Phage-loaded biomimetic apatite powder and biofilms in bone and joint infections

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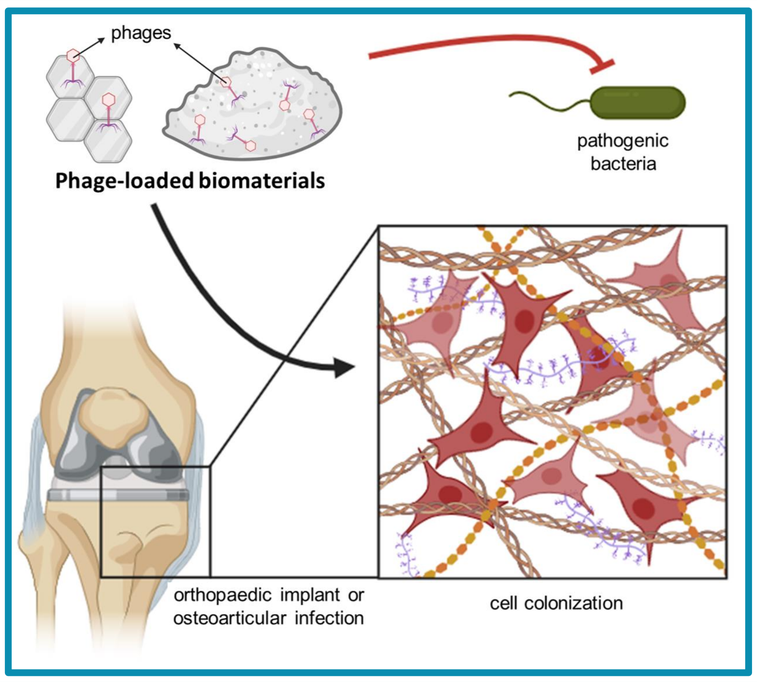
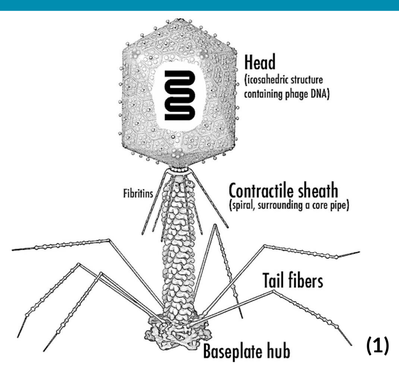
INTRODUCTION

For several decades, calcium phosphate-based ceramics such as hydroxyapatite and β-tricalcium phosphate (β-TCP) have been used as bone substitutes in orthopaedic surgery due to their mineral composition being similar to that of bone and their ability to promote biointegration. Following bone and joint infections, some patients treated with antibiotics remain asymptomatic but may later experience recurrence of the original infection. This can be explained by the presence of bacterial biofilms on prostheses or bone substitutes, which may act as silent reservoirs of infection.

We aim to develop calcium phosphate-based ceramics loaded with bacteriophages (phages) to treat these infections. The effectiveness of this strategy has already been demonstrated in our laboratory against both planktonic bacteria and 24h-mature biofilms. The objective of the present work is to improve these devices in order to achieve sustained phage release at the infection site and to facilitate phage diffusion within the biofilm. The synergistic effects of phages combined with antibiotics were also investigated to maximize antibacterial efficacy against biofilms while limiting the emergence of bacterial resistance.

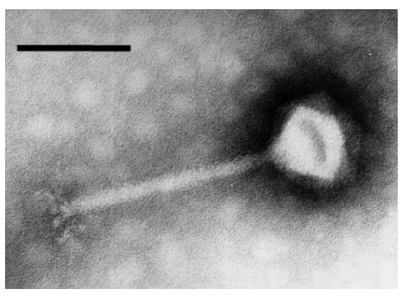


Bacteriophages : forgotten allies against bacteria



(1)

Transmission electron microscopy of Remus phage.



