# Phage therapy: History

Frederick Twort
1915

Félix d'Hérelle
1917

George Eliava

UNIVERSITEIT GENT

UZ GENT

Phages, short for bacteriophages, are bacteria-specific viruses that have been used as a treatment against pathogens such as *Shigella dysenteriae* as early as 1919.

With an estimated $10^{31}$-$10^{32}$ phages in the world at any given time, they make up the most abundant biological entity on Earth and play a crucial role in regulating bacterial populations; phages are responsible for the death of approximately 20%-40% of all marine surface bacteria every 24h.

# Le prime evidenze sull'esistenza di fagi

La prima evidenza dell'esistenza di un agente di tipo virale con proprietà antibatterica risale al 1896 con M. E. Hankin che trova nel fiume Gange un elemento termosensibile, in grado di passare il filtro di porcellana e capace di ridurre significativamente il titolo di *Vibrio cholerae* in laboratorio.

Adhya S and C. Merril. 2006. The road to phage therapy**.** *Nature* **443:** 754-755

# Prime informazioni sull'uso clinico dei fagi iniziano con d'Herelle negli anni 20

- ***d'Herelle's first clinical experiences in 1920's***

  *Per il trattamento della dissenteria…*

  d'Herelle F. (1917). Sur un microbe invisible antagoniste des bacilles dysentériques. Acad. Sci. Ser. D 165:373

  *Per il trattamento della peste…*

  d'Herelle F. (1925) Essai de traitement de la peste bubonique par le bactériophage. La Presse Med. 33: 1393-94.

- **George Eliava** starts the microbiology institute in Tbilisi (1923), has been working at the Pasteur Institute of Paris with D'Herelle (1918-21 and 1926-27)) and d'Hérelle is invited by Stalin to the Eliava Institute (1936).

d'Hérelle worked at the Tbilisi Institute and even dedicated one of his books, published in Tbilisi in 1935, to Comrade Stalin.

He had already started to build a cottage on the grounds of the Institute.

But just then, his friend Eliava fell in love with the Georgian woman with whom the head of the secret police also happened to be in love. Eliava's fate was sealed.

He was executed and denounced as an enemy of the people.
d'Hérelle ran for his life and never returned to Tbilisi.

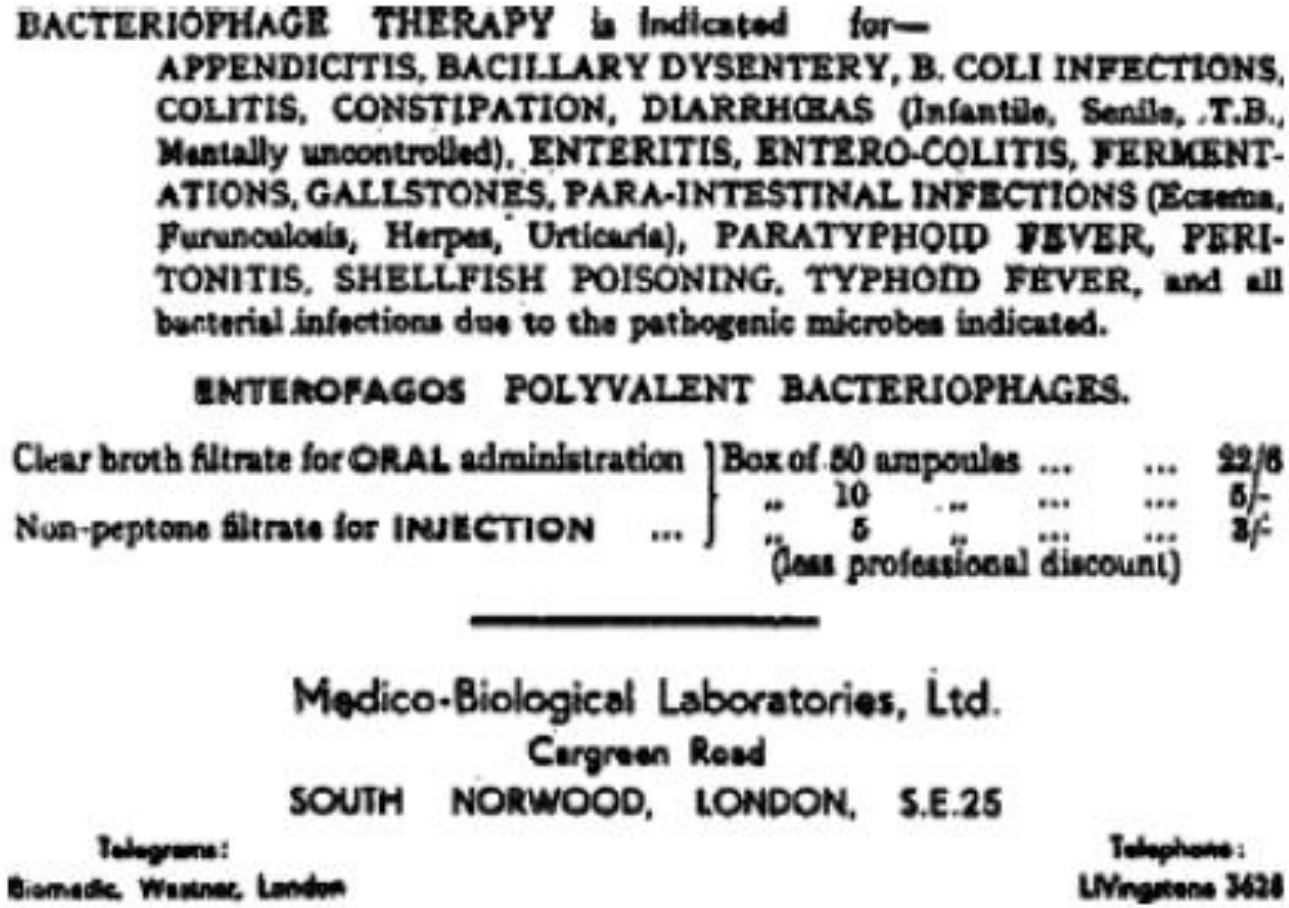



**Figure 3** Advertisement for a bacteriophage therapeutic from the 1920s. Reprinted with the kind permission of Dr James Soothill.

It was also d'Herelle who conceived of the idea to use phages therapeutically and is responsible for the first documented clinical use of phage in 1919 at the Hôpital des Enfants-Malades in Paris where phages were successfully used to treat 4 pediatric cases of bacterial dysentery[1]. Despite several successful trials, d'Herelle's early experiments were notorious for being poorly controlled and his research was vigorously disputed by the scientific community[3].

Nevertheless, d'Herelle continued to pioneer phage therapy with the treatment of dysentery, cholera, and the bubonic plague in the early 20th century with a series of phage therapy centers and commercial phage production plants throughout Europe and India[34].

One 1931 trial of phage therapy as a treatment for cholera in the Punjab region of India involved a cohort of 118 control subjects and 73 experimental subjects who received phage treatment; d'Herelle observed a 90% reduction in mortality with 74 lethal outcomes in the control group and only 5 in the experimental group[1].

## *La Phagetherapy comincia prima della scoperta degli antibiotici ma viene abbandonata con l'avvento degli antibiotici*

***Commercialization of phages in France and USA in 1930's***

L'Oréal: Bacté-intesti-phage, Bacté-pyo-phage, Bacté-staphylo-phage
Eli Lilly: Colo-lysate, Entero-lysate, Staphylo-lysate

***Phage therapy was abandoned in the West, because of***

lack of understanding of the high specificity and mode of action of phages

exaggerated claims of effectiveness: urticaria, herpes, eczema

the rise of **broad-spectrum antibiotics**

***but phage therapy research continued in Eastern Europe ...***

## Perché la phagetherapy può essere una nuova strategia?

**- Il problema della resistenza agli antibiotici  sta aumentando**

-**Il numero di nuovi antibiotici in sperimentazione è limitato**

- **Molte infezioni croniche sono sono dovute alla formazione di biofilm contro I  quali gli antibiotici hanno effetto limitato**

in CF-patients: *Pseudomonas aeruginosa*
Nelle otiti croniche *Haemophilus influenzae*, *Alloiococcus otitidis*?
Nelle infezioni urinarie uropathogenic *Escherichia coli*
Nelle vaginosi : *Gardnerella vaginalis*, *Atopobium vaginae*
Nelle ustioni *Pseudomonas aeruginosa*, *Staphylococcus aureus*
nelle infezioni di cateteri , valvole , protesi : *Staphylococcus* spp.

# Quali sono i potenziali vantaggi della phagetherapy ?

- ***Nessun effetto sul microbioma commensale***

- ***Nessun effetto di resistenza crociata***

- ***Possibilità di creare un cocktail di fagi che può essere facilmente personalizzato sul paziente /infezione***

- ***I batteri MDR (Multi Drug Resistant) possono essere trattati***

# Quali sono i possibili usi della phagetherapy?

**1. Il classico : l'uso di un cocktail di fagi litici virulenti come antibatterici**

Merril et al. 2003. The prospect for bacteriophage therapy in Western medicine. Nature Reviews/Drug Discovery 2: 489-497.

**2. l'uso di prodotti derivati da fagi quali T4-lisozima, depolimerasi della capsula, lisine etc**

Loeffler et al. 2001. (Rapid killing of *Streptococcus pneumoniae* with a bacteriophage cell wall hydrolase. Science 294: 2170-2172.

