if not, will the immune system develop antibodies to the bacteriophage treatments? In addition, there are still the problems with the cost of bacteriophage treatment and the potential for bacteriophages to kill bacteria too quickly, causing the pathogens to release toxins into the body.

**Summary Statement:**

Bacteriophages have proven to be a legitimate alternative to antibiotics. Because of our dependency on antibiotics, and because of arising resistance of bacteria to antibiotics, there needs to be more research into bacteriophages. While there is no legislation specific to bacteriophages,
they do fall under the new drug development statutes. This means bacteriophage treatments need the FDA’s approval, and this policy proposes that these treatments be fast tracked and submitted for priority review. Monetary incentives should also be given to encourage the development of bacteriophage products, as we have fallen behind other countries in this new form of treatment and have no comparative product or treatment center.

References:


Castelvecchi, D., “Biowarfare: Engineered Virus Can Invade Bacterial Film,” *Science News*


The Epitopix Home Page, October 27, 2010 http://www.epitopix.com/
