The increasing number of bacteria that are resistant to antibiotics is becoming a great problem in the treatment of infected wounds. The Hohenstein Institutes are developing novel wound dressings that use bacteriophages to combat even the most virulent pathogens.

The strategy of bacteriophages is well known. “Back at the beginning of the 20th century, bacteriophages – bacteria eaters - were shown to infect and kill bacteria. Phage therapy was used until the first antibiotics were discovered,” said Dr. Dirk Höfer, head of the Department of Hygiene and Biotechnology at the Hohenstein Institutes. With the advent of penicillin and other effective antibiotics, the therapeutic use of phage gradually fell out of favour in the USA and Western Europe. However, bacteriophage therapy was continued – virtually unnoticed by the rest of the world - in Eastern Europe, most notably in the former Soviet Union.

“The Republic of Georgia is one of the countries that continued to focus on bacteriophage research, most likely for economic reasons. The country just did not have the money to fund the relatively expensive research into antibiotics,” said Höfer. The fact that Georgia’s capital, Tbilisi, became a centre of bacteriophage research can be mainly attributed to one individual - Professor George Eliava. During his visits to the Pasteur Institute in Paris in the 1920s, Eliava worked with Professor Felix D’Herelle who discovered the phage phenomenon and has been fascinated ever since by the tiny viruses.

Phage research continued in some remote corners of the world

The G. Eliava Institute of Bacteriophages, Microbiology and Virology (IBMV) in Tbilisi, which was established in 1916, is a world renowned centre of bacteriophage research and the Hohenstein researchers have been in contact with bacteriophage experts at the IBMV. “One of our cooperation partners is Dr. Wim Fleischmann, Director of the Department of Trauma Surgery at the hospital in Bietigheim and a specialist in the treatment of wounds. He put us in contact with the Georgian scientists and is also involved in developing wound dressings into which bacteriophages are integrated,” said Höfer. Working with the Hohenstein scientists, he combed the world for methods relating to bacteria in order to be able to set up the same methods in Hohenstein. This search brought him into contact with renowned American phage experts and cooperative projects were set up.
Since known antibiotics are no longer effective against pathogenic bacteria, phage research is currently experiencing a considerable boom. A major cause of this loss of efficacy is the improper, frequent and often thoughtless use of antibiotics, which has led to the bacteria adapting their metabolism and becoming resistant to old antibiotics. This leads to major problems in the treatment of highly infectious bacteria such as the classical hospital pathogen Staphylococcus aureus.

“We have cultured bacteriophages that are effective against Staphylococcus as well as Pseudomonas aeruginosa and other bacteria that are becoming increasingly resistant to antibiotic
treatment,” said Höfer who has received some of the phage strains from cooperation partners and has isolated other strains from the environment. “Wastewater is an excellent source of bacteriophages, in particular sewage wastewater or hospital wastewater which contain huge amounts of bacteriophages due to the high density of bacteria,” said the Hohenstein researcher who has established a comprehensive collection of pure bacteriophage cultures.

Freeze-dried and practically packaged

The researchers at the Hohenstein Institutes have developed a sophisticated strategy for using the bacteriophages for specific therapeutic applications. “We set out to dry the bacteriophages and reactivate them upon contact with the wound. However, back then it was assumed that phages could not be dried. As you see, we have been able to show that this is not true,” said Höfer who, together with his team of researchers, has developed a method for carefully freeze-drying bacteriophages. “When the freeze-dried phages are added to a culture medium, they have the same morphology as they previously had as well as retaining the same function that they had prior to drying,” said Höfer, clearly pleased with their breakthrough.

Prototype of the new wound dressing which includes bacteriophages. (Photo: Hohenstein Institutes)

The researchers then had to find a suitable way to package the bacteriophages for use as bacterial killers. The researchers selected the same cellulose fibres as those used in maggot therapy. The fibres are shaped into a wound dressing by applying a special technique: “The hollow fibres are filled with phage solution by way of capillary forces. During lyophilisation, the phages attach to the inner walls of the fibres. This is reminiscent of rust in a pipe,” said Höfer. The active cellulose layer
is then embedded in a wound-friendly polypropylene bag.

Bacterial weapon with integrated safety function

On contact with the moist wound, the phages come to life again and start to eat the bacteria. The phages do not have an adverse effect on human beings. “The phages have an integrated self-regulation. They proliferate as long as they have enough bacteria to live on. When they reach uninfected wound areas where no bacteria are present, the phages will die. This biological self-regulation is a huge advantage for the therapeutic use of phages,” said Höfer.

The researchers have now shown the principle function and effect of the new wound dressings and intend to commence preclinical tests in which Höfer’s group is working in close cooperation with the hospital in Bietigheim-Bissingen. Since the phages are very effective and do not take a great deal time to kill the bacteria, one hour is usually sufficient to kill a dense slime mould. Höfer hopes that the bacteriophage dressing will only need to be applied once. “The tests will show whether this is sufficient. If the dressings work well, the ethics commission will have to evaluate the method before they are tested on the first patients,” said Höfer.

In the meantime, the Hohenstein researchers are working on the further development and optimisation of the therapeutic bacteriophages. Not all phages are equally well suited for all types of bacteria; there are differences. “We are currently working with individual phage types but hope to use phage mixtures in the future. This might for example be suitable for wounds that are infected with three different species of bacteria. Ideally, the pathogen spectrum will be analysed and the most efficient phage mixture used,” said Höfer explaining the future application of the bacteriophages in the treatment of wound infections. He is continuing to look for further information in Cyrillic publications and is working on the characterisation of new bacteriophages – in a continual quest for the best way of treating wounds.

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