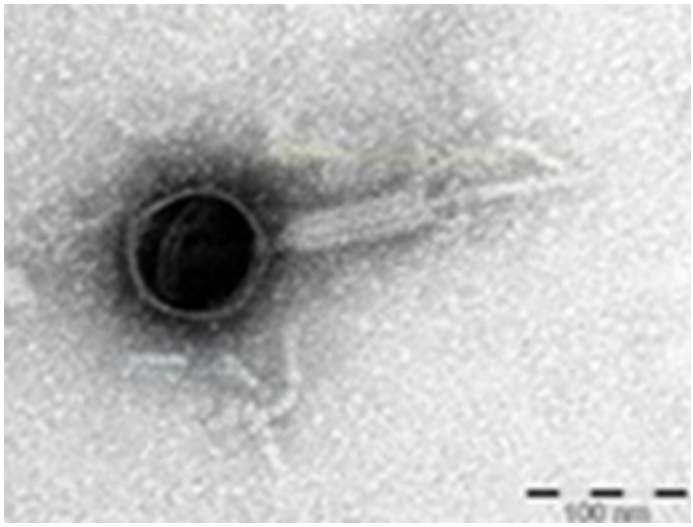
Bacteriophages as alternatives to antibiotics

Multidrug-resistant bacteria are resistant to many existing antibiotics and can be difficult to treat. There are increasing numbers of them worldwide. Although novel antibiotics are being developed, there are far too few of them to tackle the rise of multidrug-resistant bacteria. In Eastern Europe, doctors have been treating bacterial infections with viruses that infect bacteria, so-called bacteriophages, for almost 100 years. Wolfgang Beyer from the University of Hohenheim initiated the National Phage Forum in order to drive forward the application of phages in Germany.

The transparent liquid in a 10 ml glass ampoule Dr. Mzia Kutateladze passed among participants at the 1st German Bacteriophage Symposium at the University of Hohenheim in October 2017 contained several million bacteriophages. Dr. Mzia Kutateladze, head of the Eliava Institute of Bacteriophages, Microbiology and Virology in the Georgian city of Tiflis, and her colleagues use commercial phage cocktails or individually assembled phages to specifically treat antibiotic-resistant or chronic bacterial infections, including wound infections, inflammation of the nasopharynx, severe diarrhoea with vomiting and urinary tract infections.

Unlike antibiotics, which also attack the natural bacterial flora, bacteriophages are extremely picky. Anywhere bacteria are found, bacteriophages able to destroy these bacteria can also be found. The bacteriophages bind specifically to recognition molecules on their host bacterium, inject their genetic material and hijack the bacterial cell machinery. As a result, the bacterial cell produces phage copies until it finally bursts. The phage armada swarms out and attacks other bacteria until they are all extinguished. Bacteriophages are harmless to humans and animals.



"In Georgia and Russia, bacteriophages are approved for human treatment and freely available at pharmacies," reports PD Dr. med. vet. habil. Wolfgang Beyer from the Institute of Animal Science at the University of Hohenheim. Beyer was the scientific director of the 1st German Bacteriophage Symposium. In Poland, doctors at the Hirszfeld Institute of Immunology and Experimental Therapy in Wroclaw, amongst others, have administered phages to several hundred patients who had life-threatening infections and were no longer responding to standard treatment. As phages are not approved in the EU for human

Electron microscope image of a bacteriophage.
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treatment, Poland offers phage therapy for "compassionate use" only.

At the Eliava Institute, the experience of working with phage therapy goes way back to 1936 when George Eliava, a Georgian microbiologist, and Félix Hubert d'Hérelle, a former researcher at the Pasteur Institute in Paris, founded the phage centre. Independently of British bacteriologist Frederick William Twort who had identified a virus that kills bacteria in 1915, d'Hérelle discovered, also during the First World War, viruses that can kill bacteria.

Phages were previously displaced by antibiotics

As there were no antibiotics at the time, phages were used to treat wound infections, cholera or plague, to name a few examples. In addition to France and Georgia, the USA also had phage preparations that were specifically developed for human application. With the discovery of penicillin, which first became commercially available at the start of the Second World War, antibiotics began to emerge in the West. However, it was Russia, Georgia and Poland in particular that continued using bacteriophages for treating bacterial infections.

