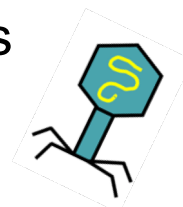


# infections osteoarticulaires, bactériophages et thérapie phagique : Histoire et perspectives

Pr. Tristan Ferry

[tristan.ferry@univ-lyon1.fr](mailto:tristan.ferry@univ-lyon1.fr)



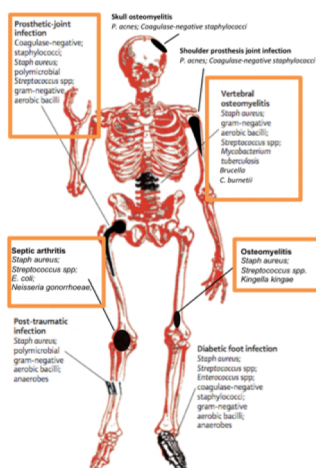
Infectious and Tropical Diseases Unit  
Croix-Rousse Hospital , Hospices Civils de Lyon  
Claude Bernard Lyon1 University, Lyon

Centre International de Recherche en Infectiologie, CIRI, Inserm U1111, CNRS  
UMR5308, ENS de Lyon, UCBL1, Lyon, France

Centre de Référence des IOA complexes de Lyon (CRIOAc Lyon)



## Les infections ostéoarticulaires



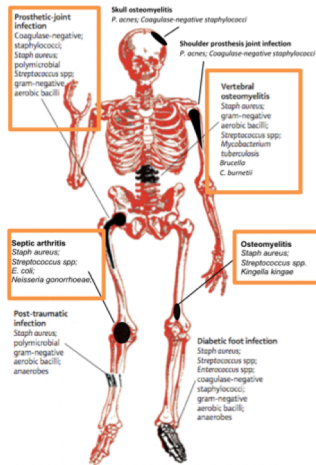
Lew et al. NEJM 1997

- Infections **hétérogènes**
- Epidémiologie bactérienne **variable**
- Incidence '**faible**'
- Différentes **stratégies**
- **La stratégie et les comorbidités** influencent le **pronostic**
- **Pourcentage de succès faible** dans certaines situations cliniques
- **Coût considérable** (individuel et collectif)
- **Peu d'essai clinique**
- **Peu de molécules anti-infectieuses approuvées**

## Les infections ostéoarticulaires

NIH U.S. National Library of Medicine

*ClinicalTrials.gov*



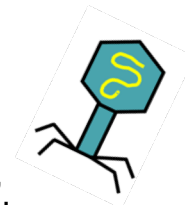
Lew et al. *NEJM* 1997

- **Osteomyelitis: 68**
- **Prosthetic-joint infection: 47**
- Meningitis: 348
- Urinary tract infection: 492
- Tuberculosis: 915
- Influenza: 2'152

**Les IOA :  
Maladies infectieuses négligées  
des pays industrialisés**

## 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.



# Marine viruses — major players in the global ecosystem

Curtis A. Suttle

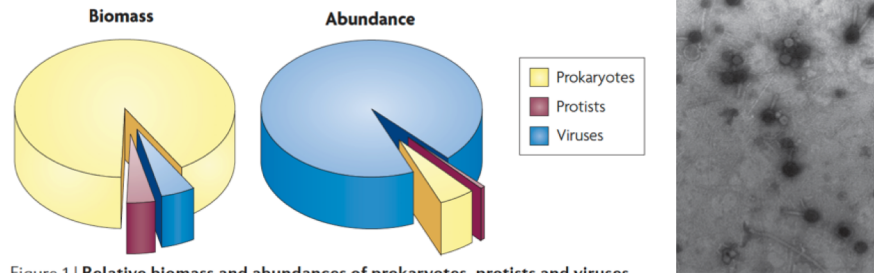


Figure 1 | Relative biomass and abundances of prokaryotes, protists and viruses.

