

# Bacteria-eating viruses

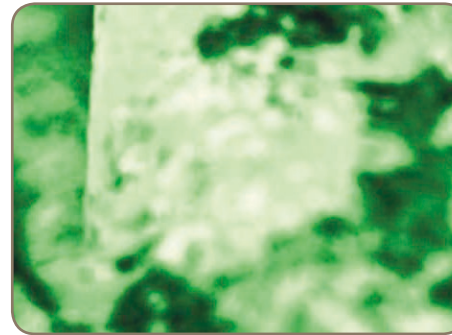
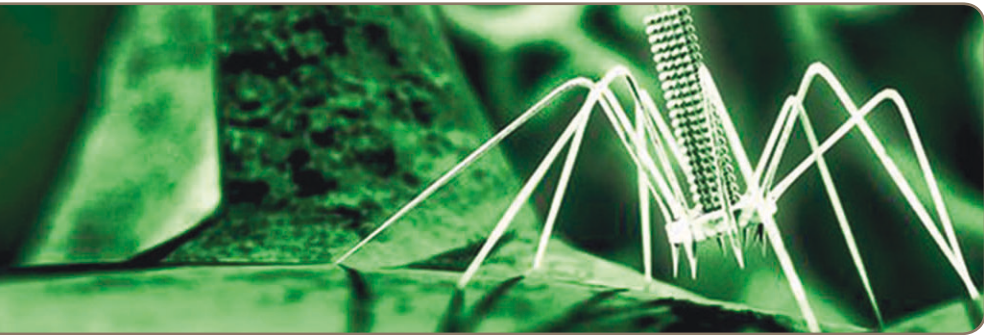


Image: Bacteriophage.

Credit: BlueSci. Cambridge University science magazine.

With the ever-growing threat of antimicrobial resistance, there is a critical need for alternatives to antibiotics. MRC-funded researchers at the University of Leicester are pursuing one such route. A team led by Dr Martha Clokie has isolated bacteriophages — viruses that ‘eat’ bacteria — targeting the hospital superbug *Clostridium difficile* or *C. difficile*.

Bacteriophages were discovered and used as a therapy for bacterial infections almost 100 years ago, long before the development of antibiotics. Dr Frederick Twort, a British bacteriologist and later recipient of MRC funding, is credited with their initial discovery in 1915. French-Canadian scientist Felix d’Herelle later developed them to treat infections following his independent discovery of them in 1917.

To date however, they are not in widespread use. Although phages did reach commercial production in the 1940s, and have been used to treat several bacterial infections, treatment does not produce consistent results. In the pre-antibiotic area, many aspects of phage biology were not well understood. Doses of phages often did not contain enough viable viruses to be effective, and viruses were used that did not kill the intended bacteria<sup>1</sup>. There were also problems with the production of a

stable contaminant-free phage stock. Perhaps the greatest barrier to phage acceptance in the west was the inadequate scientific methods used by researchers, such as the exclusion of placebos in trials<sup>2</sup>. With the advent of the antibiotic dawn, phage research and production were all but shelved, with the exception of Eastern Europe and the former Soviet Union where they continue to be used therapeutically.

## Renewed interest

Now the threat of widespread antimicrobial resistance has sparked a renewed interest in phages. Dr Clokie has been studying phages for 14 years. She says, “As their natural enemy, phages specifically target and kill bacteria. They encode a diverse set of gene products that can potentially be exploited as novel antimicrobials. They have the advantage over antibiotics of being much more specific and, as they can self-replicate at the site of

an infection, they are able to clear infections that antibiotics can’t reach.” Over the past few years, Dr Clokie has isolated and characterised 40 different phages that infect *C. difficile* — the largest known set of these phages. Of these, she has developed a specific mixture that has proved to be effective against 90 per cent of the most clinically relevant *C. difficile* strains seen in the UK. The US pharmaceutical company AmpliPhi are funding the further development of these phages, with the aim of testing them in Phase I and Phase II trials. This will involve optimising phage preparations for maximum effectiveness against *C. difficile* infections and establishing production, storage and delivery systems for the phage mixture. Dr Clokie will evaluate the effectiveness of the therapy and dosing regimes in collaboration with Dr Gill Douce at the University of Glasgow.

Dr Clokie says, “The number of bacteriophages that exist on Earth, combined with their vast genetic diversity and exquisitely specific interactions with bacterial hosts means that they have the potential to offer a real solution for the treatment of a range of human pathogens. A lot of fundamental science needs to be carried out in order to ensure that we understand how to best exploit them.”

## Phage products

A potential problem with systemic phage use is the possibility that they may be seen as foreign by the body’s immune system and be destroyed. Delivery of phages also needs to be investigated. To prevent them being damaged by the acidity of the digestive system when ingested, phages would need to be encapsulated or stabilised. A way around these problems might be to use the products of phages rather than the whole organism<sup>3</sup>.

In 2010, a team of researchers at the MRC Centre for Molecular Bacteriology and Infection (CMBI), also funded by BBSRC, determined the structure of Gp2 — a protein produced by the phage T7 that disables *E. coli* cells<sup>4</sup>. In 2012, they demonstrated how Gp2 blocks the action of the bacteria’s RNA polymerase — an enzyme that enables the instructions in the bacteria’s genes to be read and turned into proteins<sup>5</sup>. The researchers now plan to

identify small molecules that mimic the structure and function of Gp2 and use these as the basis for new drugs to combat bacterial infections.

Different bacterial infections will require different treatment solutions, but it is hopeful that both whole phage particles and their products can be developed as important alternative treatments for human infection.

## References

1. Weld RJ et al. Models of phage growth and their applicability to phage therapy. *Journal of Theoretical Biology*, Volume 227, Issue 1, 7 March 2004, Pages 1–11. DOI: 10.1016/S0022-5193(03)00262-5
2. Carlton RM. Phage therapy: past history and future prospects. *Arch Immunol Ther Exp (Warsz)*. 1999;47(5):267-74
3. Inal JM. Phage therapy: a reappraisal of bacteriophages as antibiotics. *Arch Immunol Ther Exp (Warsz)*. 2003;51(4):237-44
4. Camara B et al. T7 phage protein Gp2 inhibits the Escherichia coli RNA polymerase by antagonizing stable DNA strand separation near the transcription start site. *Proceedings of the National Academy of Sciences of the United States of America*. 2010. 107, p 2247-2252
5. E James et al. “Structural and Mechanistic Basis for the Inhibition of Escherichia coli RNA Polymerase by T7 Gp2.” *Molecular Cell*, 2012.