

# LES PHAGES DANS LES IOA

## De l'historique aux indications pertinentes

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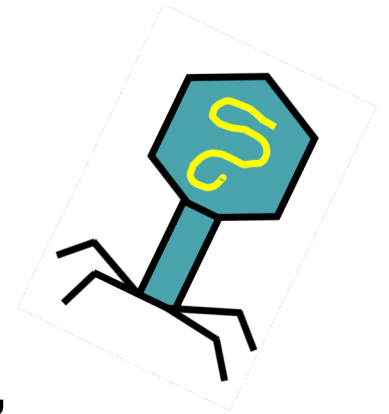
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Croix-Rousse Hospital , Hospices Civils de Lyon  
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Centre International de Recherche en Infectiologie, CIRI, Inserm U1111, CNRS  
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# What is a « bacteriophage » ?



- Suffix –phage, *phagos* φαγεῖν (*phagein*), "to eat", "to devour"
- Viruses that infect **ONLY** bacteria
- Classification (*myoviridae*, *podoviridae*, etc...)
- A phage is specific to A type of bacteria
- **Largely abundant in the biosphere:  
10<sup>31</sup> bacteriophages on the planet, more than  
every other organism**
- Especially in marine environment, sea, lake, backwater, soil, animal and human stools, etc.



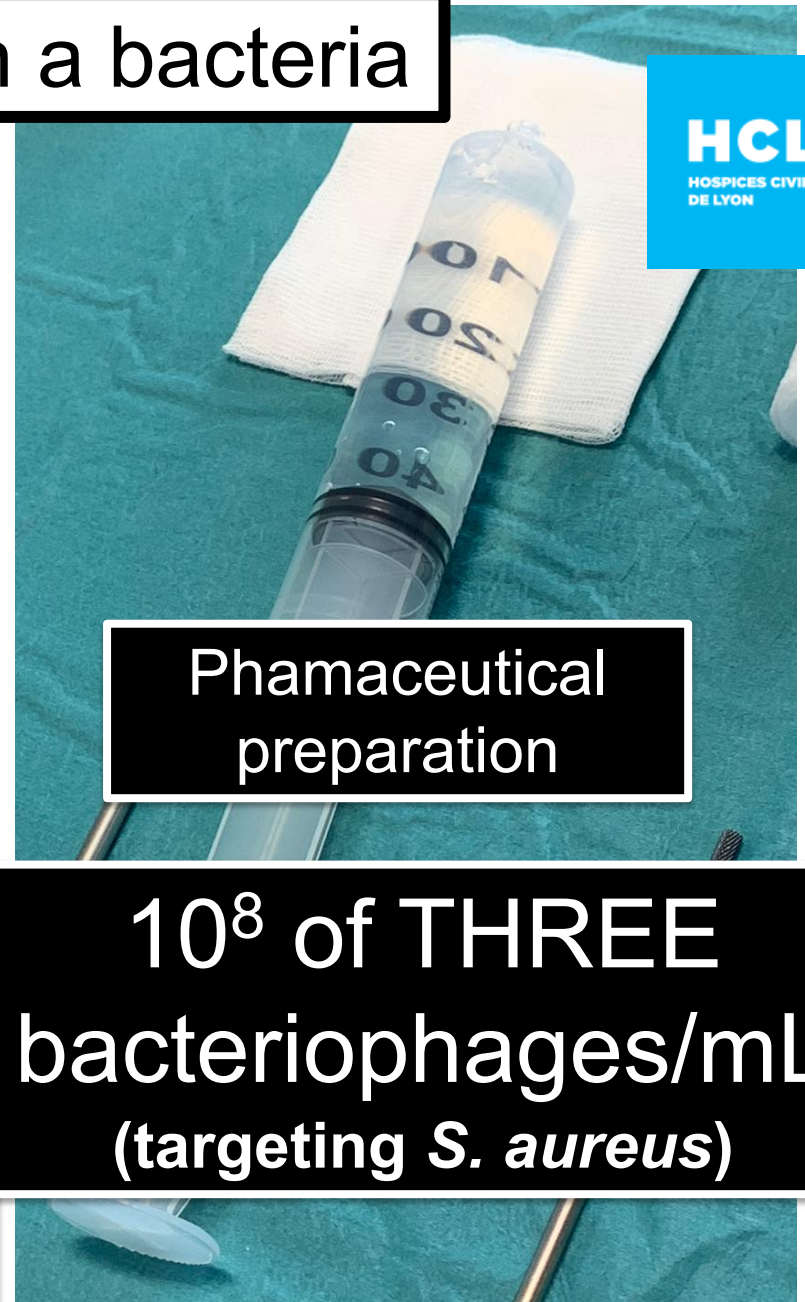


10 to 100 fold smaller than a bacteria

Translucent tap water

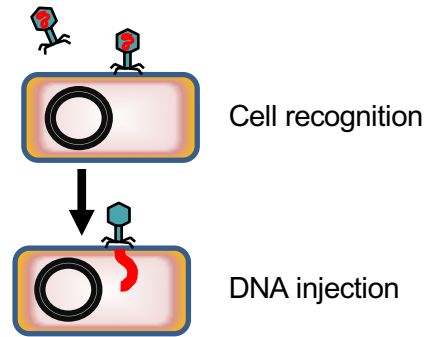


**X million of ≠  
BactériophageS !!!  
(targeting environmental bacteria)**

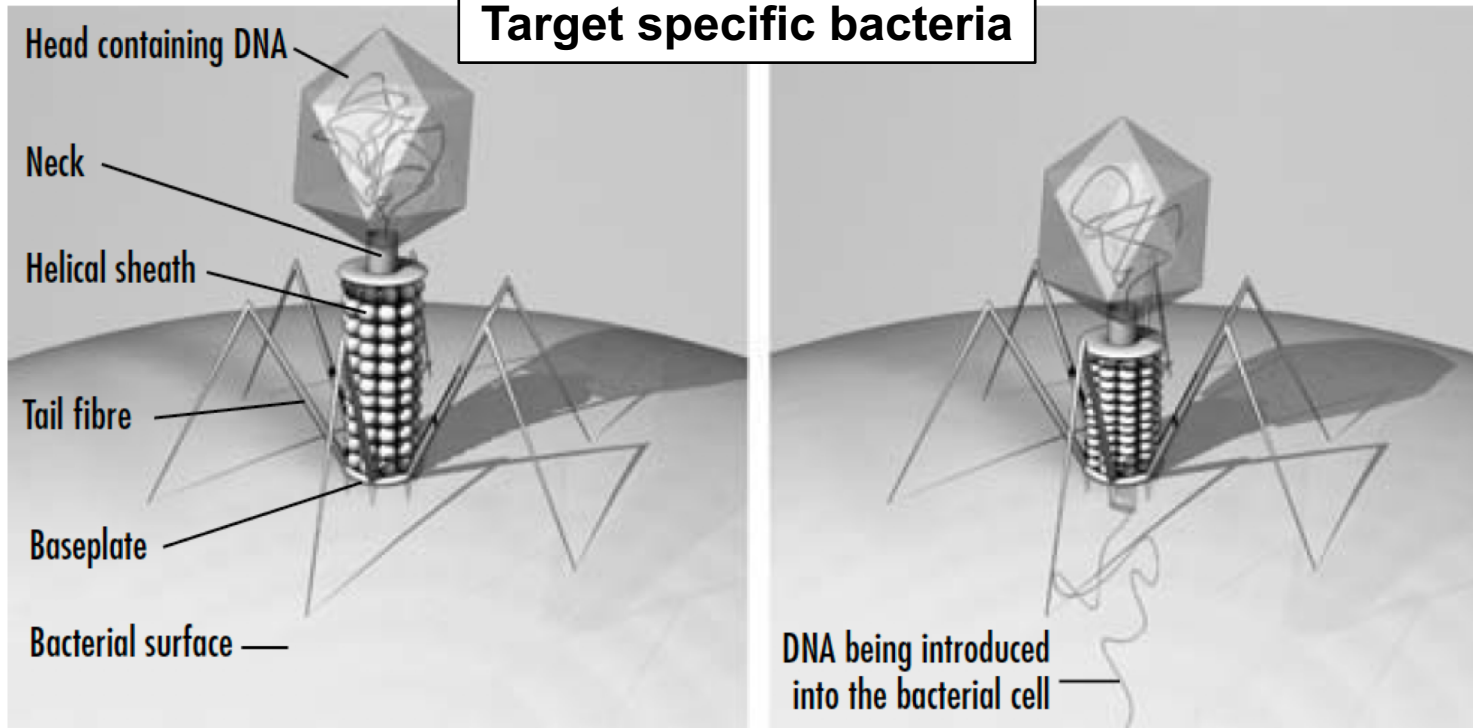


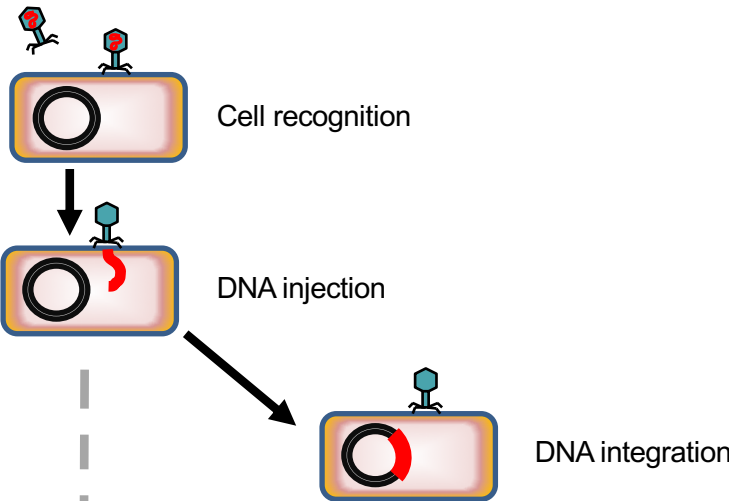
Pharmaceutical  
preparation

**$10^8$  of THREE  
bacteriophages/mL  
(targeting *S. aureus*)**



**Environmental viruses  
Target specific bacteria**

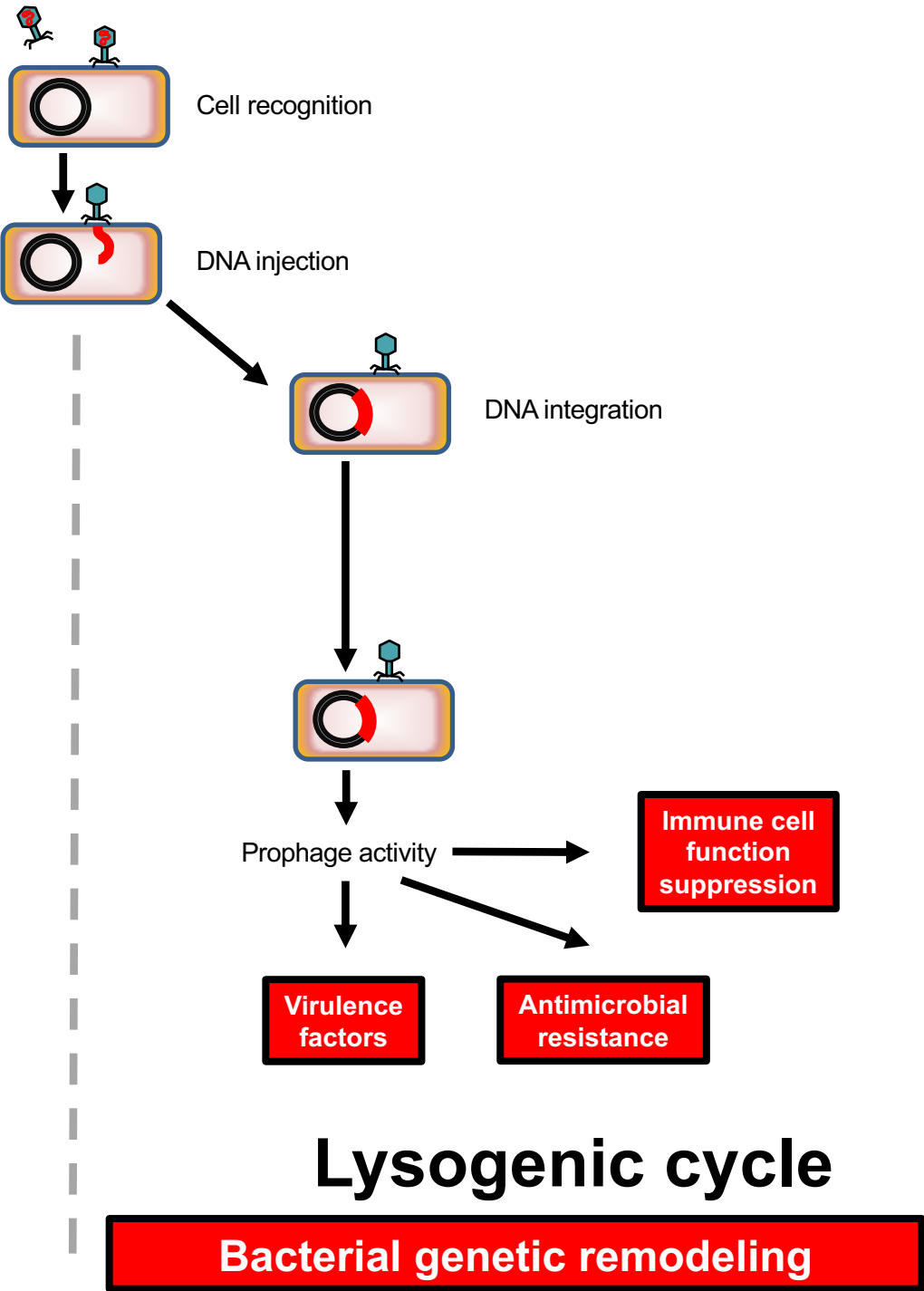


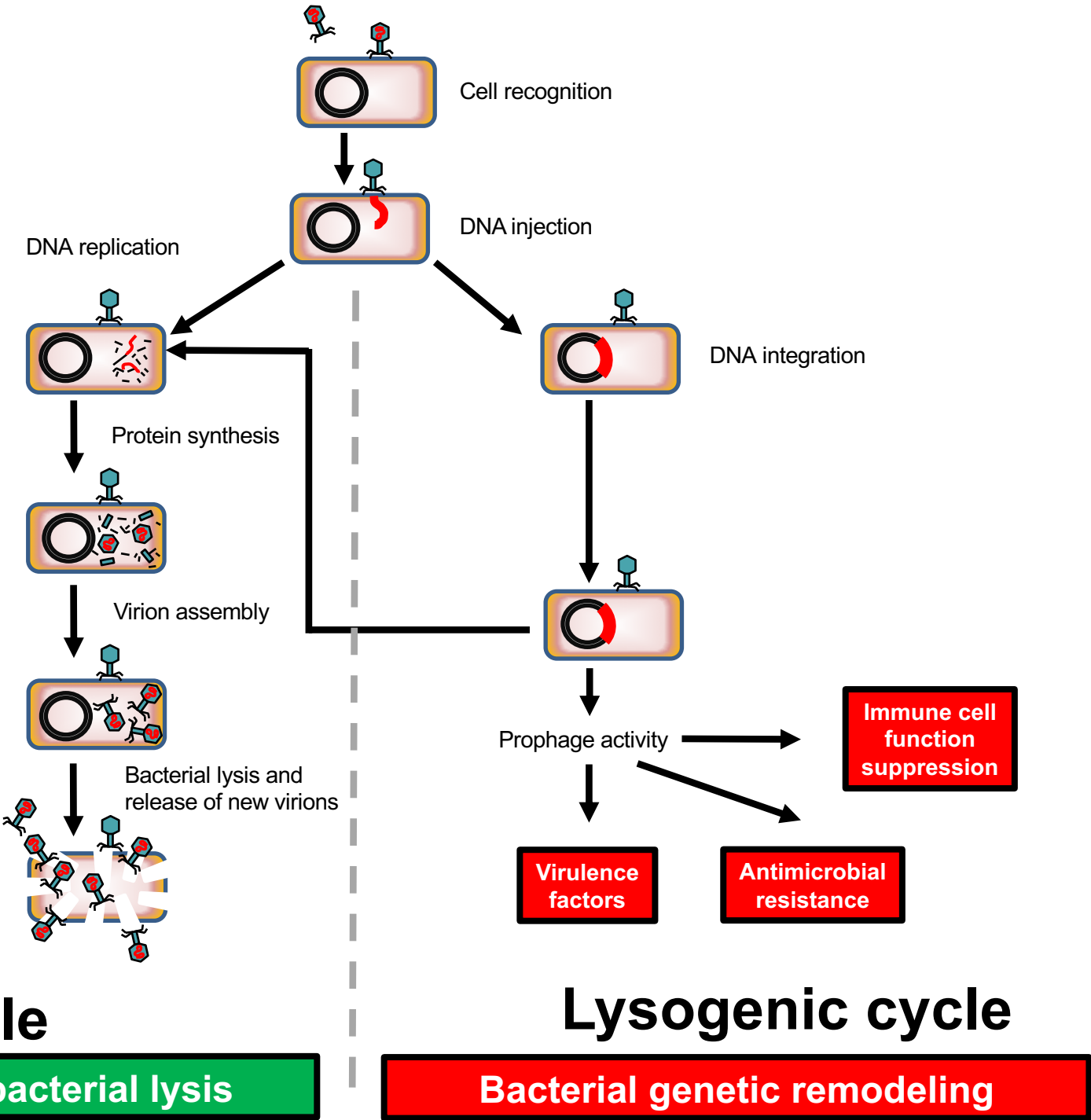


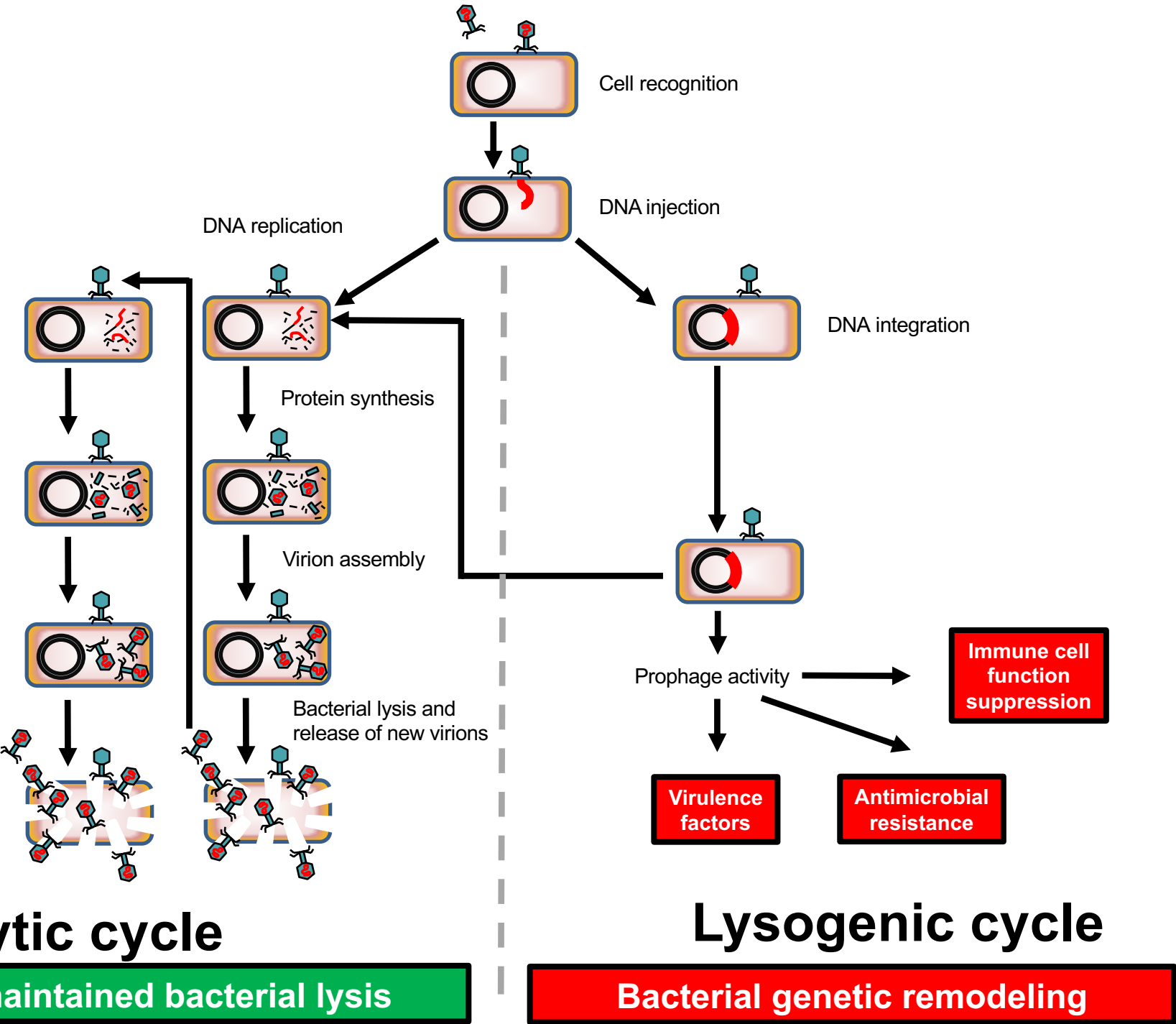
**Lysogenic cycle**

**Bacterial genetic remodeling**

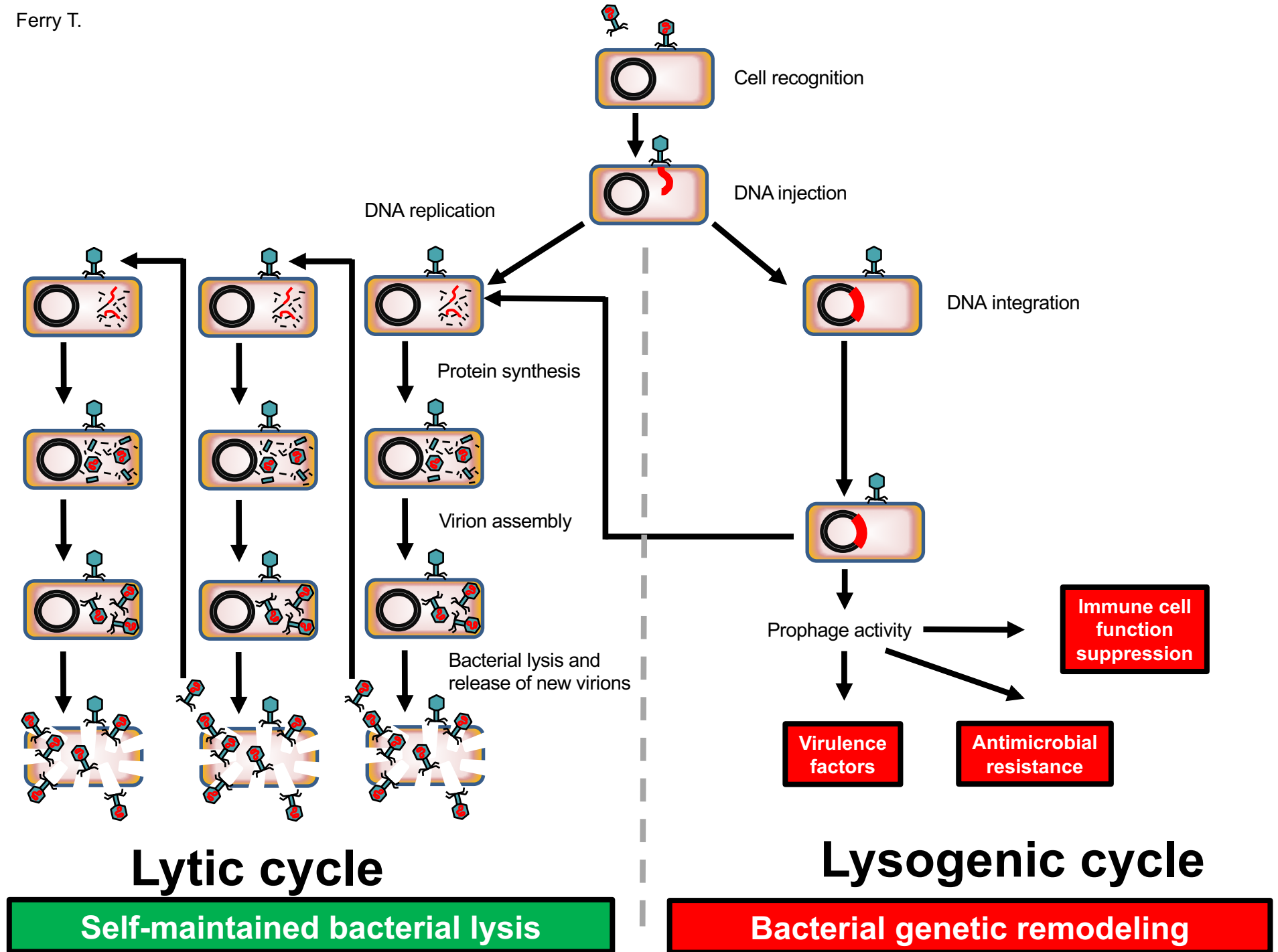














# History of phage therapy

- **Felix d'Herelle**
- Institut Pasteur, Paris





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- He treated shigellosis (diarrhea) in children with oral intake of specific “filtered” bacteriophages that he found in stools of patients who spontaneously healed from... shigellosis







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- He treated shigellosis (diarrhea) in children with oral intake of specific “filtered” bacteriophages that he found in stools of patients who spontaneously healed from... shigellosis
- He founded Eliava institute in Georgia and the “Laboratoire Français des Bactériophages” in Paris





# History of phage therapy

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- In
- H
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**LE LABORATOIRE DU BACTÉRIOPHAGE**  
Laboratoire de recherches dont les bénéfices sont destinés à des fins scientifiques  
sous le contrôle du  
**PROF. D'HERELLE**