**3. Fagi lisogenici per il rlascio in situ di geni particolari quali :**

--> *in situ* delivery to bacterial cells of

* killing genes (doc)
* antisense RNA to block translation

Westwater et al. 2003. Use of a genetically engineered phage to deliver antimicrobial agents to bacteria: an alternative therapy for treatment of bacterial infections. **Antimicrob. Agents Chemother. 47:** 1301-1307.

**4. Utilizzo dei fagi come « *probiotici* » con effetti immunomodulatori**

Phages inhibit human T-cell activation and proliferation
Phages diminish cellular infiltration into allogeneic skin allografts

Gorski et al. 2006. Bacteriophages and transplantation tolerance.
**Transplant. Proc. 38**: 31-333.

# Vi sono rischi nell'utilizzazione di fagi nella terapia?

**Phages are safe by definition: viruses which infect bacteria only**

1. Bacteriophages infect specifically bacteria since they need to recognize bacterial cell wall structures: ***peptidoglycane, LPS***.

2. Bacteriophages that were manipulated genetically to infect mammalian cells were ***not able to multiply inside*** the mammalian cells after infection.

3. ***No bacteriophage genes*** can be found ***in the human genome***, whereas retro-viruses have left hundreds of genes integrated into the human genome.

***In summary,*** bacteriophages have ***no tropism*** towards mammalian cells and ***cannot multiply*** in them

# Ma viene gia utilizzata la phagetherapy sull'uomo?

During the long history of using bacteriophages as therapeutic agents bacteriophages have been administered to **thousands of humans**

(i) orally, in tablet or liquid formulations ($log^5$ to $log^{11}$ bacteriophages/dose),

(ii) rectally,

(iii) locally: skin, eye, ear, nasal mucosa, burn wounds, rinses and creams

(iv) as aerosols or intrapleural injections, and

(v) intravenously, albeit to a lesser extent than the first four methods.

Only one group, from the Hirszfeld Insitute, Wroclaw, **Poland**, renown for its clinical application of bacteriophages reported **a few minor side effects** (e.g. nausea, fever).

These effects may have been due to the liberation of endotoxins from lysed bacteria, a phenomenon that can also be observed when antibiotics are used and therefore cannot be considered as specifically bacteriophage related.

# Perché la phagetherapy può essere un' alternativa?

- Phage therapy is one of the viable alternatives to antibiotics
- Phages are currently being used therapeutically to treat bacterial infections that do not respond to conventional antibiotics.
- Phage therapy has many applications in human medicine as well as dentistry, veterinary science and agriculture.
- An important benefit of phage therapy is that bacteriophages can be much more specific than more common drugs and thus harmless to not only the host organism (human, animal or plant).
- Because the phages replicate in the organism itself, a single, small dose is sometimes sufficient.

# Phagetherapy come vaccino??

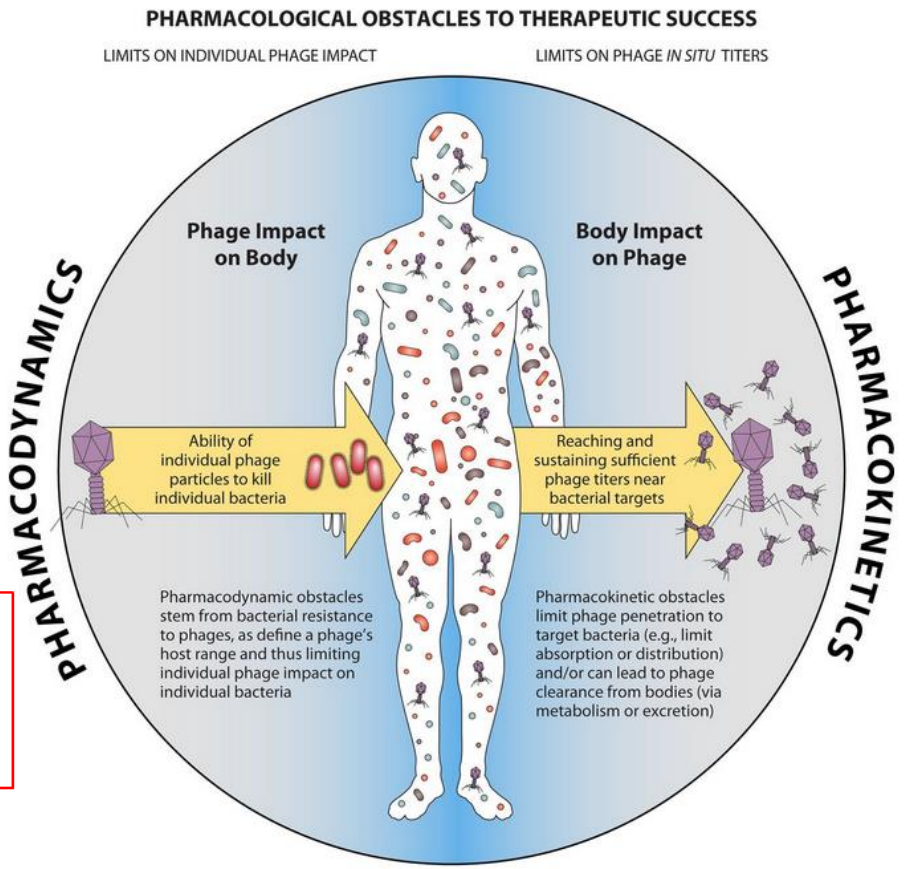
**Vaccination" study in Tbilisi, Georgia (1965)**

30.769 children aging 6 months to 7 years old.

17.044 children ingested bacteriophages against *Shigella dysenteriae*.
13.725 children, living at the opposite side of the streets, served as a control group.

Babalova *et al*. 1968. Preventive value of dried dysentery bacteriophage.
**Zh. Mikrobiol. Epidemiol. Immunobiol. 2**: 143-145.

# Quali possono essere gli ostacoli alla terapia fagica?

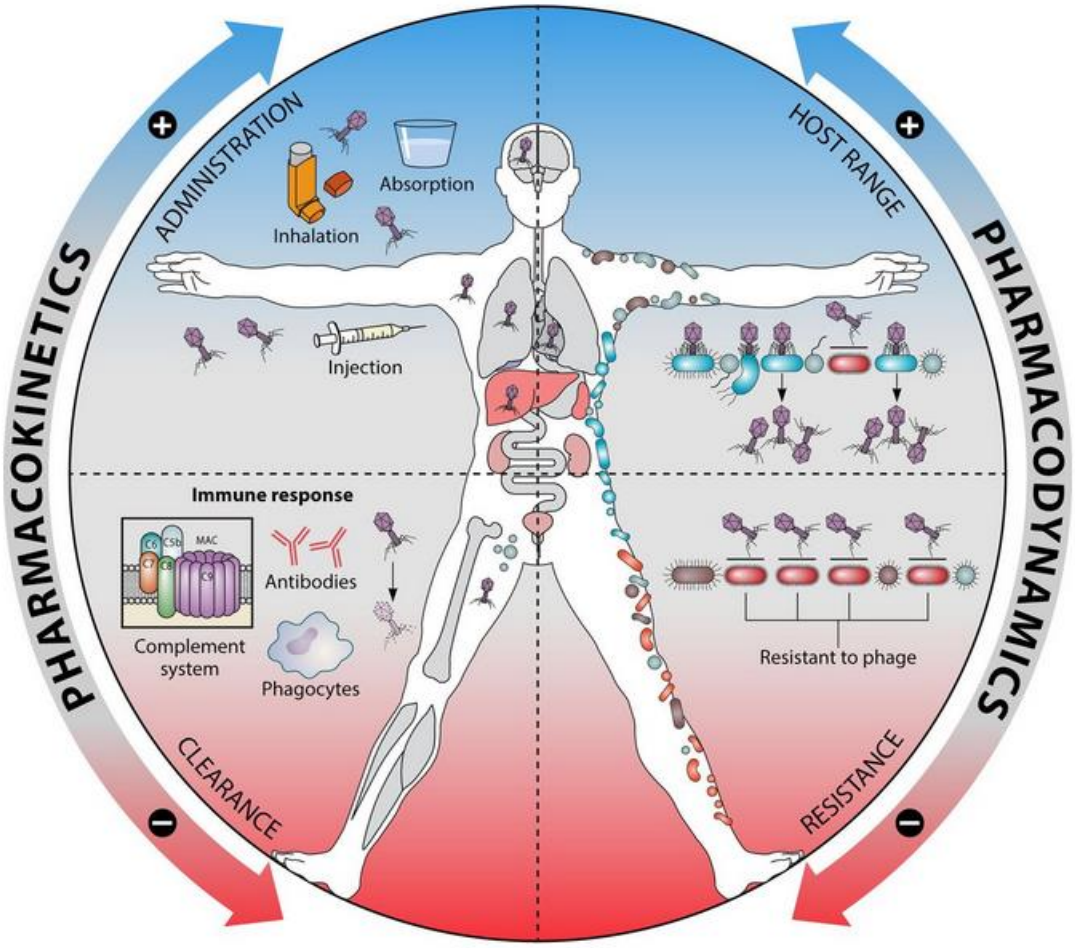



*Impatto del fago sull'ospite*

*Impatto dell'ospite sul fago*

Farmacodinamica: l'impatto del farmaco sull'ospite inteso come tessuti e microbioma associato.
Gli ostacoli sono costituti dai meccanismi di resistenza dei batteri al fago che possono essere assoluti o parziali ( il fago è inattivato, ne batterio ne fago sopravvivono, infezione parziale)