**Probing this vast reservoir of genetic and biological diversity continues to yield exciting discoveries.**

*Nature Review Microbiology 2007*

# Self-limiting nature of seasonal cholera epidemics: Role of host-mediated amplification of phage

Shah M. Faruque\*, M. Johirul Islam\*, Qazi Shafi Ahmad\*, A. S. G. Faruque\*, David A. Sack\*, G. Balakrish Nair\*, and John J. Mekalanos†

Proc Natl Acad Sci U S A. 2005

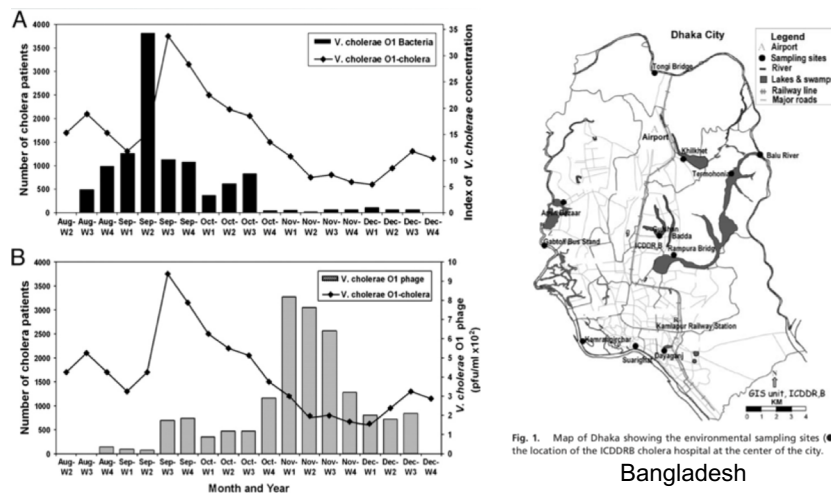



Fig. 1. Map of Dhaka showing the environmental sampling sites (●) and the location of the ICDDR,B cholera hospital at the center of the city.

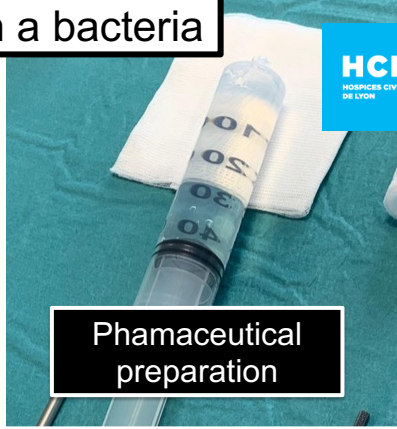
Bangladesh

10 to 100 fold smaller than a bacteria

Translucent tap water

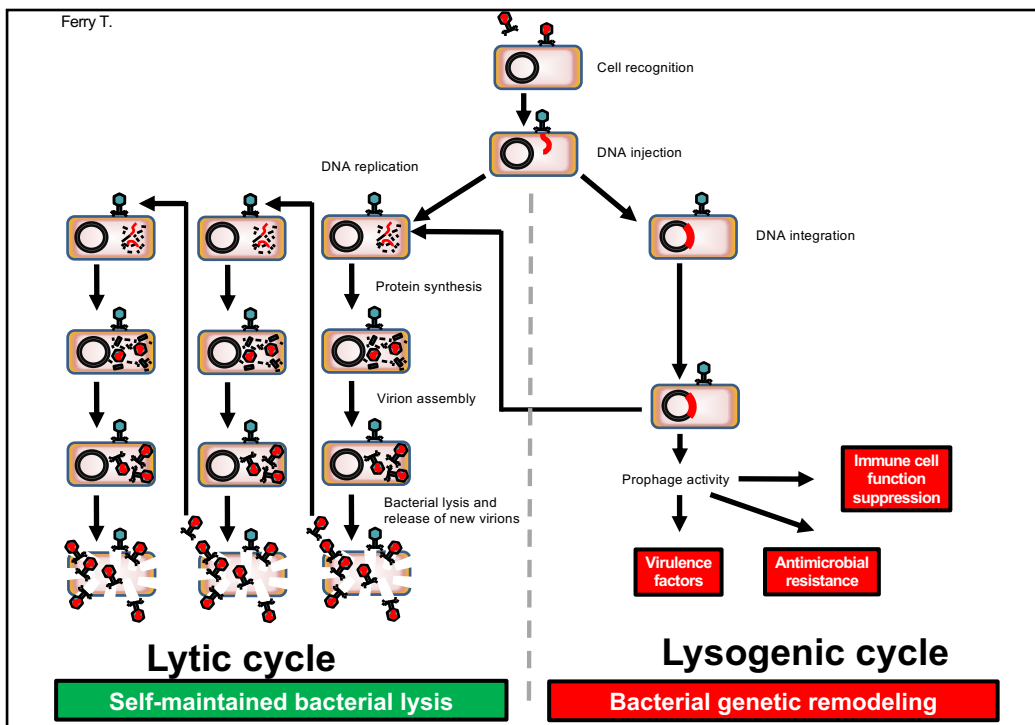



X million of ≠ BactériophageS !!!  
(targeting environmental bacteria)