<b><i>Bacté-coli-phage</i></b> Colibacilluries . Pyélonéphrites . Cystites	<b><i>Bacté-rhino-phage</i></b> Grippe . Coryza . Rhino-pharyngites
<b><i>Bacté-intesti-phage</i></b> Entérites . Colites . Diarrhées infantiles	
<b><i>Bacté-pyo-phage</i></b> Panaris . Phlegmons . Plaies Infectées	<b><i>Bacté-staphy-phage</i></b> Furunculose . Anthrax

AGENTS GÉNÉRAUX  
**LABORATOIRES ROBERT & CARRIÈRE** — 37, rue de Bourgogne — Paris

and the “Laboratoire Français des Bactériophages” in Paris

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## Docteur André RAIGA

Ancien Interne lauréat des Hôpitaux  
Ex-Chef de Clinique chirurgicale à la Faculté

■ ■ ■

*At the stage of bone necrosis, it will only succeed in stopping the progression of the infection, but it will be able to do nothing against the dead bone deprived of circulation; this bone will become sequestered and the lesion is no longer a matter of surgery. To do otherwise is to commit, in my opinion, an error of therapeutic indication.*

Au stade de nécrose osseuse, il ne réussira plus qu'à enrayer la progression de l'infection, mais il ne pourra plus rien contre l'os que la mort a privé de circulation ; cet os va se séquestrer et la lésion ne relève plus maintenant que de la chirurgie. Agir autrement c'est commettre, à mon sens, une erreur d'indication thérapeutique.





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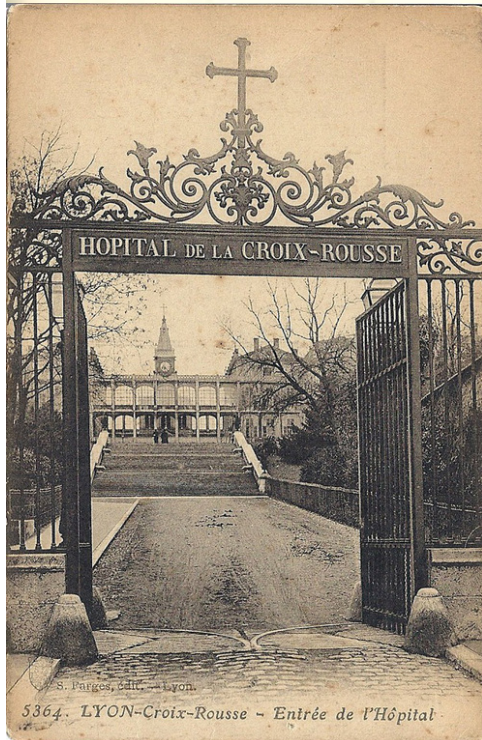
■ ■ ■

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## Traitement des infections à bacilles pyocyaniques par des bactériophages adaptés par sélection.

Par MM. André BERTOYE et A.-L. COURTIEU.



Les bacilles pyocyaniques sont fréquemment résistants aux antibiotiques usuels. Cependant, leur existence de bactériophages adaptés par sélection à une variété de bactériophage a la souche isolée du malade permet une action nutritif ordinaire indispensable de pouvoir l'introduire intraveineuse, in Un certain nombre de ces infections ont été rapportés dans cette publication.

**Antimicrobial resistance**

**Phage banking  
Phage training**

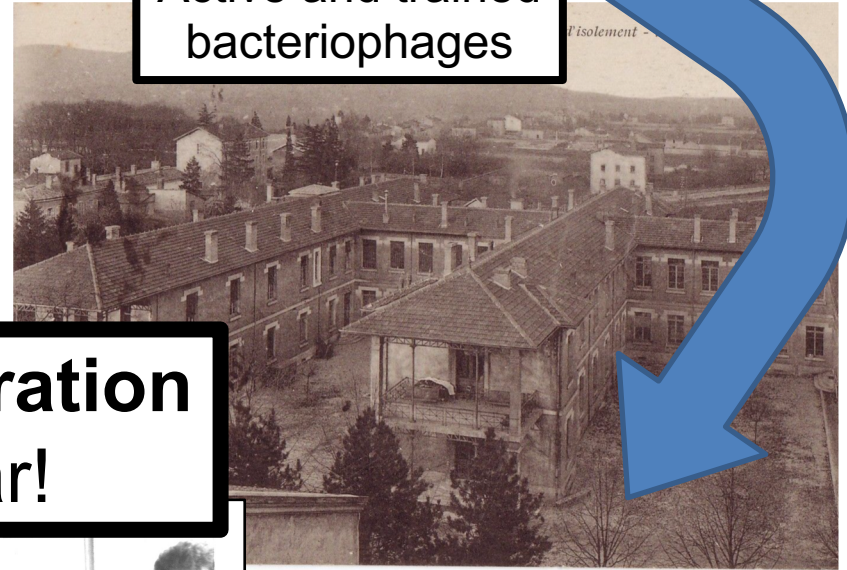
**Meningitis  
Skin and soft tissue  
Bone and joint**