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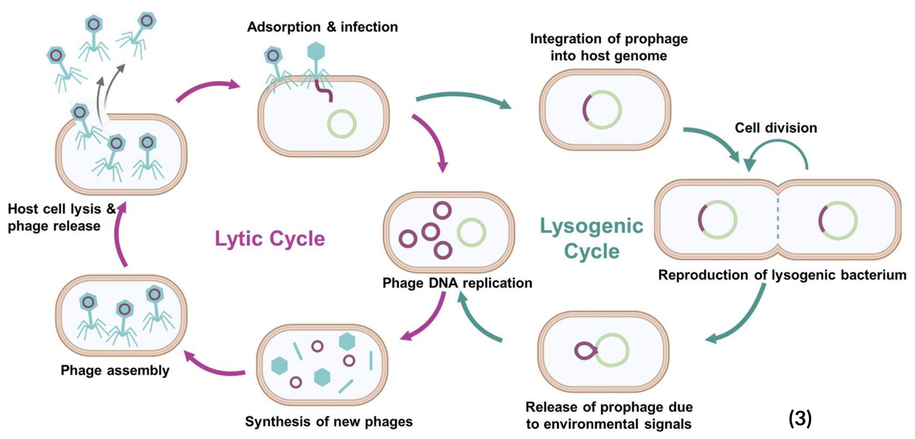
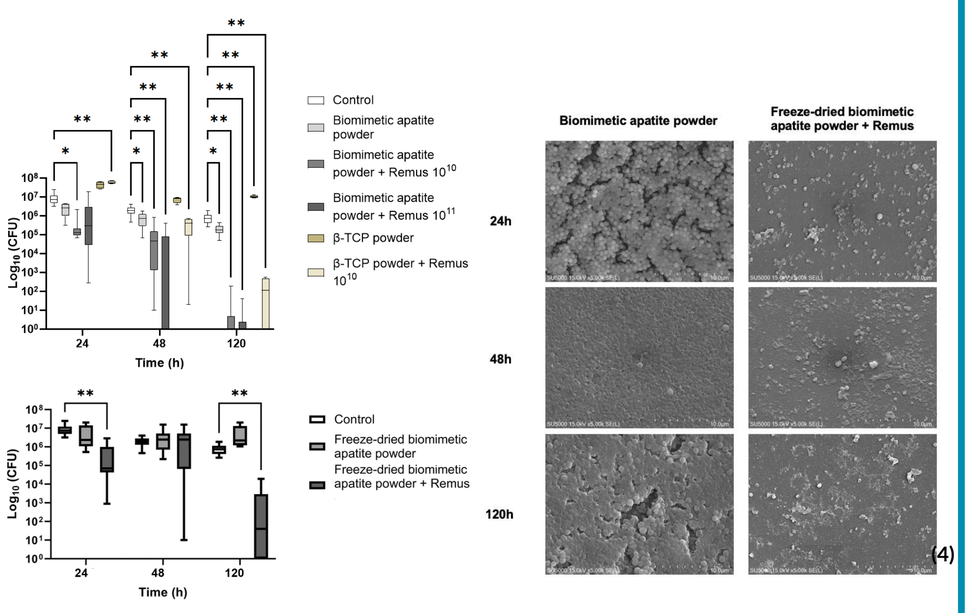


(3)

- Bacteriophages are viruses that exclusively infect bacteria.
- They hijack the cellular machinery of their host to produce new phage particles, which are ultimately released through bacterial lysis.
- Bacteriophages were first used therapeutically in 1919 by Félix d'Hérelle, who introduced the concept of phage therapy.
- The emergence and widespread success of antibiotics led to a decline in the use of phage therapy.

Antibacterial activity against homogeneous bacterial biofilm



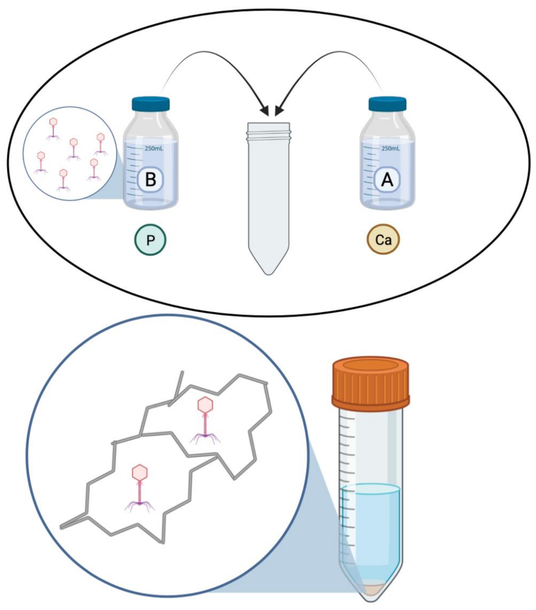
(4)

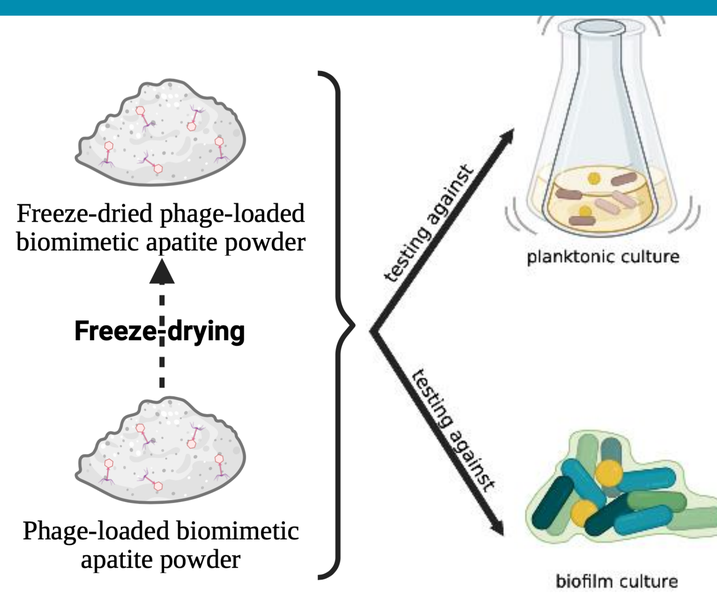
- Phage-loaded powder treatment is effective against homogeneous *S.aureus* biofilm.

