Antimicrobial formulations from the environment

Phages act very specifically against the bacteria they eradicate. With special phage cocktails, they can be a gentle alternative to antibiotics.

Illustration: wirDesign/DZG

The word “bacteriophage” comes from the Greek and means “bacteria eater”. Bacteriophages are viruses: they can only multiply by injecting their genetic material into bacteria and utilising the bacteria's replication machinery for their own purposes. Once the new phages are “ripe”, the host cell bursts—and dies. This effect has been used therapeutically in the former Soviet Union since the 1920s, primarily as a substitute for antibiotics, which were long in short supply there for cost reasons. To this day, patients from all over the world with persistent infections travel to the Georgian capital Tbilisi, the Mecca of phage therapy, to obtain customised phage cocktails from pharmacies.

“The therapy was not always successful. However, as we now know, this was mostly due to the fact that too few phages were used, sometimes the wrong ones and not well purified ones,” says Dr Christine Rohde, microbiologist and (until August 2024) head of the “Clinical Phages and Regulation” working group at the Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures, a member institution of the German Center for Infection Research (DZIF) in Braunschweig. A constantly growing collection of phages and suitable host bacteria is collected, characterised, stored and made available for research worldwide.

Harnessing evolution

A prerequisite for successful therapy is a detailed phagogram, in which the respective infectious agent is identified and exposed to suitable phages in the laboratory as a test. A phage species fits a very specific bacterial species like a key in a lock—because only this species can dock to the surface receptors of the bacterium with its tail fibres. In this way, bacteria and their viruses have evolved together since time immemorial—and are also found in abundance in the human microbiome as pairs, so to speak. “We are therefore not only looking for medically relevant phages in compost, forest soils, faeces and manure from the local zoo, but above all in hospital wastewater,” says Dr Johannes Wittmann, head of the DSMZ working group “Phage Genomics and Application” and an expert in phage biodiversity. The collected samples are first sterile filtered to remove all the microorganisms they contain. “Then we grow the bacterial species against which we are looking for phages—as bait, so to speak—and incubate them with the environmental sample.” If successful, the researchers find small plaques, holes in the bacterial lawn in which bacteria have been infected and killed. The phages can simply be ‘washed off’ from agar plates with such plaque holes and obtained in this way. From a large number and variety of phages that specifically target a bacterial species—for example the bacterium Enterococcus faecium in the EVREA-Phage project (the abbreviation stands for: Eradication of intestinal vancomycin-resistant E. faecium (VRE) using oral phage therapy)—a few phage species that are most effective against these target bacteria are then selected via numerous tests.

A virus as a drug

In order for phage therapies to finally be authorised in Germany, the drug authorities require at least one successful, systematic, controlled study that proves the efficiency of this form of therapy. Christine Rohde is confident that this could soon be achieved with “Phage4Cure”, a phase I study at the Charité - Universitätsmedizin Berlin, funded by the Federal Ministry of Education and Research. There, the effect of inhaling a highly purified phage cocktail against *Pseudomonas aeruginosa* is currently being tested in the metabolic disease cystic fibrosis (CF) and in non-CF bronchiectasis, a chronic respiratory disease.

The fields of indication for phage therapies are diverse: Dried and encapsulated to be resistant to gastric acid, they could be used for intestinal infections, for example. They are also interesting for the treatment of bacterial meningitis because, unlike most drugs, phages cross the blood-brain barrier. “They will find widespread application, particularly in the treatment of superficial and deep wounds, which we are currently investigating with the Federal Armed Forces Hospital Berlin in the ‘PhagoFlow’ project,” emphasises Johannes Wittmann. Phages are not intended to replace antibiotics, but to be an alternative. A very gentle alternative, in fact, because the viral way of life turns them into unique drugs: Unlike antibiotics, they do not destroy the patient's intestinal flora and they only replicate as long as they find the exact infectious agent to which they have been applied. After that, the phages die and are simply cleared by the body.

Excerpt from the German article “Antimikrobielle Rezepturen aus der Umwelt” (author: Catarina Pietschmann) published in the research magazine SYNERGIE (01/2024), a joint publication of the German Centers for Health Research (DZG). Translated by Nicola Wittekindt