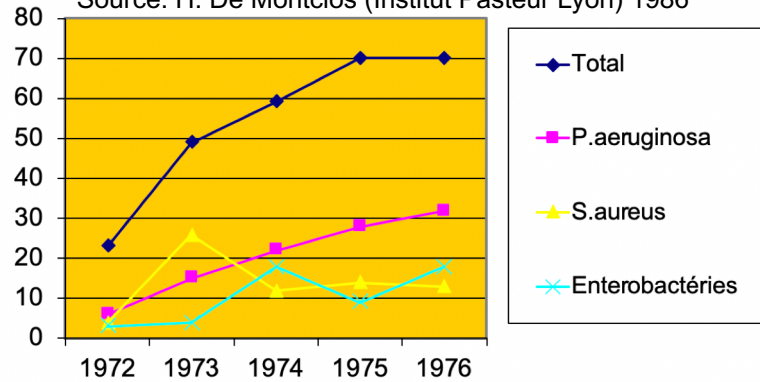


# Institut Pasteur Lyon

Active and trained  
bacteriophages



Source: H. De Montclos (Institut Pasteur Lyon) 1986



**Bactériophages thérapeutiques  
préparés à l'Institut Pasteur de Lyon  
dans les années 1970**

**Academic collaboration  
70 patients/year!**

Pathogenic bacteria  
from the patient



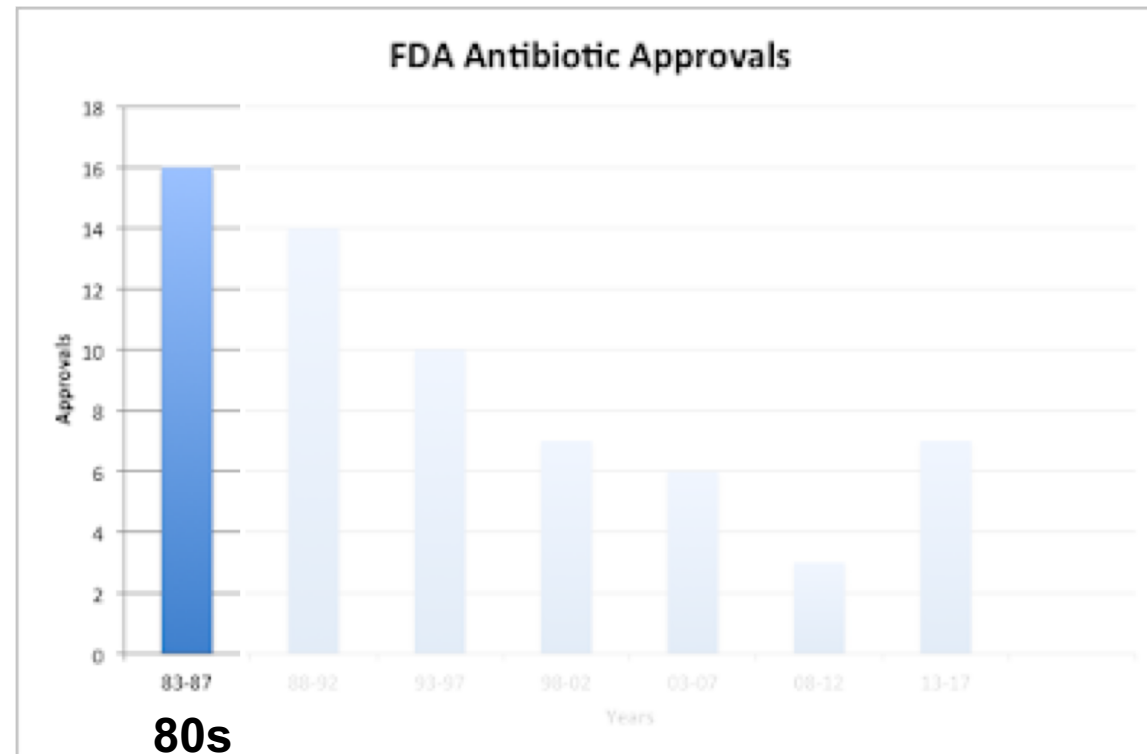
1978

Pr. Bertoye

**Infectious  
Disease  
clinic**

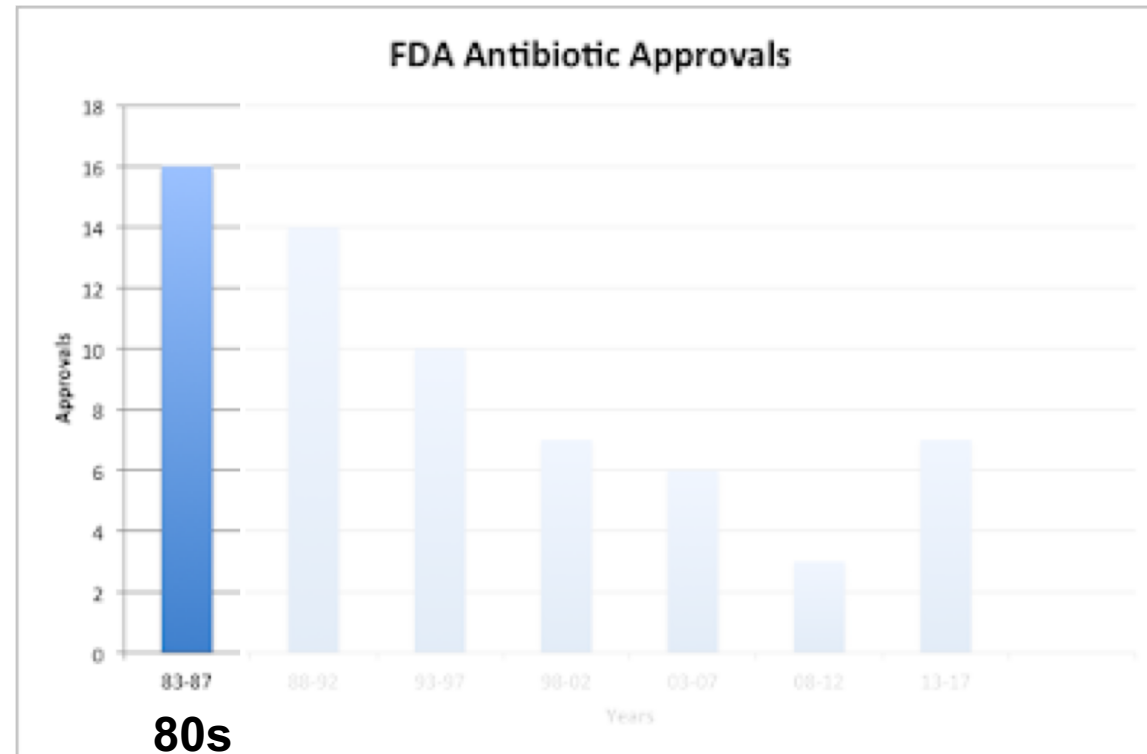
# Large production of antibiotics in 1970-1980 killed the phage therapy

- Industrial production
- Large spectrum
- Bactericidal activity
- Oral and IV
- Systemic diffusion to the infected site
- Numerous different kinds of families, with different mechanism of action



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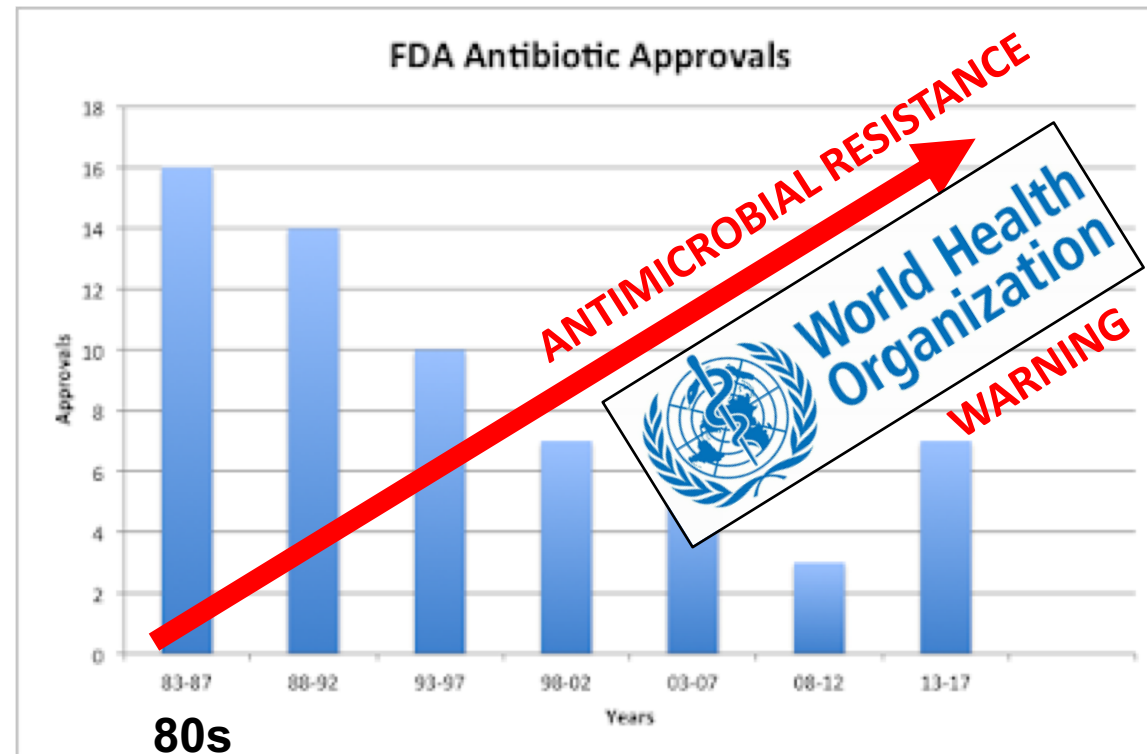
VS.



Complex virus-based personalized treatment without clear industrial process, not considered as a drug

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## Phages as the Phoenix?



VS.

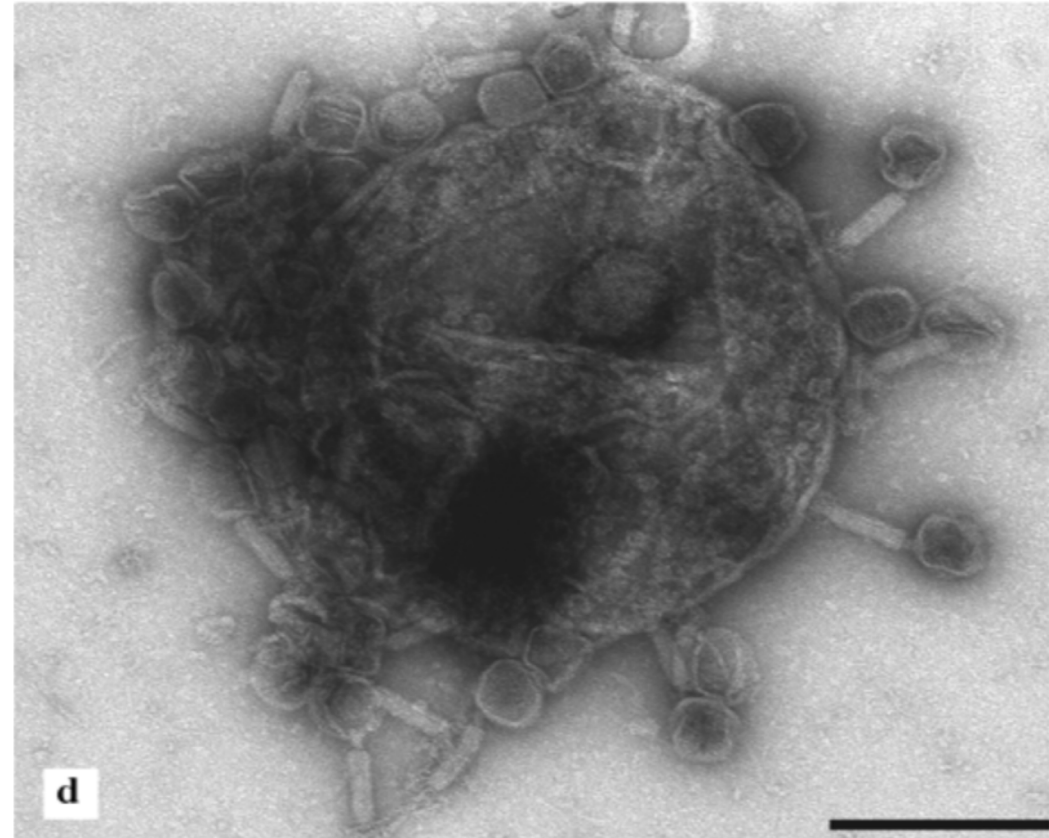
Complex virus-based personalized treatment without clear industrial process, not considered as a drug