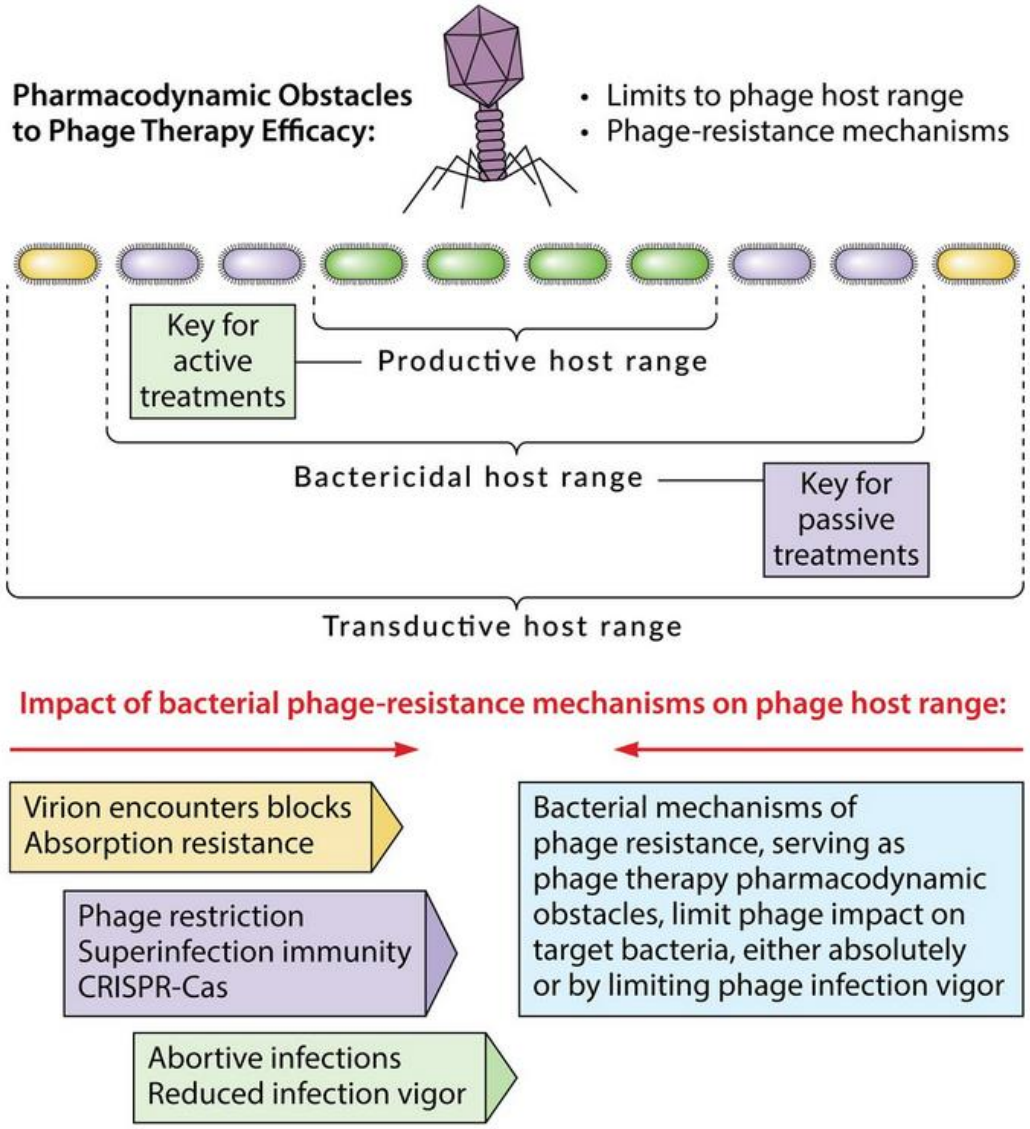
Farmocinetica si intende l'impatto dell'ospite sul farmaco.
Gli ostacoli possono essere costituiti dalla capacità del fago di raggiungere il sito di azione e mantenersi attivo nel tempo.




1. La capacità di un batteriofago di entrare nell'ospite e raggiungere il sito bersaglio è determinante per il successo della terapia.
2. La concentrazione del fago diminuisce in seguito alla pressione del sistema immunitario ed a meccanismi aspecifici di inattivazione.

Ulteriori fattori rilevanti per il successo della terapia vanno ricercati

3. nella resistenza dei batteri al fago e
4. nello spettro d'ospite del fago




Quali sono gli ostacoli all'azione del fago definiti come meccanismi di resistenza al fago. Che si ricollegano allo spettro d'ospite

1. Il fago penetra nella cellula ma non indice produzione fagica
2. Il fago penetra uccide la cellula ma non riesce ad indurre una forte induzione di progenie fagica
3. Il fago produce progenie fagica. In questo caso la progenie potrebbe essere inferiore del previsto

Qui sono riportati i diversi meccanismi di antibiotico resistenza

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Oxford Journals › Medicine › The Journal of Infectious Diseases › Volume 201, Issue 7 › Pp. 1096-1104.

# Bacteriophages Can Treat and Prevent *Pseudomonas aeruginosa* Lung Infections

Laurent Debarbieux[1], Dominique Leduc[2], Damien Maura[1], Eric Morello[1], Alexis Criscuolo[1], Olivier Grossi[3], Viviane Balloy[2] and Lhousseine Touqui[2]

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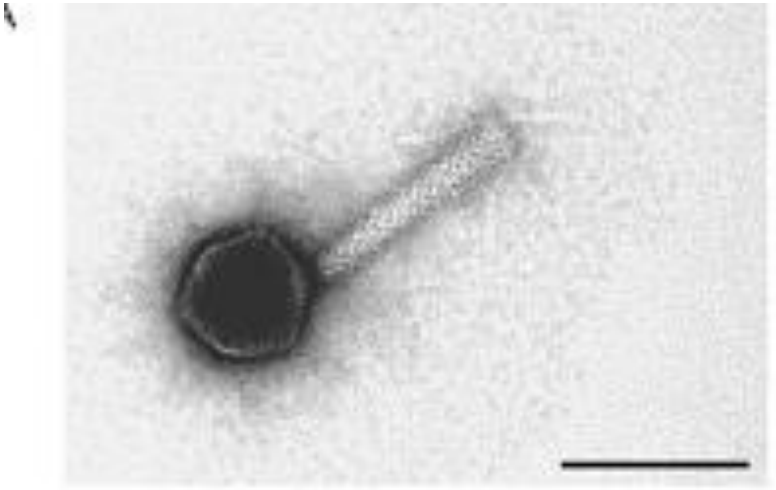
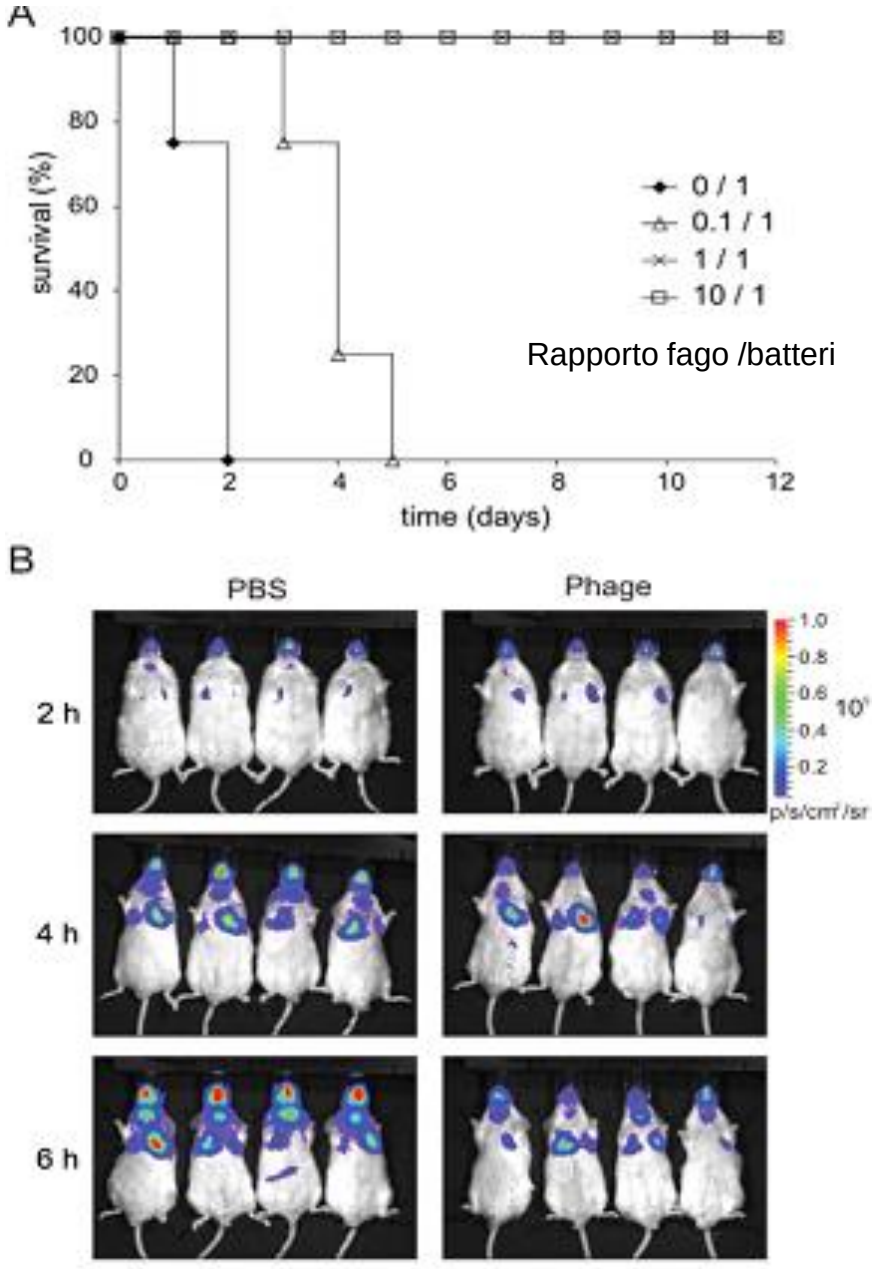


Characterization of the PAK-P1 bacteriophage. A, Electron microscopic analysis of the PAK-P1 bacteriophage (scale bar, 100 nm).