Phamaceutical preparation

10<sup>8</sup> of THREE bacteriophages/mL  
(targeting *S. aureus*)










## History of phage therapy

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



- F
- In
- H
- ch
- pu
- in
- ho
- H

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

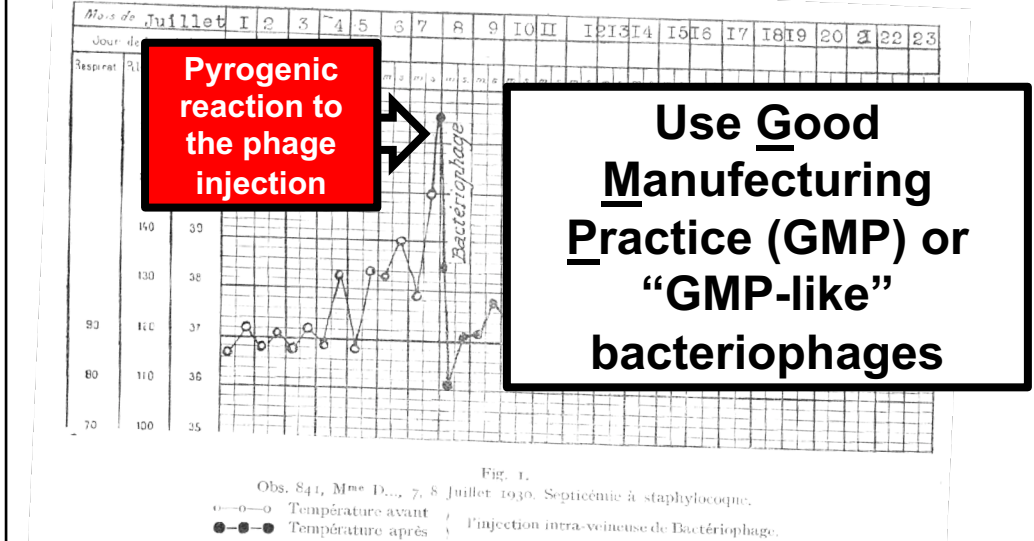
<i><b>Bacté-coli-phage</b></i> <small>Colibacilluries - Pyelonephrites - Cystites</small>	<i><b>Bacté-rhino-phage</b></i> <small>Grippe - Coryza - Rhino-pharyngites</small>
<i><b>Bacté-intesti-phage</b></i> <small>Entérites - Colites - Diarrhées infantiles</small>	
<i><b>Bacté-pyo-phage</b></i> <small>Panaris - Phlegmons - Plaies infectées</small>	<i><b>Bacté-staphy-phage</b></i> <small>Furonculose - Anthrax</small>

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

and the “**Laboratoire Français des Bactériophages**” in Paris

## Lessons to be learned of phage therapy of the 20<sup>th</sup> century




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.

1961



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Ex-Chef de Clinique chirurgicale à la Faculté

\*\*\*

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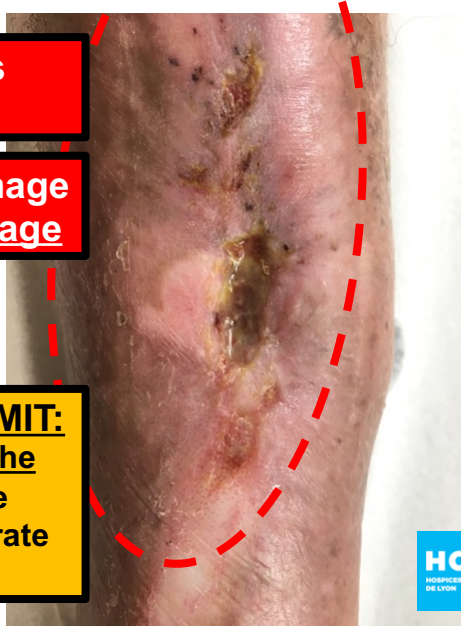
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1961