# Cocktails produced in 2020 by the Eliava Institute

- PYO Bacteriophage
- FERSIS Bacteriophage
- STAPHYLOCOCCAL Bacteriophage
- SES Bacteriophage
- INTESTI Bacteriophage
- ENKO Bacteriophage

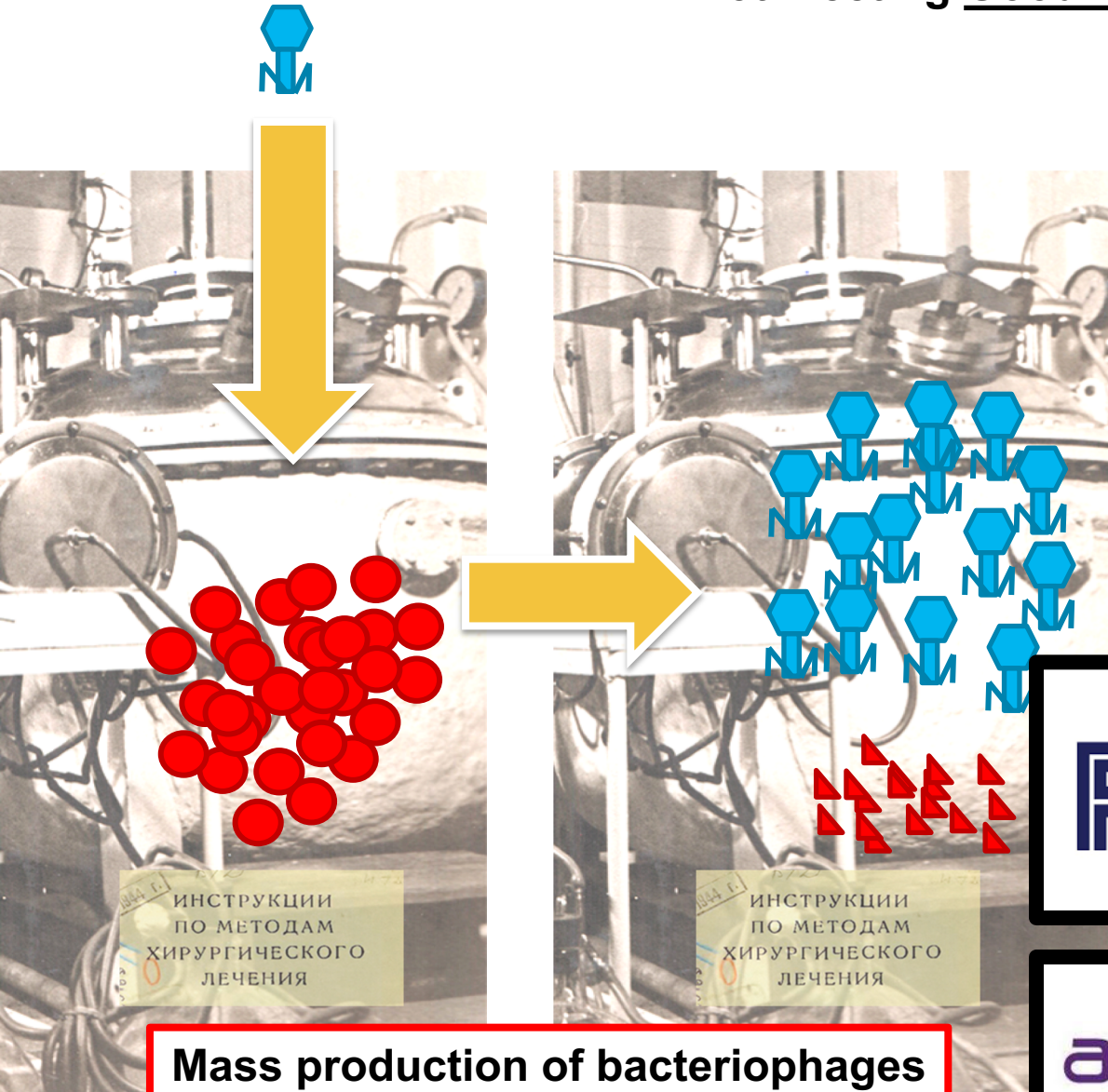
Bacteriophage ISP (*Myoviridae*)



Merabishvili et al. PloS ONE 2009



# Not meeting Good Manufacturing Practices (GMP)



Pyrogenic  
Bacterial  
remnant?



$10^6$  phages/mL



**GMP**

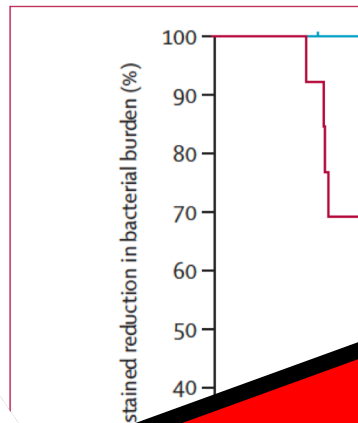


**Mass production of bacteriophages  
in Soviet Union during WWII**

*T. Ferry. The story of Phage therapy*

# Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial

Patrick Jault, Thomas Leclerc, Serge J  
Ronan Le Floch, Jean Vivien Schaal, C



**COMPASSIONATE  
USE**

2: Time to observe reduction

Kaplan-Meier analysis of median time


highest daily bacterial burden compared with day 0. HR=hazard ratio. PP1131=cocktail of 12 natural lytic anti-*Pseudomonas aeruginosa* bacteriophages.

*osa*

RECYDES  
RMA





 PHOSA & Phagothérapie Consortium PHOSA Communication Contact



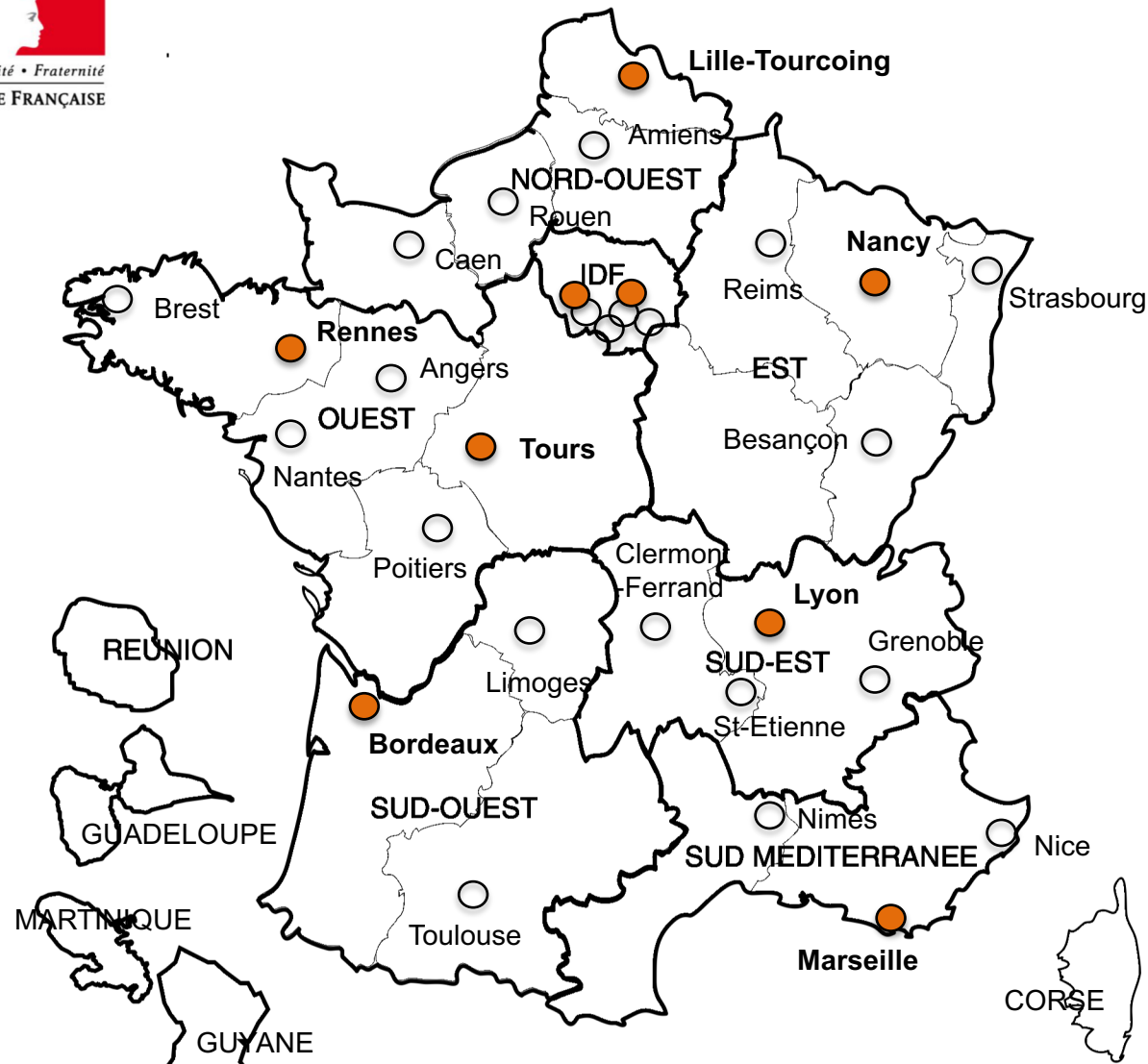
**Phage discovery  
to find active  
bacteriophages  
against Staphylococci**