Debarbieux L et al. J Infect Dis. 2010;201:1096-1104

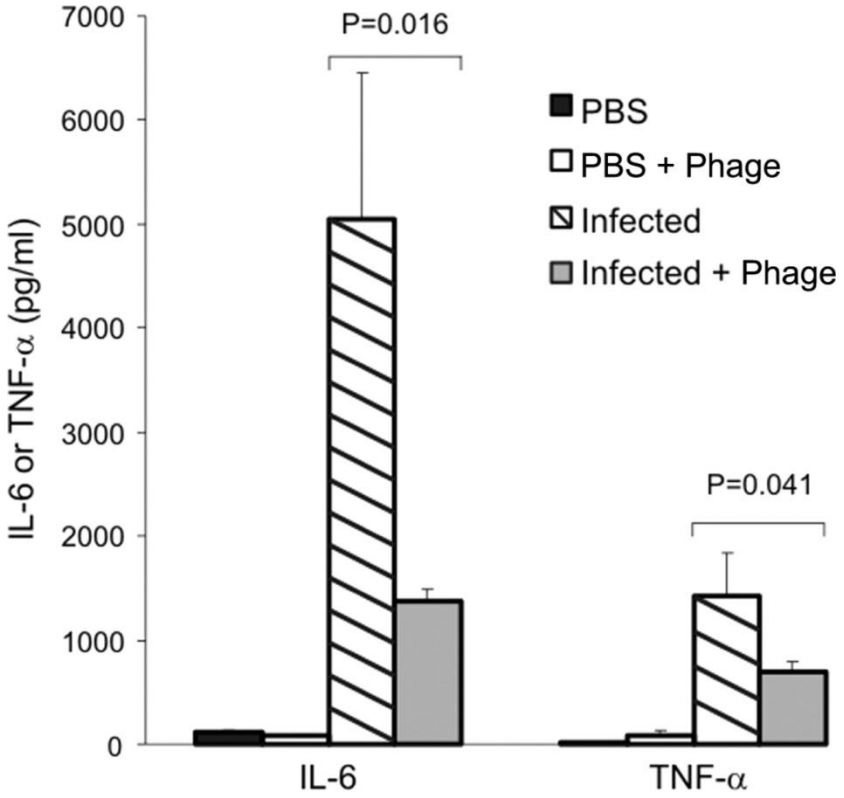
## Effect of bacteriophage treatment on deadly infection in mice.

.*A*, Survival curves of infected animals treated with phosphate- buffered saline (PBS) or bacteriophages at indicated bacteriophage-to bacterium ratios. The amount of bacteria required to induce a deadly lung infection in Balb/c mice by way of intranasal instillation (was set to 1 × 107 bacteria, because we found that 100% of mice survived challenge by 5 × 10 6 bacteria for up to 4 days and that a dose of 1.5 × 107 bacteria was 100% lethal within 24 h.

*B*, Example of time-course images of mice infected with bioluminescent *Pseudomonas aeruginosa* and treated with PBS (*left*) or treated with the PAK-P1 bacteriophage at a bacteriophage-to-bacterium ratio of 10:1 (*right*). .

Necessario un rapporto di 10/1 a fago/batterio per avere un effetto sulla sopravvivenza

# *Reduction of inflammation by bacteriophage treatment.*




Cytokine levels were measured in bronchoalveolar lavages of mice (*n* = 4) 24 h after instillation of phosphate-buffered saline (PBS) (*black bars*), PBS and PAK-P1 bacteriophage (*white bars*), bacteria with PBS 2 h later (*hatched bars*), or bacteria with PAK-P1 bacteriophage2hlater(*gray bars*). Bars show the mean, and error bars show the standard error. IL6, interleukin 6; TNF-α, tumor necrosis factor α.

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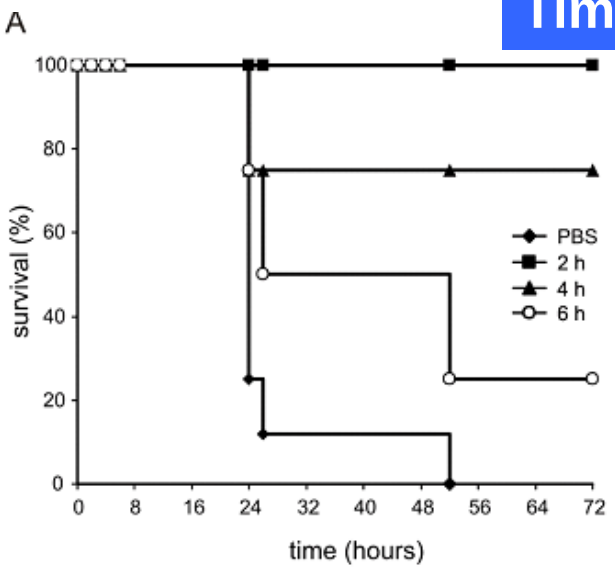
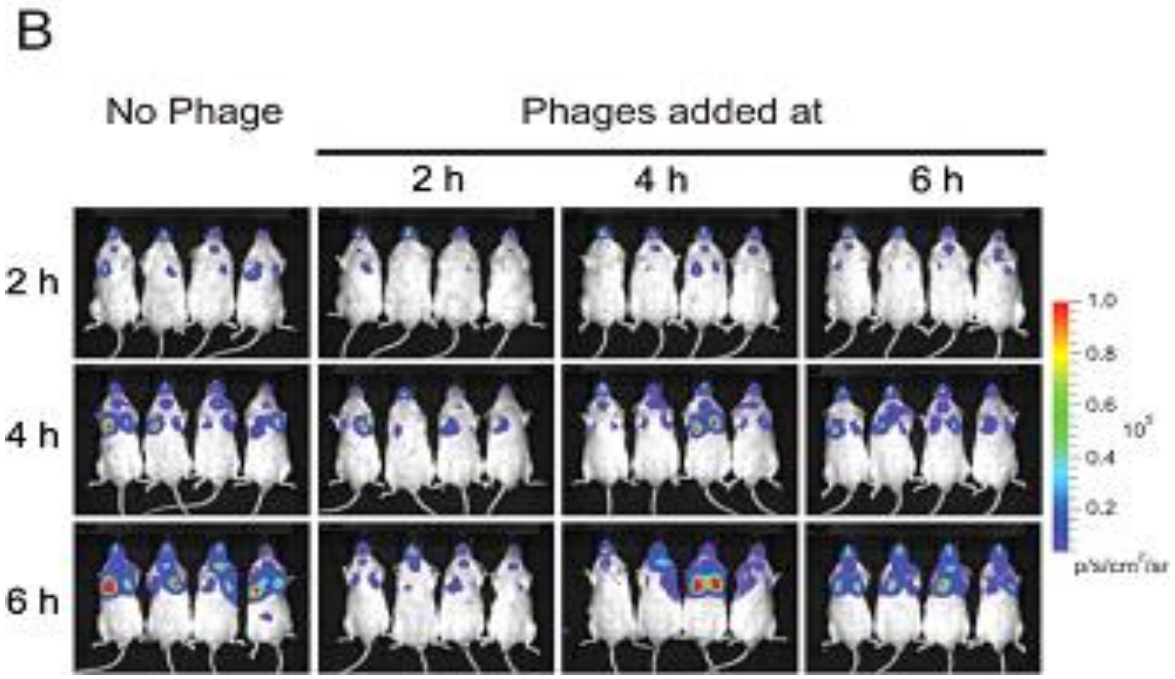
# Time-course images of bacteriophage treatment