**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 sof tissue




Patient with a relapsing infection after Phage therapy in Tbilissi



*Le Journal de Médecine de Lyon* **After d'Herelle, the story continued in Lyon**

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

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




**Antimicrobial resistance**

**Phage banking**  
**Phage training**

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

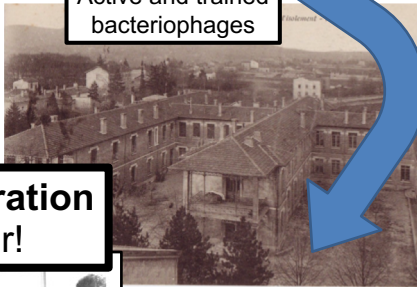
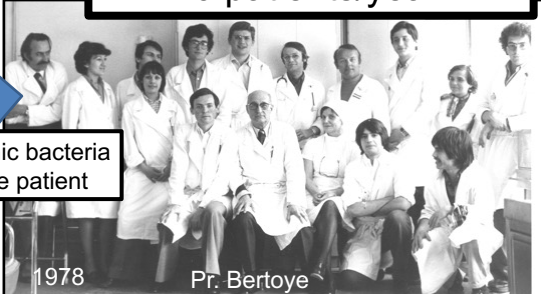
Les bacilles pyocyaniques sont fréquemment résistants aux antibiotiques usuels. Cependant, leur caractère rebelle est une de leurs caractéristiques. L'existence de bactériophages adaptés par sélection à une variété de bactériophage à la souche isolée du malade permet une action nutritive ordinaire indispensable de pouvoir l'introduire intraveineuse, in Un certain de cette publication.

Clinique des Maladies Infectieuses, Hôpital de la Croix-Rousse  
Hopscas Civils de Lyon 1958-1960



## Institut Pasteur Lyon

Active and trained bacteriophages

**Academic collaboration**  
70 patients/year!

**Infectious Disease clinic**


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

Year	Total	P.aeruginosa	S.aureus	Enterobactéries
1972	20	10	10	0
1973	45	15	30	0
1974	55	20	35	0
1975	65	25	40	0
1976	70	30	40	0

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

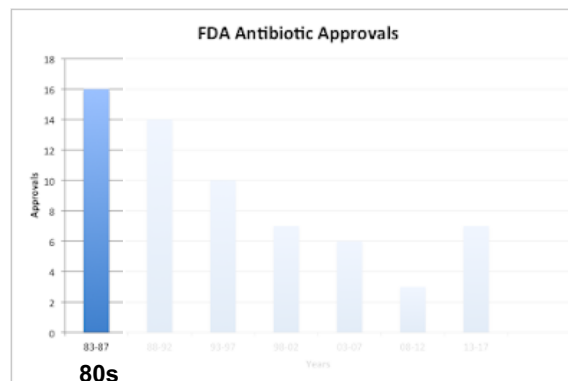
Pathogenic bacteria from the patient

1978 Pr. Bertoye



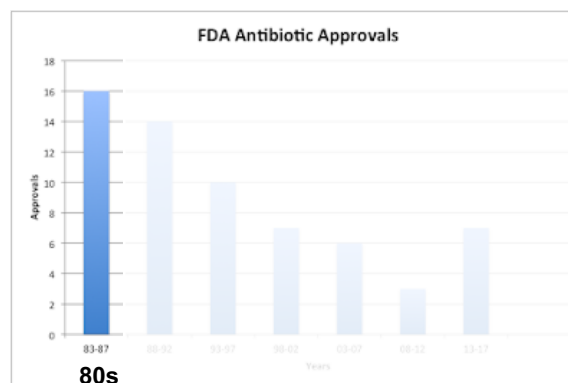
## Large production of antibiotics in 1970-1980 killed the phage therapy

- **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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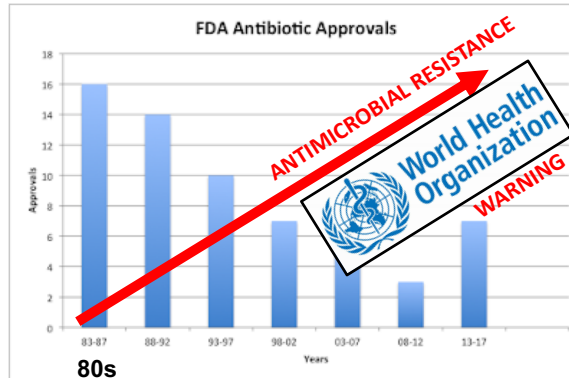
VS.