***Phages anti-S. aureus***



# REFERENCE CENTERS FOR THE MANAGEMENT OF BONE AND JOINT INFECTION



● CRIOAc coordonateur ○ Centres correspondants

## “CRIOAc” Network



## CRIOAc Lyon



**Pr. Tristan Ferry**  
MD, PhD  
Infectiologist



**Pr. Sébastien Lustig**  
MD, PhD  
Orthopaedic surgeon



**Pr. Frédéric Laurent**  
PharmD, PhD  
Microbiologist



**Multidisciplinary management of the patient**

**Better understanding of the pathophysiology of BJI**

**Promotion of innovative treatments**

# Declaration of Helsinki

## Medical Research Involving Human Subjects



WORLD  
MEDICAL  
ASSOCIATION

Special Communication

World Medical Association Declaration of Helsinki  
Ethical Principles for Medical Research  
Involving Human Subjects

**JAMA** 2013  
The Journal of the  
American Medical Association

World Medical Association

- **Unproven Interventions in Clinical Practice**

- 37. In the treatment of an **individual patient, where** proven interventions do not exist or other known interventions have been **ineffective, the physician**, after seeking expert advice, **with informed consent from the patient** or a legally authorised representative, **may use an unproven intervention** if in the **physician's judgement** it offers **hope of saving life, re-establishing health** or alleviating suffering.

In France: **compassionate** use,  
**magistral preparation** by the hospital pharmacist





**Partial bone necrosis  
requiring surgery**

**Skin and soft tissue damage  
requiring surgical coverage**

**MAJOR BIOLOGICAL LIMIT:**

**Bacteriophages have not the capacity to perform bone debridement nor to regenerate skin and soft tissue**

# Clinical case #4

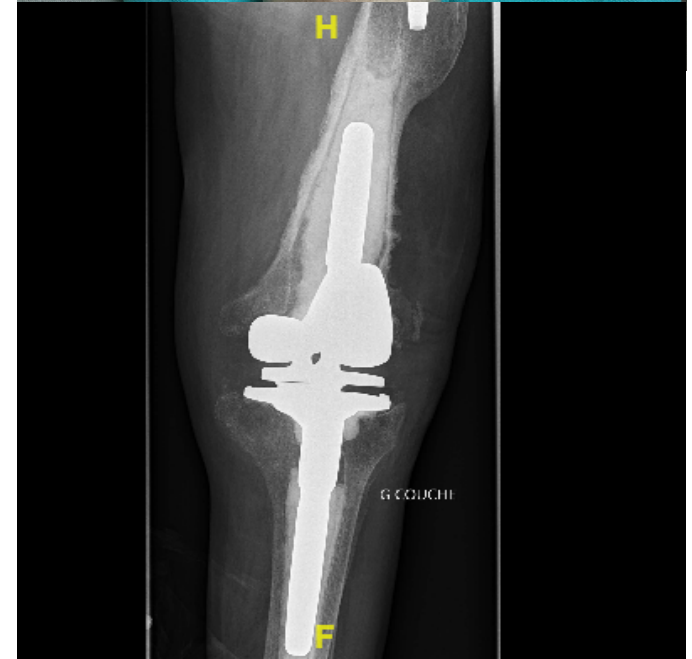
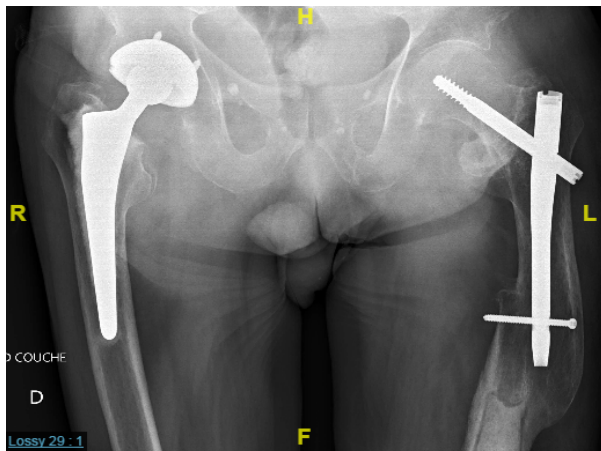
80-year-old man

**Relapsing MSSA** prosthetic left knee infection (past revision)

**Failure under suppressive oral antimicrobial therapy**

Complex orthopaedic situation with past femoral fracture

Impossible to walk (painful knee)







**Fistula and  
purulent discharge**



# Clinical case #4

Amputation  
(but not feasible !) ?



VS.



Doing nothing, but poor clinical situation with risk of complication and death

Conservative surgery  
“Debridement And Implant Retention” (DAIR) +  
innovative approach to  
disrupt biofilm +  
suppressive antimicrobial therapy ?

# Lyon Phage team



**Pr. Tristan Ferry**  
MD, PhD  
Infectiologist



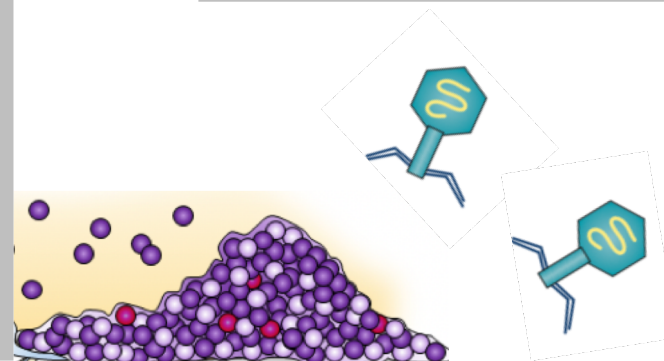
**Pr. Sébastien Lustig**  
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**Pr. Frédéric Laurent**  
PharmD, PhD  
Microbiologist



**Dr. Gilles Leboucher**  
PharmD  
Pharmacist





ID Clinic



**HCL**  
HOSPICES CIVILS  
DE LYON

Surgery



**HCL**  
HOSPICES CIVILS  
DE LYON

**CRIOAc**  
LYON

Lab



**HCL**  
HOSPICES CIVILS  
DE LYON

Under the supervision of

**ansm**

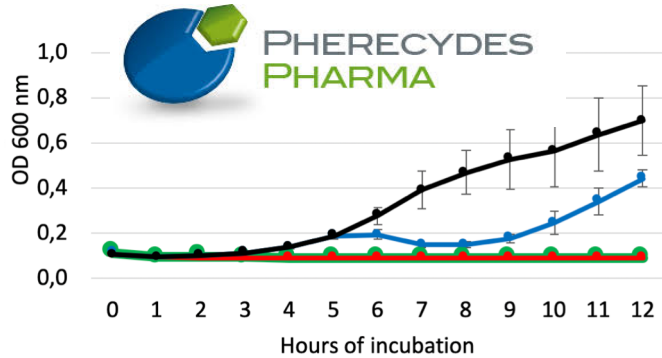
Agence nationale de sécurité du médicament  
et des produits de santé