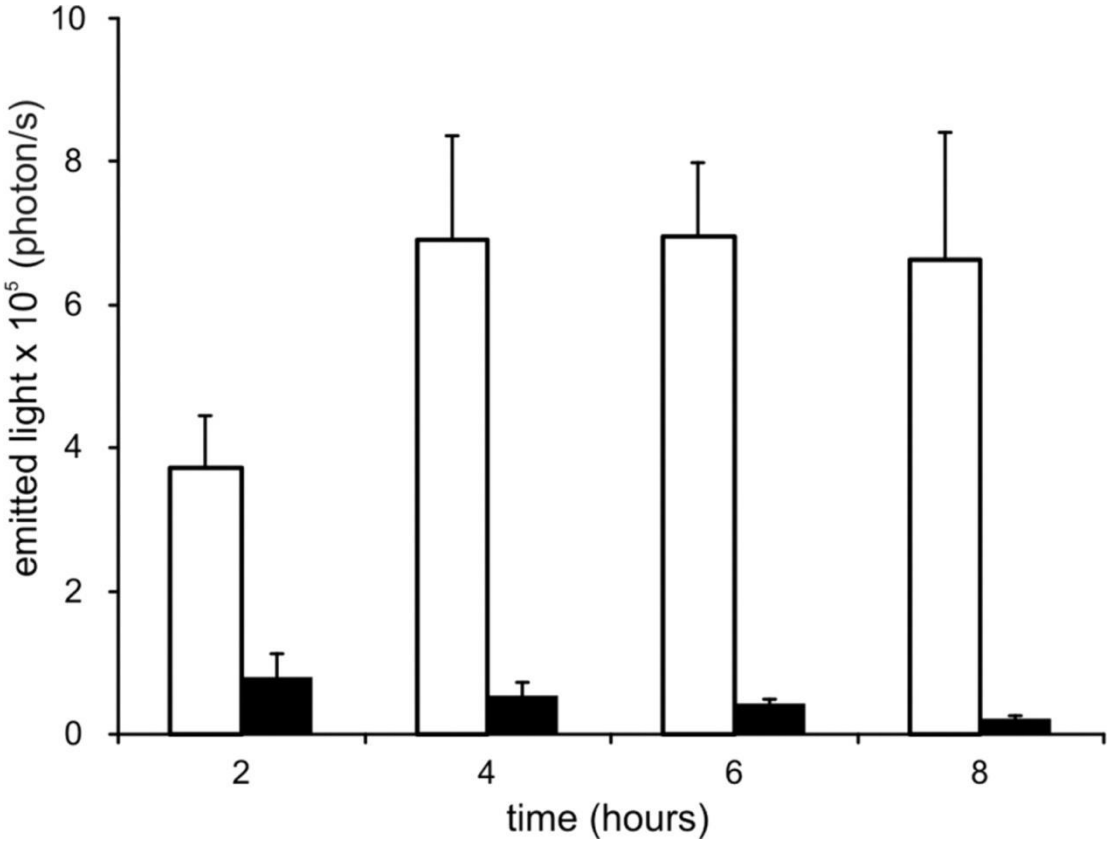



*A*, Survival curves of infected mice treated with phosphate-buffered saline (PBS) (*diamonds*) or with the PAK-P1 bacteriophage at a phage-to-bacterium ratio of 10:1 at 2 h (*squares*),4h (*triangles*),or 6h(*circles*) after the infection was initiated.




*B*, Images corresponding to the early time points of the experiment presented in panel *A*. p/s/cm2/sr, photons/s/ cm2/steradian.

## Efficacy of bacteriophage pretreatment 24 h before infection.




Shown is the time course of light emitted (in photons/s) from the chest area of mice pretreated with phosphate-buffered saline (PBS) (*white bars*) or with PAK-P1 bacteriophage (*black bars*) 24 h before infection with *Pseudomonas aeruginosa* (*n* = 4 for each group). Bars show the mean, and error bars show the standard error.

**Debarbieux L et al. J Infect Dis. 2010;201:1096-1104**

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Article

# Synergy between the Host Immune System and Bacteriophage Is Essential for Successful Phage Therapy against an Acute Respiratory Pathogen

Dwayne R. Roach [1, 6], Chung Yin Leung [2, 3, 6], Marine Henry [1], Eric Morello [1], Devika Singh [2], James P. Di Santo [4, 5], Joshua S. Weitz [2, 3] ✉, Laurent Debarbieux [1, 7] ✉

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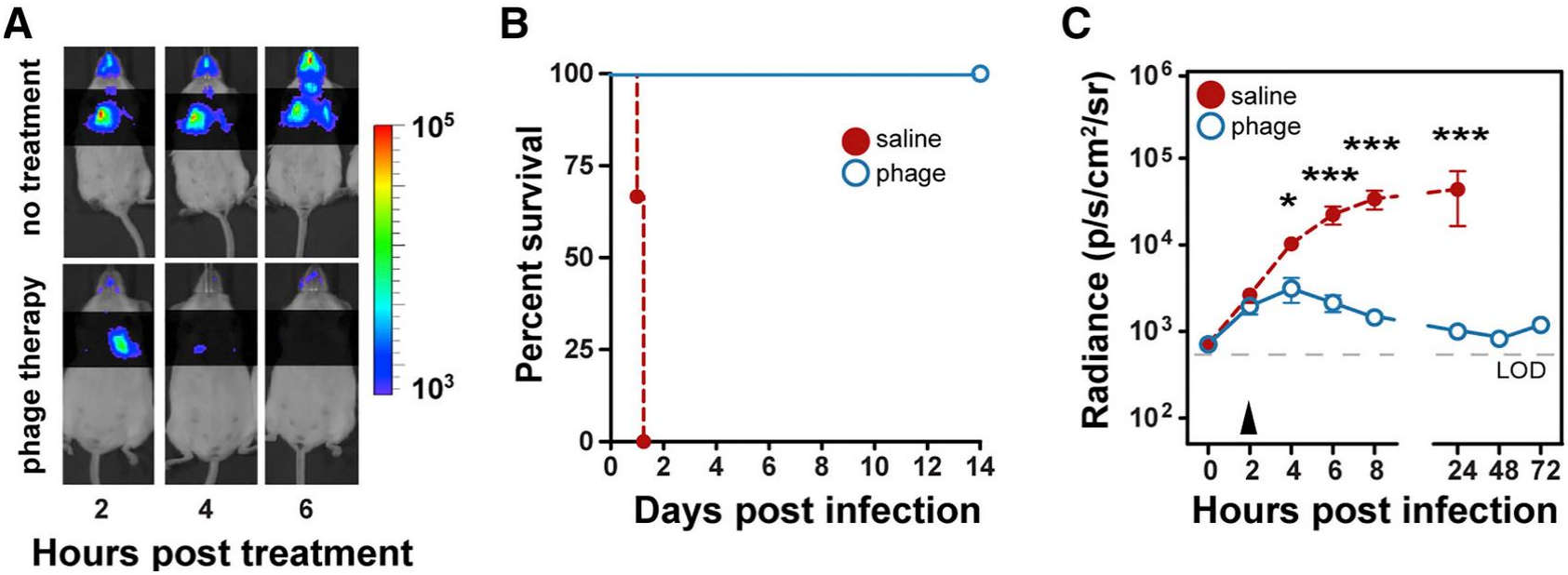



Figure 1. Immunophage Therapy Efficacy in the Immunocompetent Host

(A) Post-treatment representative *in vivo* imaging of bioluminescent *Pseudomonas aeruginosa*-infected live mice; color scale is radiance ($p/s^2/cm^2/sr$).

(B) Single-dose inhaled monophage treatment (MOI of 10) of fatal acute respiratory infection by *P. aeruginosa* ($10^7$ CFU) after a 2 hr delay provided immunocompetent WT mice 100% survival compared to saline-mock-treated control group (n = 6 per group).

(C) Colonization pattern of the bioluminescent *P. aeruginosa* in the lungs of live mice plotted as mean radiance over time indicating phage antibacterial activity by a significant reduction in bacterial burden beyond 2 hr post-treatment. Arrow marks treatment point; *in vivo* radiance limit of detection (LOD); error bars indicate SEM ($^*p < 0.05$; $^{***}p < 0.001$).