Since then, more and more bacteria have been becoming resistant to antibiotics - amongst other things due to their massive and often inappropriate use. Some years ago, researchers discovered bacteria with transmissible colistin resistance in human patients and poultry. Colistin is an antibiotic that is currently used as a 'last-line' therapy to treat infections caused by multidrug-resistant Gram-negative bacteria when no other options are available. Researchers in the West are now increasingly falling back on phages.

PD Dr. Wolfgang Beyer is a veterinarian specialised in microbiology and anthrax specialist at the University of Hohenheim.

"Research into the application of phages has not made much progress anywhere in the world, but Germany lags at least 20 years behind," says Wolfgang Beyer, who is clearly distressed that this is the case. On the eve of the Bacteriophage Symposium, Beyer came up with the idea of improving cooperation between phage researchers in Germany. During the three-day conference, Beyer and the Research Centre for Health Sciences at the University of Hohenheim launched the "National Phage Forum" (NFP), which now serves as a point of contact. "The forum is open to researchers from academic institutions as well as to researchers from pharmaceutical companies, clinics and general practitioners or veterinarians," says the microbiologist.

Those interested in phage issues can contact the forum or find information about who deals with which phage topics in Germany from the forum's homepage. The forum's website also contains up-to-date research news, information on regulatory developments as well as information on conferences and grants. The first forum meeting will take place in June and aims to identify the activities the forum will undertake in the future.

Lack of approval procedures for living systems

"What hinders us the most is that there is simply no procedure to regulate the approval of bacteriophages for treating humans," says Beyer explaining that attempts are being made to get together and discuss the issue with regulatory authorities, relevant ministries and agencies that fund the studies that need to be carried out in order to obtain marketing authorisation. "Our approval procedures are geared to drugs with clearly defined, unalterable substances," explains Beyer. Bacteriophages are living systems, they mutate continuously in order to adapt to their hosts, multiply and then die once all bacterial hosts are eliminated.

Beyer further points out that the patient groups eligible for phage therapy need to be clearly defined. The quality requirements the product must meet also need to be determined. Based on this information, phage products must be produced according to good manufacturing practice and only contain lytic phages that immediately cause their bacterial hosts to burst. Temperate phages initially slumber unnoticed in the genome of bacteria and can bring in unwanted foreign genes such as antibiotic resistance genes from other bacteria. The phage product must also be free of poisons from the bacterial strain used to produce it.

Once the regulatory framework for the approval process is clarified, the product's efficacy and safety has to be tested in clinical trials. Recent success stories from the East are mostly based on uncontrolled studies. "Even though phage therapy has not always been successful, it has never had side effects," says Beyer.

"Trials that are carried out according to Western standards go on for years and are expensive, and the pharmaceutical industry is not interested in paying for them. So who will pay for them?" asks Beyer. The solution could be small-scale clinical trials with a small number of patients carrying a specific multiresistant bacterium and with a specific clinical picture that no longer responds to standard treatment. "Several small-scale trials could be worth as much as a large multi-centre trial. What is more important is to help patients now and not in ten years' time," says Beyer.

A broad range of applications

Phages are not only interesting for the field of medicine. In 2006, the first phage preparation against listeria, with which ready-to-eat meat and poultry products can be sprayed before packaging, was approved in the USA. Since then, Australia, Canada, Switzerland and some EU countries have used phage preparations to protect food against contamination by bacteria. In future, phages might also be used as alternatives to antibiotics in factory farming.

Bacillus anthracis, the bacteria responsible for anthrax, on an agar plate. Phages have lysed the bacteria inside the bacterial colonies.

In his capacity as an anthrax expert, Beyer was until recently involved in a European scientist exchange project in which researchers studied phages for use as decontaminants of anthrax pathogens. Although B. anthracis primarily attacks ungulates, the bacteria can also be life-threatening for humans. They are especially feared as biological warfare weapons following the anthrax attack in the USA in 2001 when letters with resistant anthrax spores were mailed to several news agencies and senators. “In the laboratory, bacteriophages that are triggered by a specific bacterial signal are able to reduce the number of anthrax pathogens in soils by up to four logarithmic levels,” said the veterinarian.

Beyer hopes to use the National Phage Forum to advance all these phage applications. What can be achieved also depends on future funding. At the moment, the forum is funded by the university. Either way, bacteriophages are making a full-scale global comeback.

Article

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Further information

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- National Phage Forum
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