

# Comment fonctionne la synergie entre bactériophages et réponse immunitaire

DEBARBIEUX Laurent  
Pasteur Microbes & Santé

# THE MAIN CHALLENGE IN PHAGE THERAPY RESEARCH

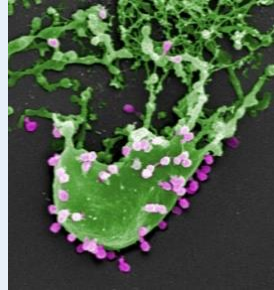
in the laboratory



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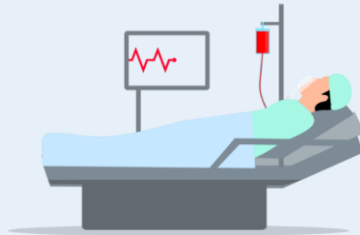
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in the hospital



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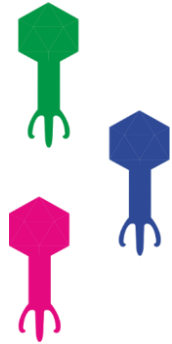
?



Translational  
Research

# EXPERIMENTAL MODELS OF PHAGE THERAPY

**Bacteriophages**



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**Bacteria**



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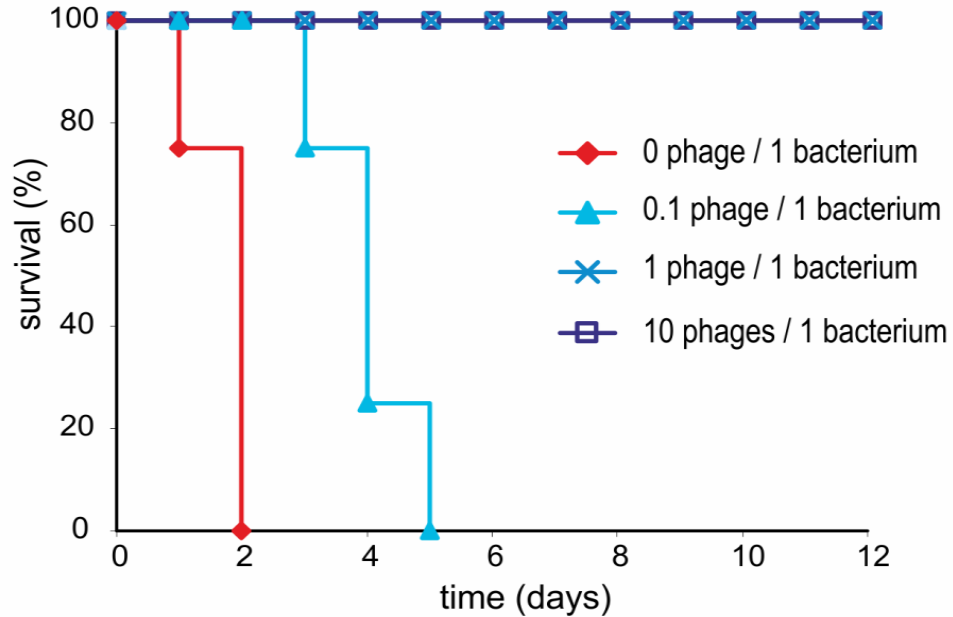
**Host**



We aim to characterize **tripartite interactions** to identify factors controlling bacteriophage infection