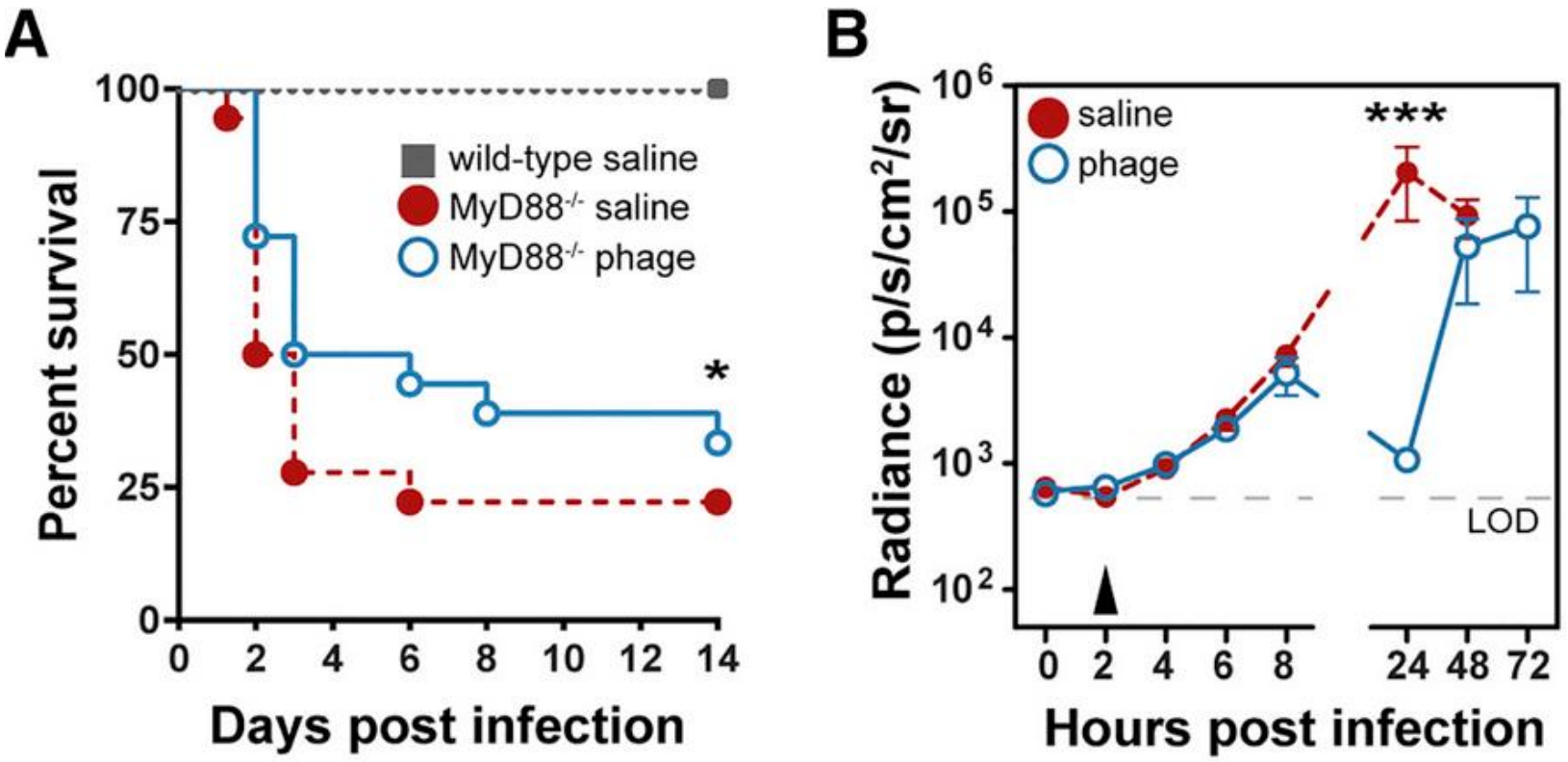
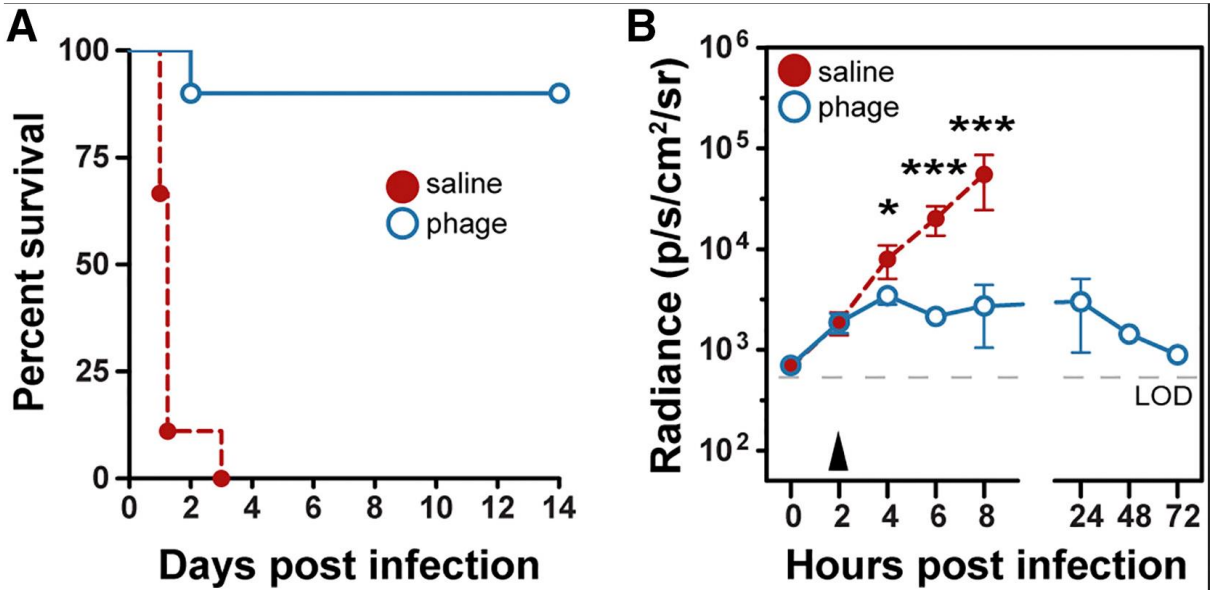


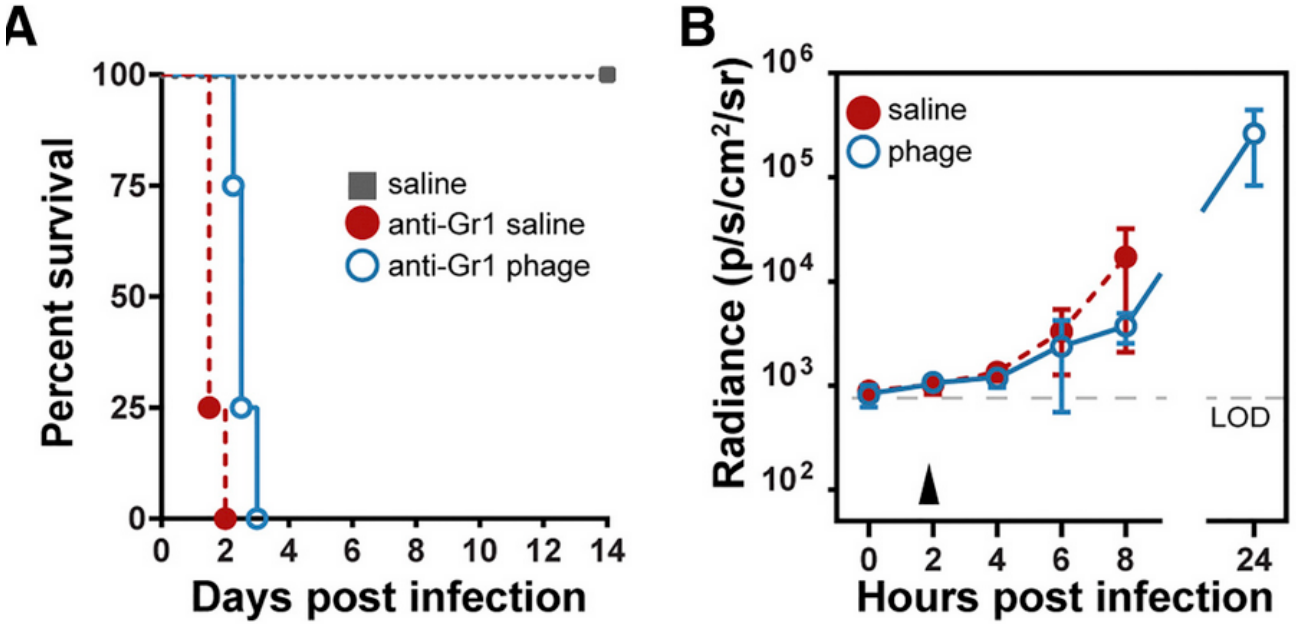

Figure 3. Phage Therapy Is Inefficient in the Innate Immunity Activation-Deficient Host

(A) Myeloid differentiation primary response gene 88-deficient mice (*MyD88*$^{-/-}$) had a 15% higher survival of acute respiratory infection by *Pseudomonas aeruginosa* ($10^5$ CFU) when inhaled monophage therapy (MOI of 10) was given at 2 hr post-infection compared to saline-mock-treated (n = 15 per group). In contrast, WT mice recovered from the $10^5$ CFU challenge without phage treatment.

(B) Colonization pattern of the bioluminescent pathogen in the mouse lungs plotted as mean radiance (p/s$^2$/cm$^2$/sr) over time to indicate phage antibacterial activity by a brief reduction in bacterial load followed by outgrowth of phage-resistant clone post-infection. Arrow marks treatment point; *in vivo* radiance limit of detection (LOD); error bars indicate SEM ($^*p < 0.05$; $^{***}p < 0.001$).




Phage Therapy Is Efficient in the Innate and Adaptive Lymphocyte-Deficient Host




Phage Therapy Is Ineffective in the Neutropenic Host ( lack of neutrophils)

# I fagi possono ridurre biofilm formatisi su  superfici abiotiche

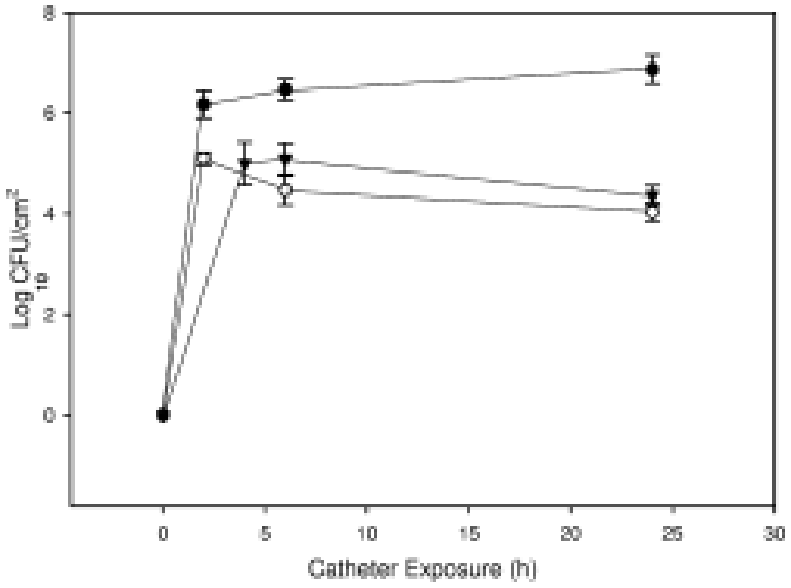



FIG. 1. Effect of *P. aeruginosa* phage M4 pretreatment and post-treatment of catheter surface on biofilm formation by *P. aeruginosa* M4 during a 24-h exposure period. Closed circle, untreated; open circle, pretreated; closed triangle, posttreated. Data are means ± standard deviations ($n = 3$).