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



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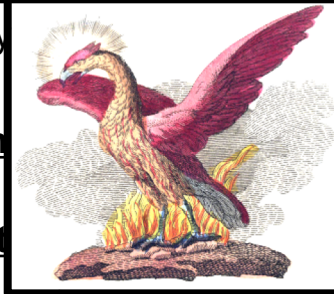



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**Phages as the Phoenix?**

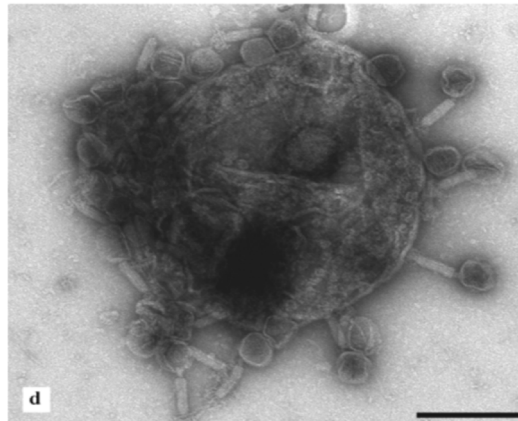


VS.  **Complex virus-based personalized treatment without clear industrial process, not considered as a drug**

## Cocktails produced in 2020 by the Eliava Institute

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

Bacteriophage ISP (*Myoviridae*)

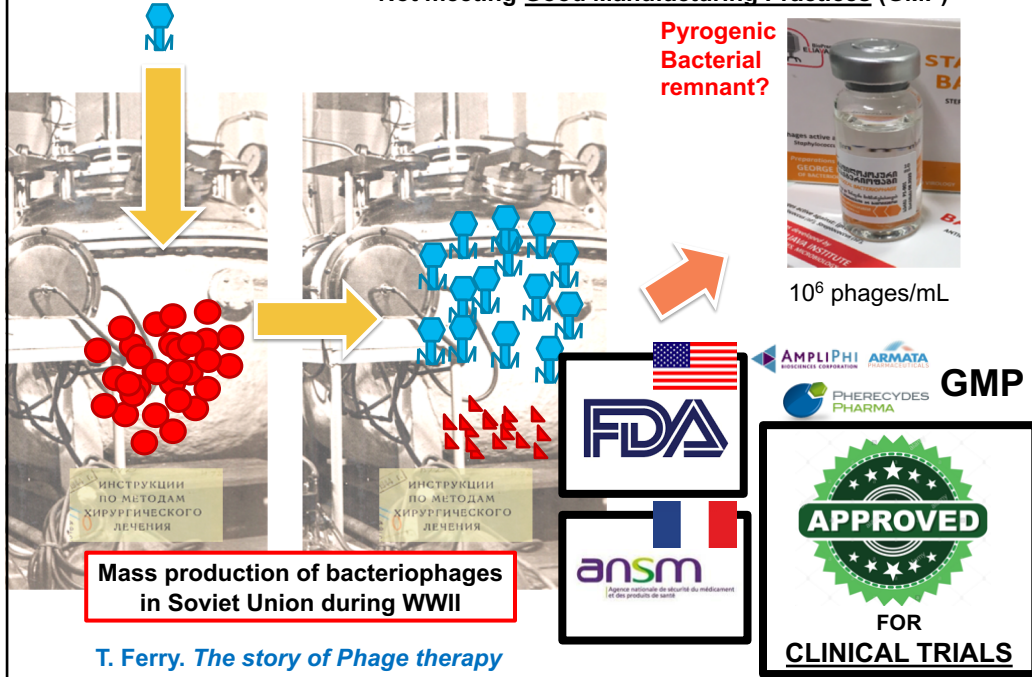


T. Ferry

Merabishvili et al. PloS ONE 2009

T. Ferry. *The story of Phage therapy*

### Not meeting Good Manufacturing Practices (GMP)



**Pyrogenic Bacterial remnant?**

$10^6$  phages/mL

**FDA**

**ANSM**

**GMP**

**APPROVED FOR CLINICAL TRIALS**

ИНСТРУКЦИИ ПО МЕТОДАМ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ

ИНСТРУКЦИИ ПО МЕТОДАМ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ

**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**

...ained reduction in bacterial burden (%)