# MURINE MODEL OF RESPIRATORY INFECTION

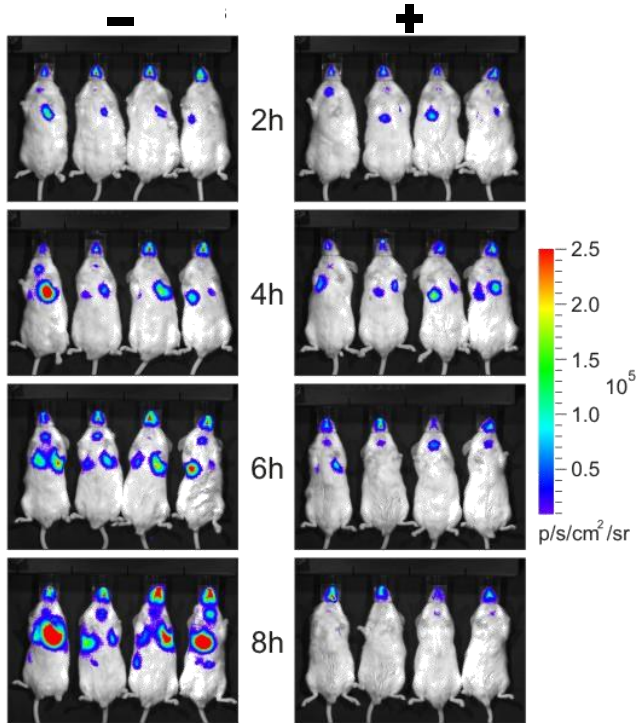
Infection by  $1.0 \times 10^7$  CFU and treatment 2 h later (both by IN)



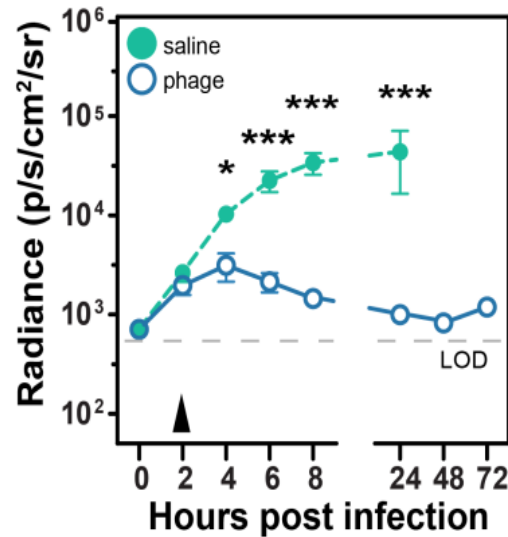
# EXPLOITING LIVE IMAGING TO ASSESS IN VIVO KINETICS

**Infection** at time 0  
by  $1.0 \times 10^7$  CFU

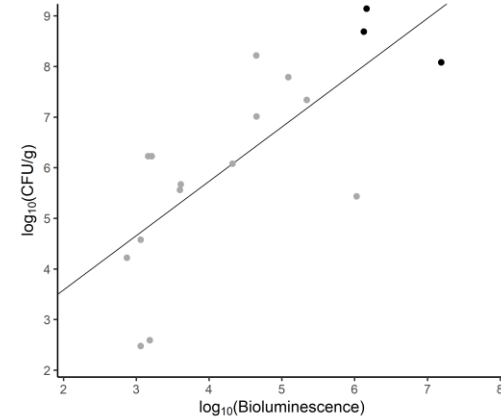
**Treatment** at 2 h  
by  $1.0 \times 10^8$  PFU