Effetto del trattamento con il fago M4 della superficie di un catetere infettata con Pseudomonas aeruginosa

Sia il pretrattamento con il fago che il post trattamento provocano un a riduzione significativa dell'assorbimento del batterio

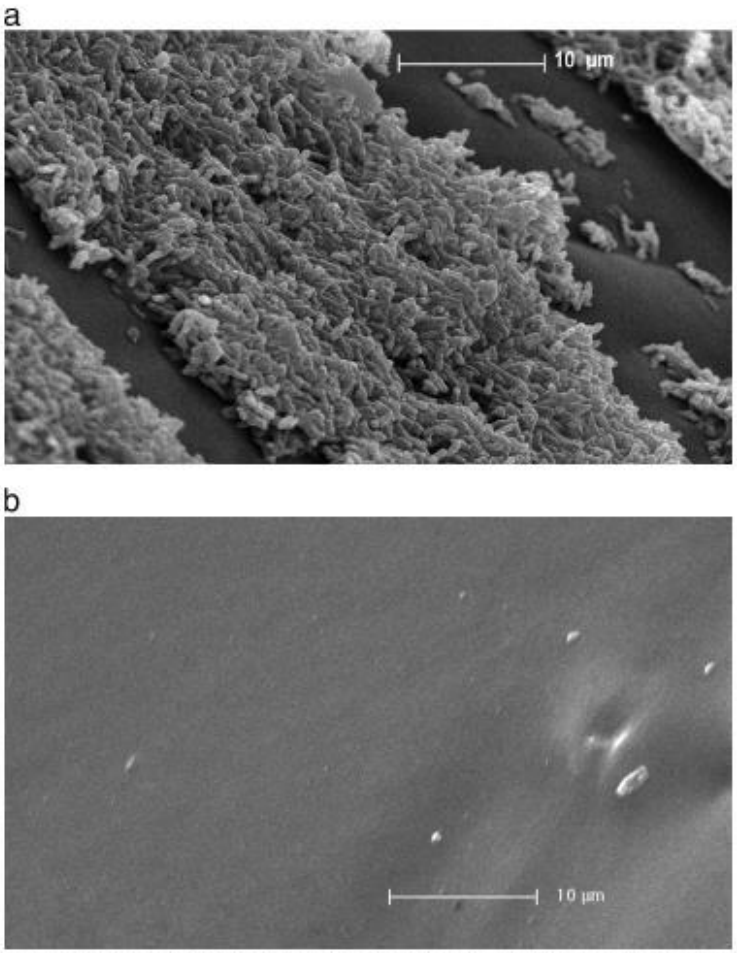



FIG. 2. (a) Scanning electron micrograph of the luminal surface of a section of an untreated *Lubri-sil* hydrogel-coated all-silicone Foley catheter after biofilm formation by *P. aeruginosa* M4 for 24 h (2,500× magnification [Magn]). (b) Scanning electron micrograph of the catheter luminal surface pretreated with *P. aeruginosa* phage M4 and exposed for 24 h to *P. aeruginosa* M4 (2,500× magnification).

Immagine al microscopio a scansione di un biofilm di *P.aeruginosa* formatosi sulla superficie di un catetere di silicone dopo 24 h

Il pretrattamento con il fago M4 impedisce la formazione del biofilm sulla superficie del catetere infettata x 24 ore

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Volume 11, Issue 7
July 2017

EDITOR'S CHOICE

# Bacteriophages Targeting Adherent Invasive *Escherichia coli* Strains as a Promising New Treatment for Crohn's Disease

Matthieu Galtier, Luisa De Sordi, Adeline Sivignon, Amélie de Vallée, Damien Maura, Christel Neut, Oumaira Rahmouni, Kristin Wannerberger, Arlette Darfeuille-Michaud, Pierre Desreumaux ... Show more

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RESEARCH ARTICLE

# Phage production is blocked in the adherent-invasive *Escherichia coli* LF82 upon macrophage infection

**Pauline Misson[1], Emma Bruder[2], Jeffrey K. Cornuault[1], Marianne De Paepe[1], Pierre Nicolas[3], Gaëlle Demarre[2], Goran Lakisic[1], Marie-Agnès Petit[1], Olivier Espeli[2], François Lecointe[1]***

**1** Université Paris-Saclay, INRAE, AgroParisTech, Micalis Institute, Jouy-en-Josas, France, **2** Center for Interdisciplinary Research in Biology (CIRB), College de France, CNRS, INSERM, Université PSL, Paris, France, **3** Université Paris-Saclay, INRAE, MaIAGE, Jouy-en-Josas, France

# Bacteriophage LM33_P1, a fast-acting weapon against the pandemic ST131-O25b:H4 Escherichia coli clonal complex.

Nicolas Dufour [1, 2, 3], Olivier Clermont [2], Béatrice La Combe [2, 3], Jonathan Messika [3, 2], Sara Dion [2], Varun Khanna [4], Erick Denamur [5, 2], Jean-Damien Ricard [2, 3], Laurent Debarbieux [1, *] Détails

* *Auteur correspondant*

1 BMGE - Biologie Moléculaire du Gène chez les Extrêmophiles
2 IAME - Infection, Antimicrobiens, Modélisation, Evolution
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5 Hôpitaux Universitaires Paris Nord Val de Seine

Amongst the highly diverse Escherichia coli population, the ST131-O25b:H4 clonal complex is particularly worrisome as it is associated with a high level of antibiotic resistance. The lack of new antibiotics, the worldwide continuous increase of infections caused by MDR bacteria and the need for narrow-spectrum antimicrobial agents have revived interest in phage therapy. In this article, we describe a virulent bacteriophage, LM33_P1, which specifically infects O25b strains, and provide data related to its therapeutic potential.

**Genomic characteristics of bacteriophage LM33_P1, its four closest homologs and the reference bacteriophage T7, all belonging to the *Autographivirinae* subfamily of viruses.**

| Bacteriophage | Host | Genome size (bp) | ORFs (n) | GC % | Accession number |
|---|---|---|---|---|---|
| LM33-P1 | *E. coli* | 38 979 | 49 | 50.8 | PRJEB12445 |
| T7 | *E. coli* | 39 937 | 60 | 49.0 | NC_001604.1 |
| PE3-1 | *E. coli* | 39 093 | 48 | 50.4 | NC_024379.1 |
| K1F | *E. coli* | 39 704 | 43 | 49.8 | NC_007456.1 |
| EcoDS1 | *E. coli* | 39 252 | 53 | 49.9 | NC_011042.1 |
| Dev2 | *C. turicensis* | 38 966 | 45 | 52.6 | NC_023558.1 |

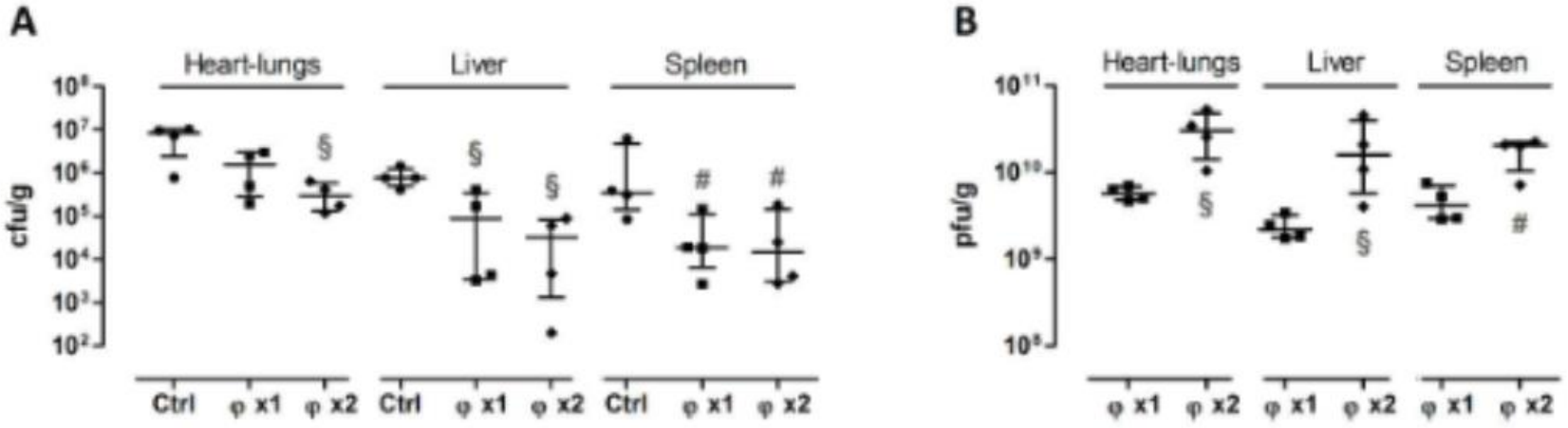



**Figure 5. Bacteriophage LM33_P1 *in vivo* activity in a septicemia model.** Bacterial (panel A) and viral (panel B) counts 20 hours post-infection in the indicated organs of mice infected with $1x10^9$ cfu of strain H1659 (ST131-O25b:H4). Two hours post-infection, the mice received intraperitoneally either PBS (Ctrl) or bacteriophage LM33_P1 at a MOI of 60 (φ X1: one dose 2 hours post-infection, φ X2: two doses 2 and 12 hours post-infection). The results are expressed as individual values (4 animals per condition) with median and interquartile ranges ($25^{th}$ and $75^{th}$ percentiles). §, #: $p < 0.05$ (§) or $p=0.057$ (#) compared to the control group (panel A) or the single-dose treatment (panel B).