References

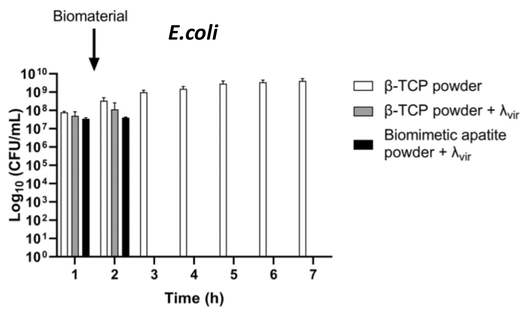
- (1) Biotechnological applications of bacteriophages : State of the art, Harada et al. (2018)
- (2) Romulus and Remus, Two Phage Isolates Representing a Distinct Clade within the Twortlikevirus Genus, Display Suitable Properties for Phage Therapy Applications, Vandersteegen et al. (2013)
- (3) Genetically engineered bacteriophages as novel nanomaterials: applications beyond antimicrobial agents, Kim et al. (2024)
- (4) Phage-Loaded Biomimetic Apatite Powder With Antibiofilm Activity to Treat Bone- Associated Infections, Decodts et al. (2025)

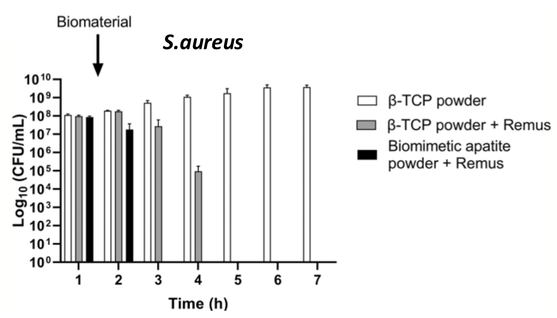
Preparation of phage-loaded powder for antimicrobial assays





Antibacterial activity against planktonic cells





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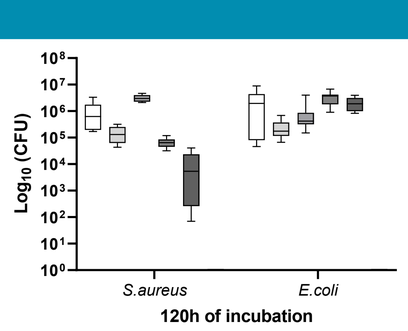
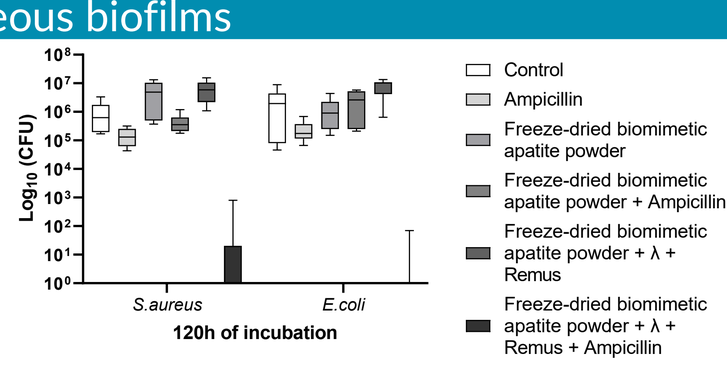
- Phage-loaded powder eradicates *E.coli* and *S.aureus* planktonic cultures within 2 hours of incubation

Synergistic antibacterial activity of phages and ampicillin against heterogeneous biofilms





- Neither ampicillin nor phage-loaded powder treatments were able to eradicate both bacterial species within the biofilm.
- Combination of antibiotic and phage therapy showed a synergistic effect, leading to almost a complete eradication of both *S.aureus* and *E.coli* in the biofilm.

Conclusion and perspectives

- Co-precipitation model results in an efficient encapsulation of phages.
- Phage-loaded biomimetic powder is efficient against both planktonic and homogeneous biofilms cells.
- Synergy with ampicillin therapy allows to efficiently remove heterogeneous biofilm cells.
- Co-encapsulation of both phage and antibiotic should be designed to improve treatment delivery.
- In vivo studies would better assess the efficiency of this synergy.