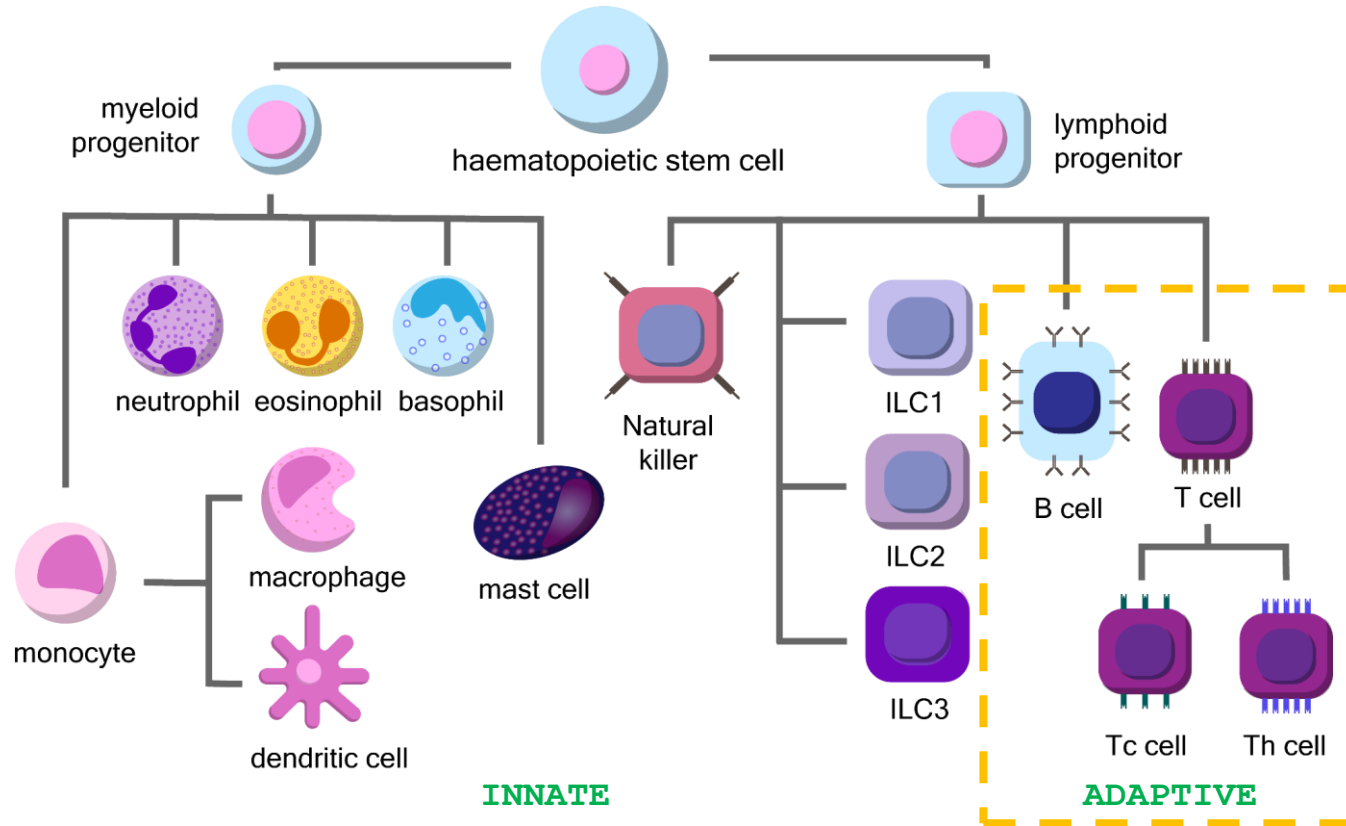
Quantification of emitted light



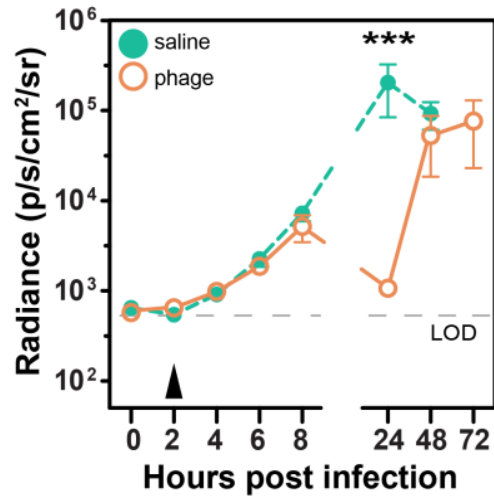
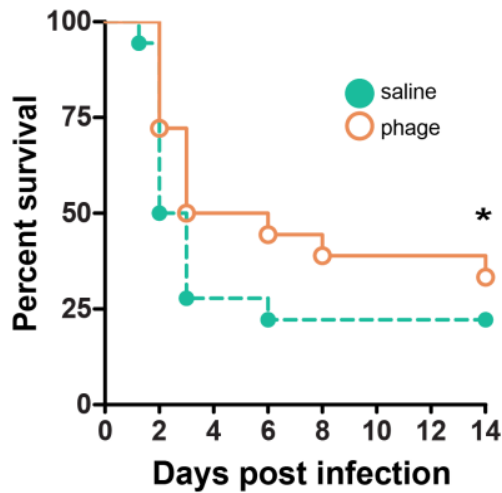
Correlation luminescence/CFU