...Kaplan-Meier analysis of median time to observe reduction compared with day 0. HR=hazard ratio. PP1131=cocktail of 12 natural lytic anti-*Pseudomonas aeruginosa* bacteriophages.

*Pseudomonas*

PHAGOCYDES PHARMA

Lancet Infect Dis 2018

**PHOSA**

PHERECYDES PHARMA

PHOSA & Phagothérapie Consortium PHOSA Communication Contact

LES PÔLES DE COMPÉTITIVITÉ

ARF ASSOCIATION DES RECHERCHES EN BIOMÉDECINE

bpi france

CRIOAc LYON

BioFilm Control

UFR Lyon 1

Vivexia laboratory

HCL HOSPICES CIVILS DE LYON

ciri Centre International de Recherche en Infectiologie

PHERECYDES PHARMA

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

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

CENTRE HOSPITALIER INTERCOMMUNAL VILLENEUVE-SAINT-GEORGES Lucie & Raymond AUBRAC

**REFERENCE CENTERS FOR THE MANAGEMENT OF BONE AND JOINT INFECTION**

**“CRIOAc” Network**

- HOPITAUX UNIVERSITAIRES LYON
- CRIOAc Grand Est
- UNIVERSITÉ DE NANTES
- CRIOAc NANTES
- CRIOGO
- CRIOAc LYON
- Crioac GSO

● CRIOAc coordonateur ○ Centres correspondants

Adapted from Ferry T, et al. Orthop Traumatol Surg Res. 2019;105(1):185-190

**REFERENCE CENTERS FOR THE MANAGEMENT OF BONE AND JOINT INFECTION**

<http://www.crioac-lyon.fr>

**CRIOAc Lyon**

@CrioacLyon

**Multidisciplinary management of the patient**

**Better understanding of the pathophysiology of BJI**

**Promotion of innovative treatments**

Adapted from Ferry T, et al. Orthop Traumatol Surg Res. 2019;105(1):185-190

## Comité scientifique des CRIOAc

Président : Pr. T. Ferry (Infectiologue, Lyon)  
 Pr. E. Senneville (Infectiologue, Lille-Tourcoing)  
 Pr. A. Stein (Infectiologue, Marseille)

Dr. S. Marmor (Orthopédiste, Paris)  
 Pr. E. Steindel (Orthopédiste, Brest)  
 Pr. D. Meynard (Orthopédiste, Strasbourg)

Dr. P. Bemer (Microbiologiste, Nantes)  
 Pr. V. Dubois (Microbiologiste, Bordeaux)

Centraliser les idées pour la réalisation de projets de recherche à l'échelle nationale