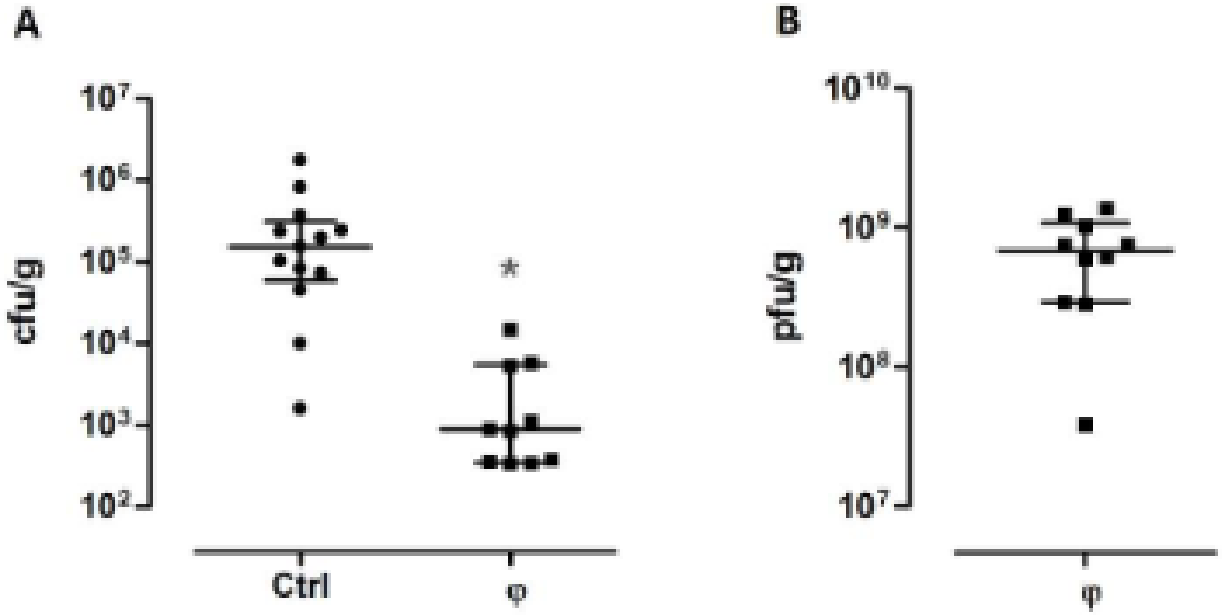


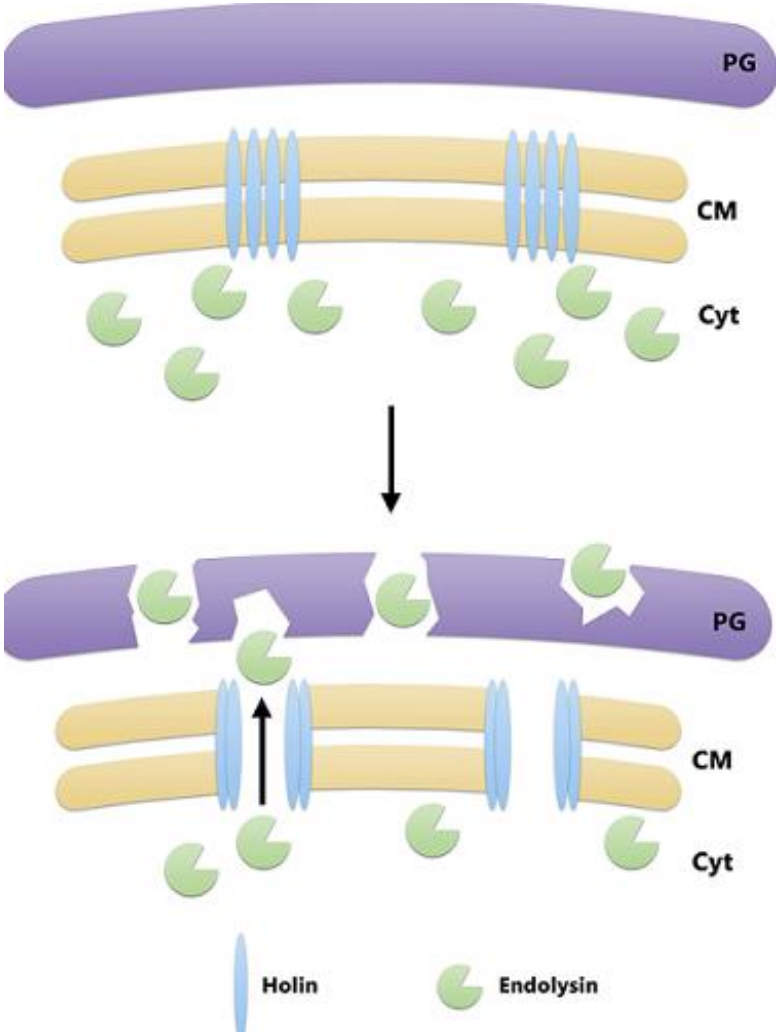

**Figure 6. Bacteriophage LM33_P1 *in vivo* activity in a urinary tract infection model.** Bacterial (panel A) and viral (panel B) counts 48 hours post-infection in kidneys homogenates of mice infected with $5x10^7$ cfu of strain LM33. Twenty four hours post-infection, the mice received intraperitoneally either PBS (Ctrl, n=13) or bacteriophage LM33_P1 (φ, MOI 200, n=10). The results are expressed as individual values with median and interquartile ranges ($25^{th}$ and $75^{th}$ percentiles). *: $p < 0.001$ compared to control group.

# Phagetherapy negli animali

Currently there are no phage therapy products approved for human use in the EU or United States. However, in the food industry, there are several commercial phage preparations used for biocontrol of bacterial pathogens that are approved by the FDA under the classification of “generally considered as safe.” These preparations are used against *Salmonella* spp., *Listeria monocytogenes*, MRSA, *E. coli* O157:H7, *Mycobacterium tuberculosis*, *Campylobacter* spp., and *Pseudomonas syringae*, among others

Among the most promising of advances in phage therapy is the isolation of phage-encoded lytic enzymes, which are functionally similar to the eukaryotic enzyme lysozyme. Genes for these enzymes are expressed by the bacterial host during the lytic cycle and assist the phage by hydrolyzing the cell wall to release viral progeny. The discovery and analysis of these proteins opens the possibility for the development of novel phage-based pharmaceuticals.

# Oline ed endolisine : antibatterici promettenti contro i Gram+




Phage lysins alone are capable of bacterial cell lysis, whereas holins are not; therefore lysins have received a lot of attention as potential antimicrobial agents. These proteins are fast acting, potent, and inactive against eukaryotic cells. Lysins have successfully saved mice from bacteremia caused by multidrug-resistant *A. baumannii*, *Streptococcus pneumoniae*, and MRSA, among others. A combination of phage lysins and antibiotics has been shown to be much more effective than antibiotics alone in eliminating *C. difficile* colonization in both an *in vitro* and an *ex vivo* colon model in the presence of intestinal contents.

Among the most promising of advances in phage therapy is the isolation of phage-encoded lytic enzymes, which are functionally similar to the eukaryotic enzyme lysozyme. Genes for these enzymes are expressed by the bacterial host during the lytic cycle and assist the phage by hydrolyzing the cell wall to release viral progeny. The discovery and analysis of these proteins opens the possibility for the development of novel phage-based pharmaceuticals.

Two major protein classes are employed by the majority of phage species during the lysis of the bacterial host. One of which is the transmembrane protein holin and the other is a peptidoglycan cell wall hydrolase called endolysin (lysin). These two proteins work together in triggering the lysis of the bacterial cell. The holin protein acts as a molecular "clock" in the lytic cycle. During the process of viral assembly within the cytoplasm, holin molecules accrue in the cell membrane. At the end of the lytic cycle the holin proteins trigger an opening on the cytoplasmic side of the cell membrane, allowing the lysin proteins to access and hydrolyze the cell wall.

Although both of these enzymes are present across the majority of phage species, there is huge structural and biochemical variability and therefore little sequence conservation among species. Each phage can encode for several unique lysin and holin enzymes, some of which are highly specific but others can exhibit broad-spectrum activity between strains and even between species as in the case of recently discovered lysin ABgp46. ABgp46 has the ability to lyse several gram-negative and multidrug-resistant pathogens, including *A. baumannii*, *P. aeruginosa*, and *Salmonella typhimurium*.

**Table 3:** Summary of phage-encoded endolysins tested in vivo.

| Target pathogen | Endolysin | Animal model | References |
|---|---|---|---|
| *Acinetobacter baumannii* | PlyF307 | Bacteraemia | [97] |
| *Bacillus anthracis* | PlyG<br>PlyPH | Sepsis<br>Peritonitis | [98, 99] |
| *Pseudomonas aeruginosa* | LoGT-008<br>(Artilysin) | Gut decolonization | [100] |
| *Staphylococcus aureus* | ClyS<br>λSa2-E-lyso-SH3b<br>LysK/CHAPk<br>LysGH15<br>MV-L<br>PhiSH2<br>Phi11<br>PlySs2<br>Ply187AN-KSH3b<br>SAL-1<br>Twort<br>WMY<br>80α<br>2638A | Nasal decolonization<br>Bacteraemia<br>Sepsis<br>Mastitis<br>Endophthalmitis | [101–111] |
| *Streptococcus agalactiae* | PlyGBS/PlyGBS90–1<br>PlySK1249 | Vaginal decolonization<br>Oropharynx decolonization<br>Bacteraemia | [112–114] |
| *Streptococcus pneumonia* | Cpl-1<br>Cpl-771<br>PAL | Bacteraemia<br>Sepsis<br>Endocarditis<br>Meningitis | [115–120] |
| *Streptococcus pyogenes* | PlyC (formerly C1)<br>PlyPy<br>PlySs2 | Oral decolonization<br>Bacteraemia | [84, 97, 106] |