# IS THE IMMUNE SYSTEM INVOLVED IN PHAGE THERAPY EFFICACY ?

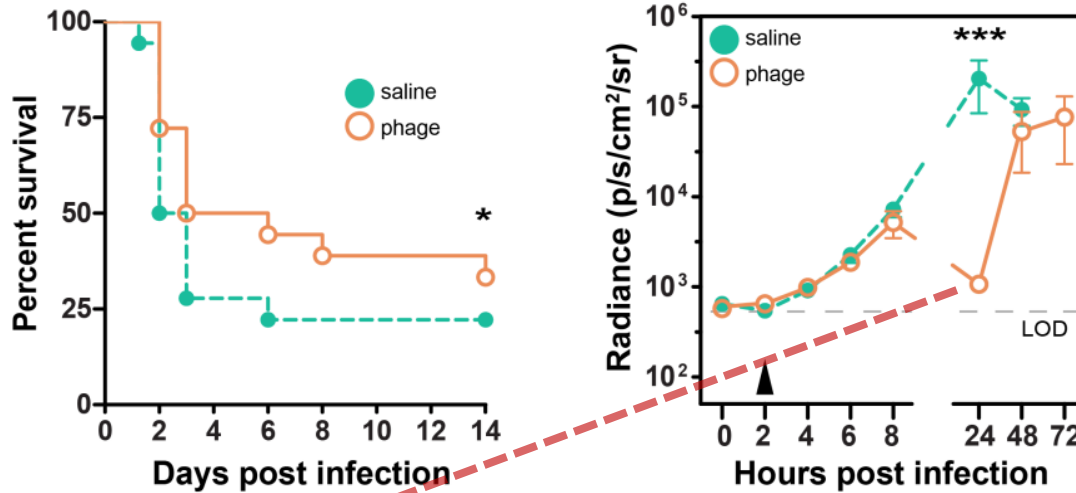


# PHAGE THERAPY EFFICACY IN MYD88<sup>-/-</sup> MICE ?



24 h p.i., reduction of bacteria load = bacteriophages work.

# PHAGE THERAPY EFFICACY IN MYD88<sup>-/-</sup> MICE ?



24 h p.i., reduction of bacteria load = bacteriophages work.

72 h p.i., failure = growth of bacteriophage resistant bacteria

In WT mice “Immunophage” synergy prevents the growth of phage resistant



# DEVELOPING AN *IN SILICO* MODEL OF PHAGE THERAPY

Joshua Weitz

Georgia Tech School of Biological Sciences

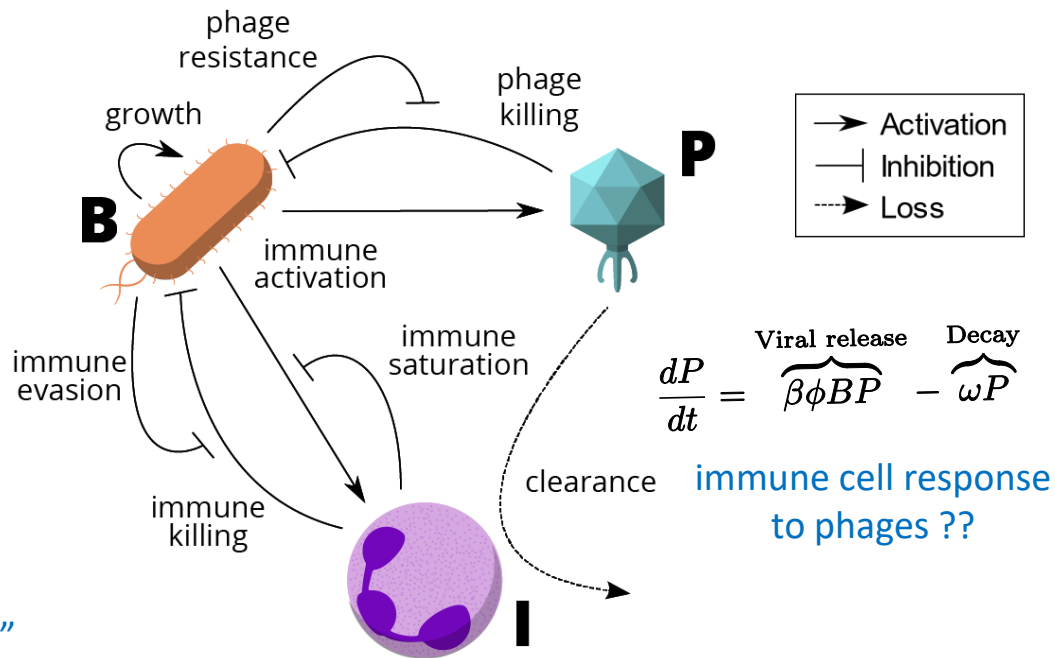
$$\frac{dB}{dt} = \overbrace{rB \left(1 - \frac{B}{K_C}\right)}^{\text{Growth}} - \overbrace{\frac{\epsilon IB}{1 + B/K_D}}^{\text{Immune killing}} - \overbrace{SF(P)}^{\text{Lysis}} + \overbrace{\mu rS \left(1 - \frac{S+R}{K_C}\right)}^{\text{Mutation}}$$