French Health Authority

Pharmacy



**HCL**  
HOSPICES CIVILS  
DE LYON



**Phagogram**  
**Selection of active bacteriophages**

**PHERECYDES  
PHARMA**

**Active *S. aureus* Bactériophages**



1 mL

Phage A



1 mL

Phage B



1 mL

Phage C





ID Clinic

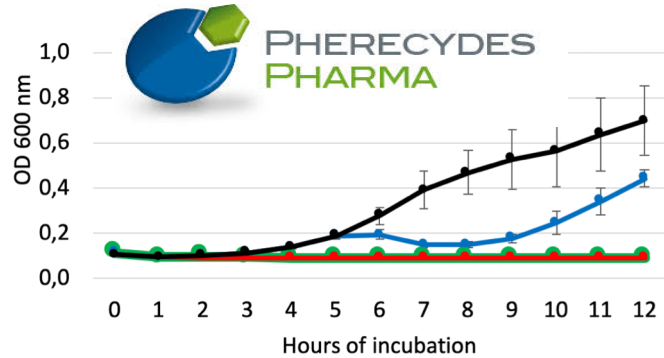


**HCL**  
HOSPICES CIVILS  
DE LYON

Surgery



**HCL**  
HOSPICES CIVILS  
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Lab



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Pharmacy



**HCL**  
HOSPICES CIVILS  
DE LYON

Extemporaneous  
magistral  
preparation of the  
mix of  
bacteriophages



Active *S. aureus* Bactériophages



1 mL

Phage A



1 mL

Phage B

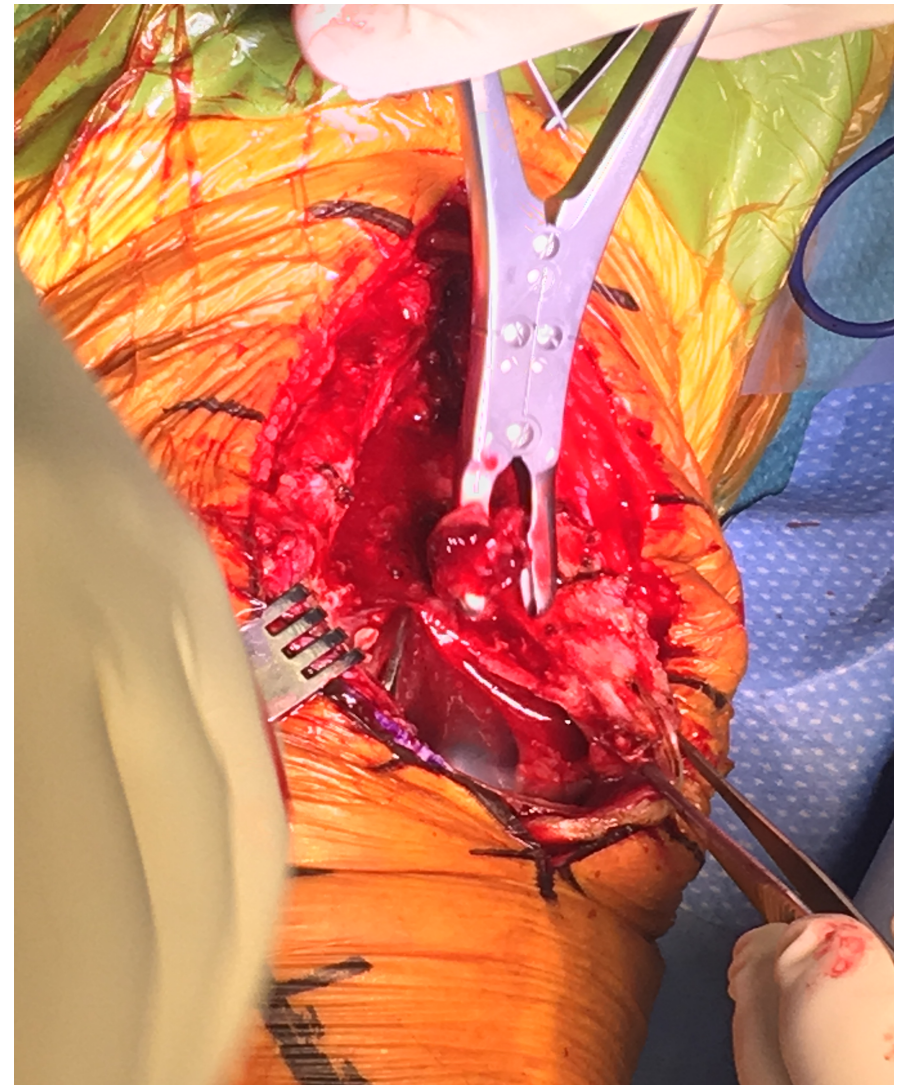


1 mL

Phage C









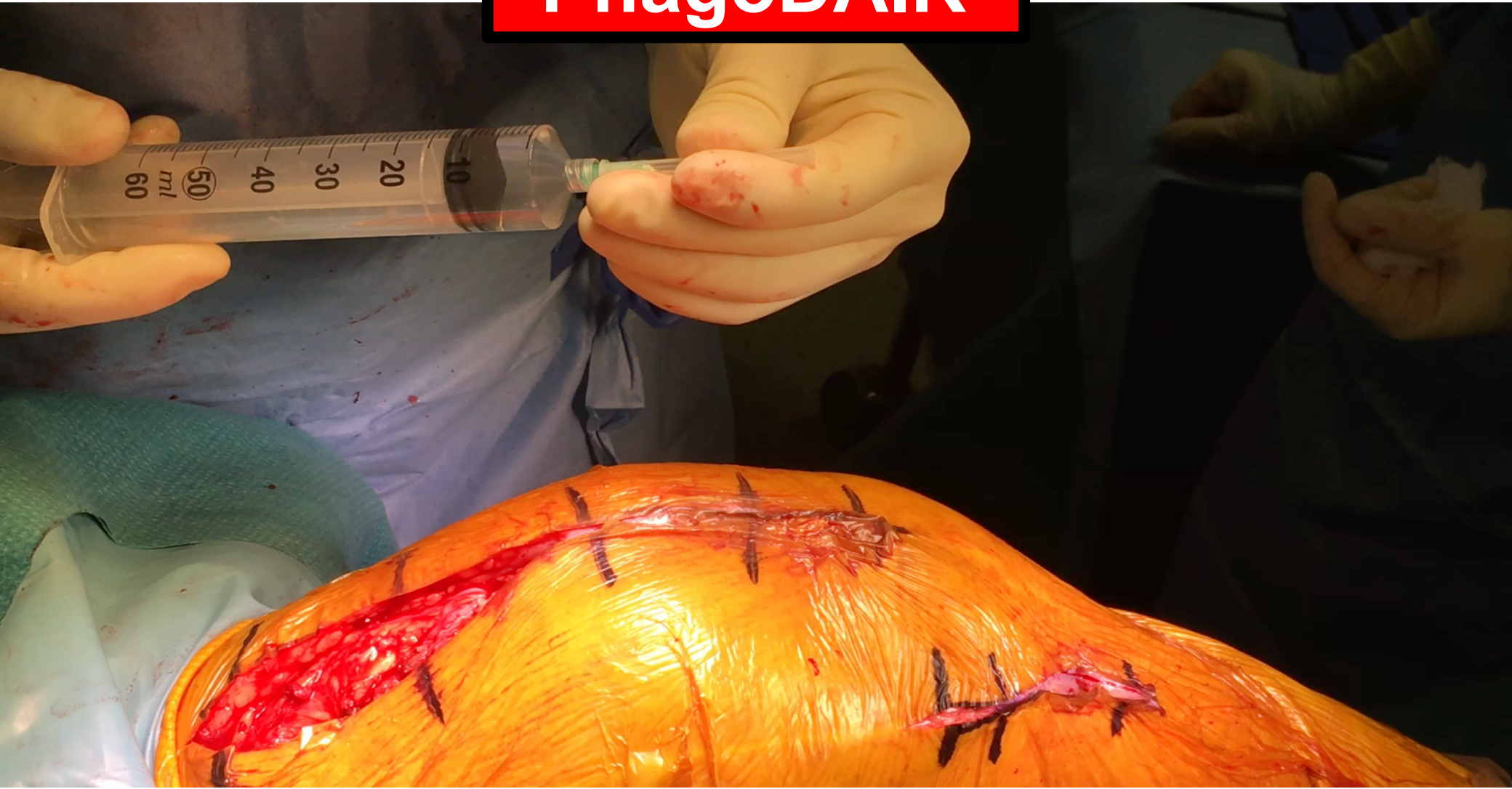








# “PhagoDAIR”



**One shot peroperative phage  
application after “DAIR”**

**HCL**  
HOSPICES CIVILS  
DE LYON

**C**RIOAc  
LYON



# Clinical case #4

## Post-operative antibiotics:

Daptomycin + Rifampin

## At day 4 (only MSSA in all intraoperative samples):

Levofloxacin + Rifampin

## Then:

Cefalexin as suppressive antimicrobial therapy





*"The bacteriophages saved my life, he insists. I never thought one day to walk again. And to say that doctors were talking about cutting my leg off!"* R.N.

# Conclusion



- Crucial need for (alternatives) **additional therapies to antibiotics** to maximize clinical success in complex bacterial infections



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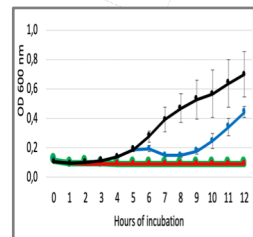
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- Industry / health authority / academic **collaborations**



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- **Need for national phage therapy center(s)**