Expertise pluridisciplinaire

Utilisation du système d'information pour les études de faisabilité

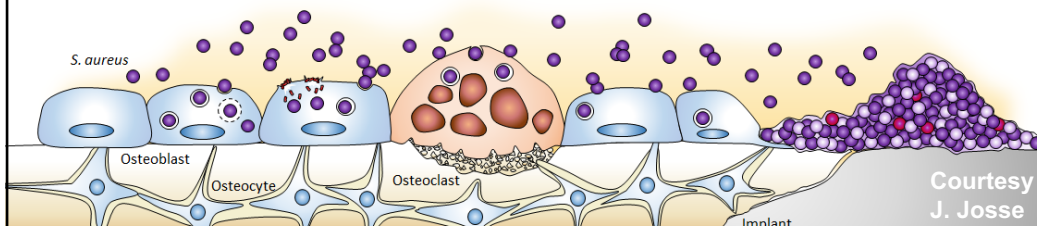


DIRECTION GÉNÉRALE DE L'OFFRE DE SOINS

Promotion de la recherche et de l'innovation

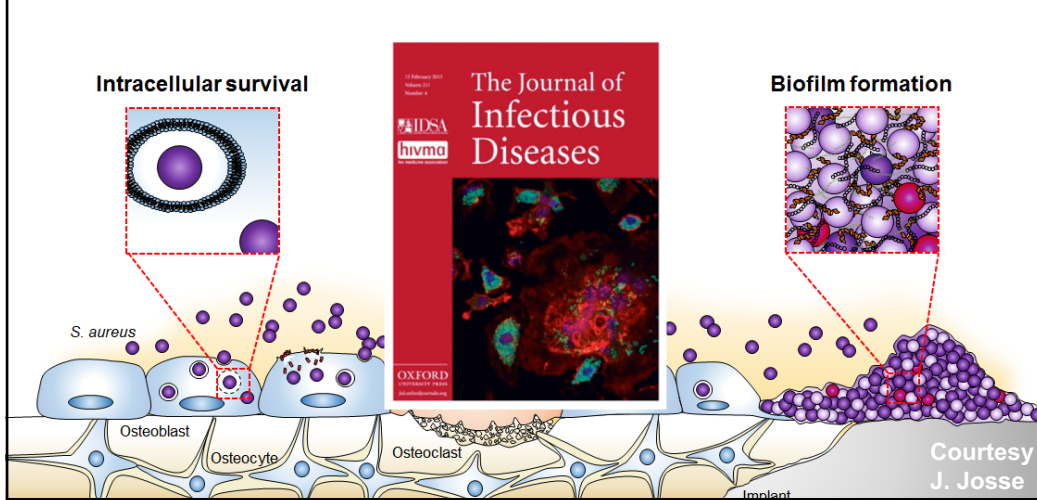
## Persisters in chronic BJI

**“Bacterial cells that escape the effects