bacteria can develop resistance to phage

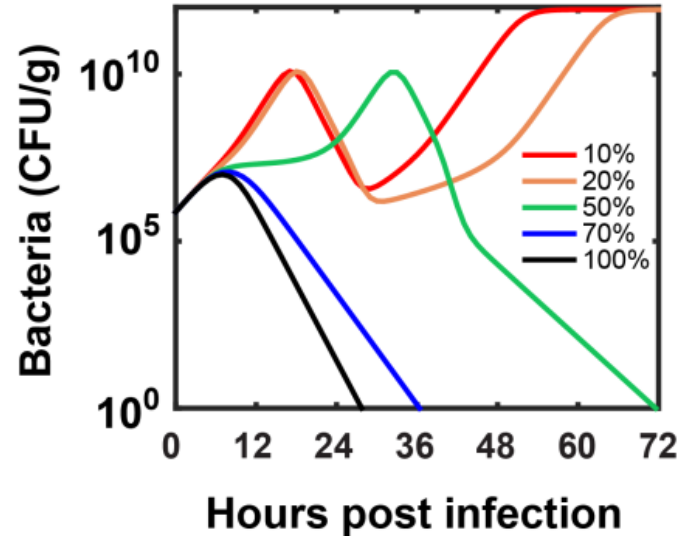
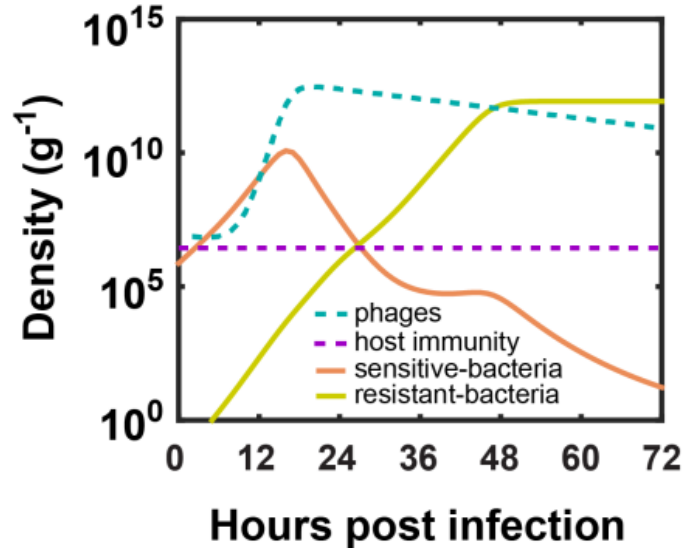
bacteria can evade the immune response

$$\frac{dI}{dt} = \overbrace{\alpha I \left(1 - \frac{I}{K_I}\right) \left(\frac{B}{B + K_N}\right)}^{\text{Immune stimulation}}$$

Immune stimulation has a maximum “carrying capacity”



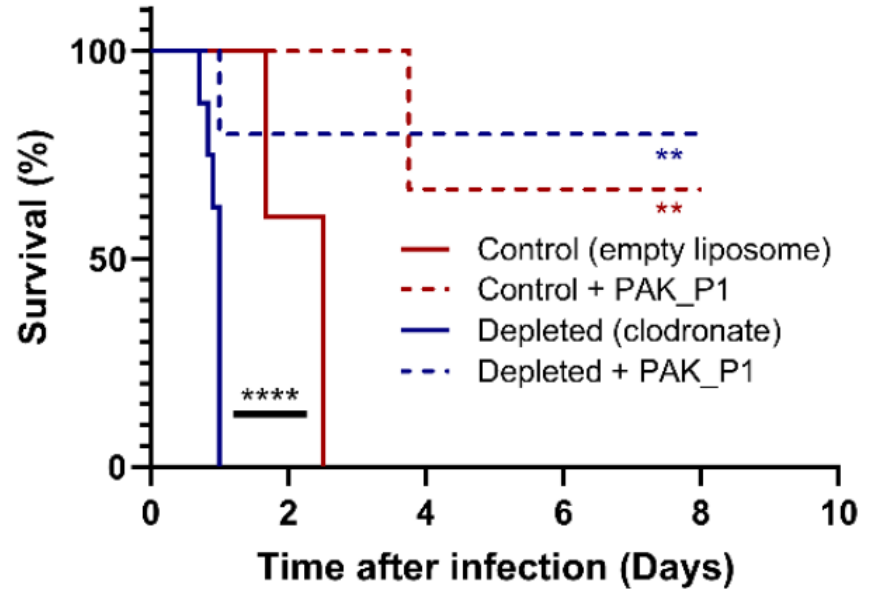
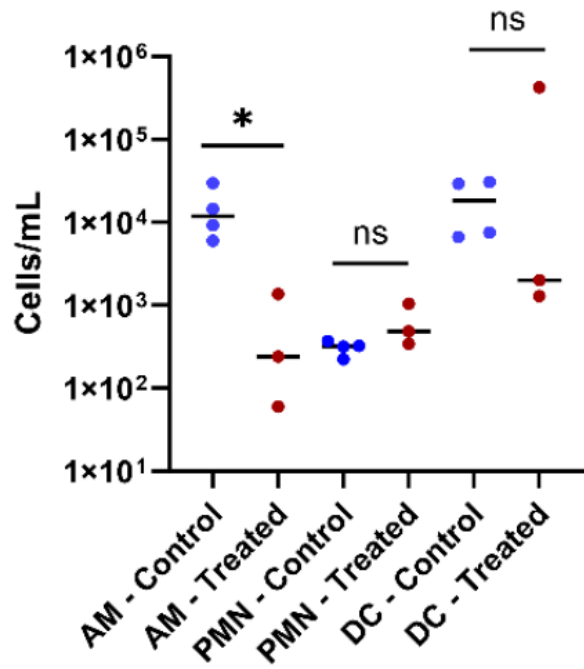
# MODELING THE LACK OF IMMUNE ACTIVATION



Neutrophils are essential for phage therapy

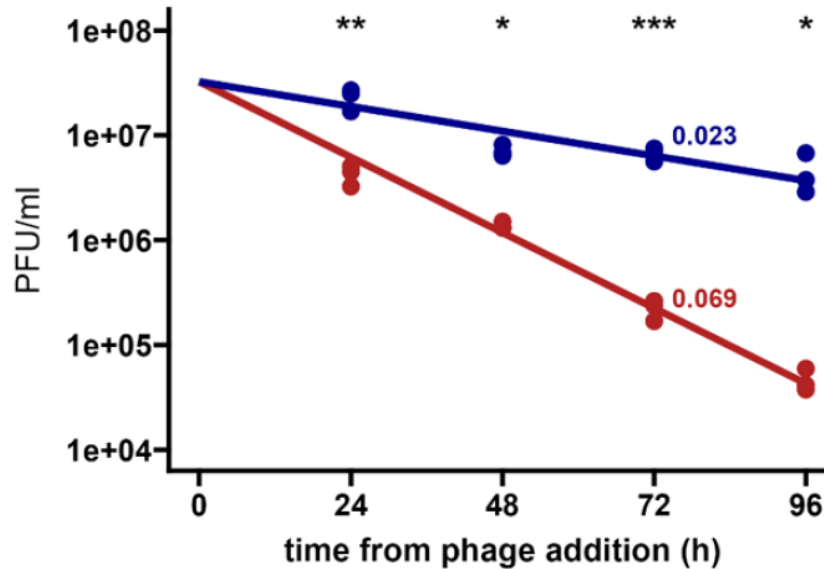
# LOOKING BEYOND NEUTROPHILS

Clodronate induces macrophages death  
without affecting other immune cells



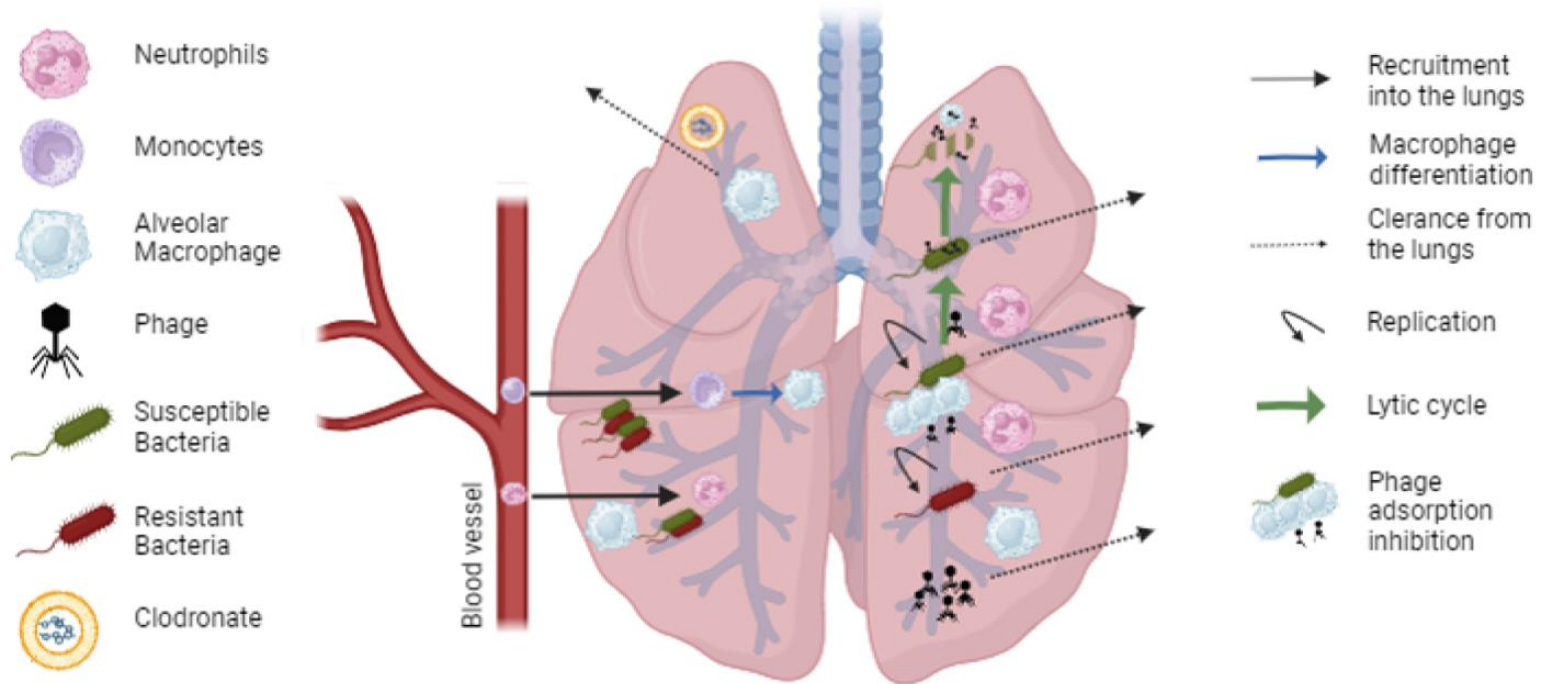
The lack of macrophages is  
**beneficial** to phage therapy !

# MACROPHAGES REDUCE BACTERIOPHAGES LOAD



Macrophages are also preventing the diffusion of bacteriophages

# INTEGRATING FACTORS INFLUENCING PHAGE THERAPY EFFICACY



<https://research.pasteur.fr/en/team/bacteriophage-bacterium-host>



## Team members

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de la recherche



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Infectious Diseases



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# Merci