of antibiotics without undergoing genetic change”**



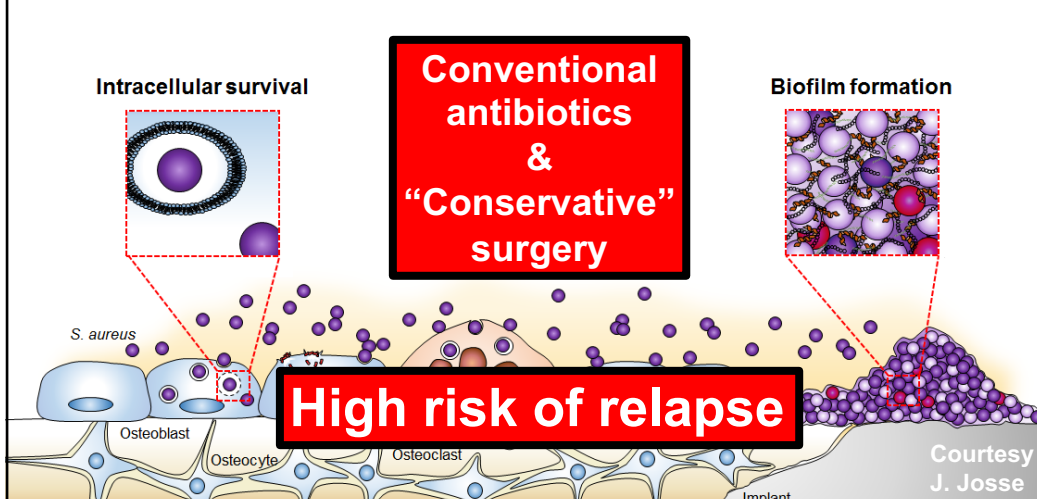
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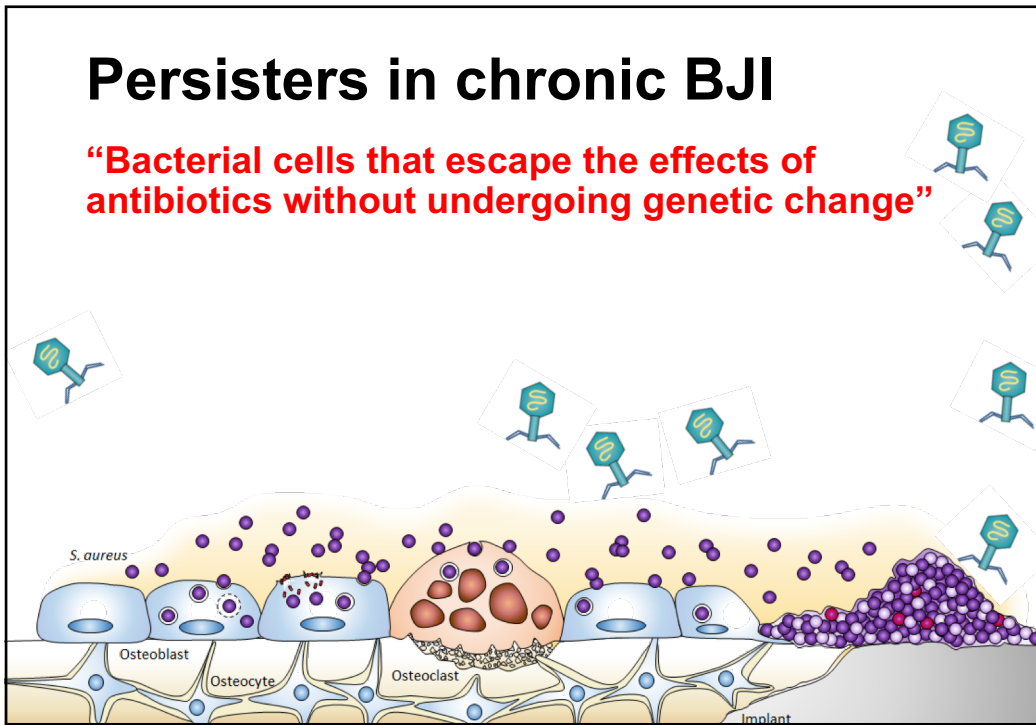
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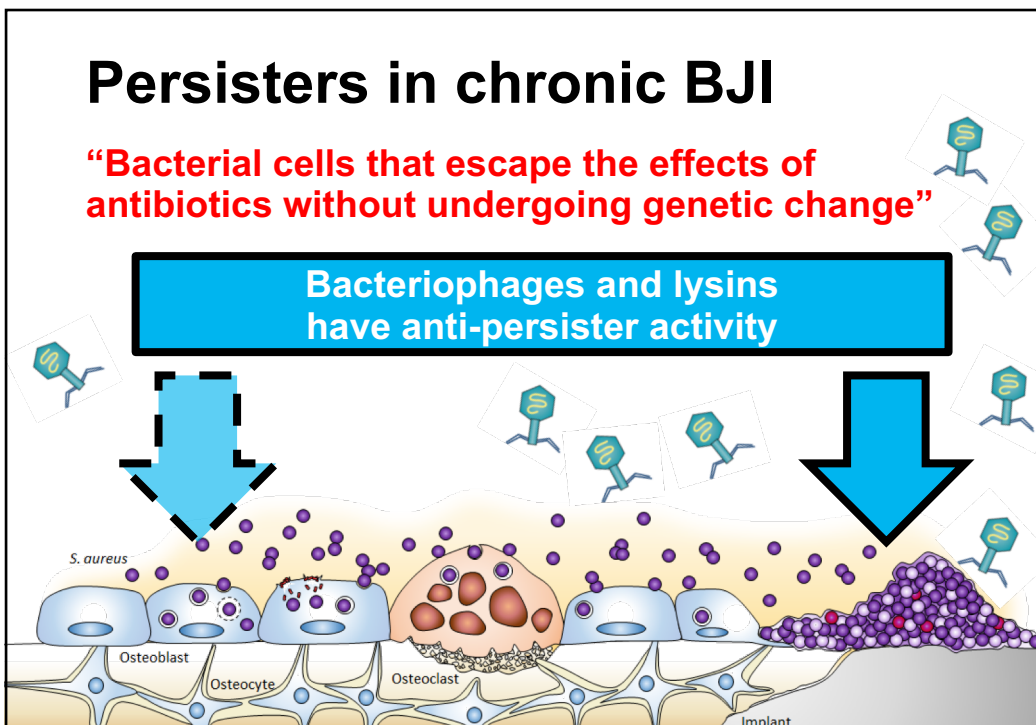
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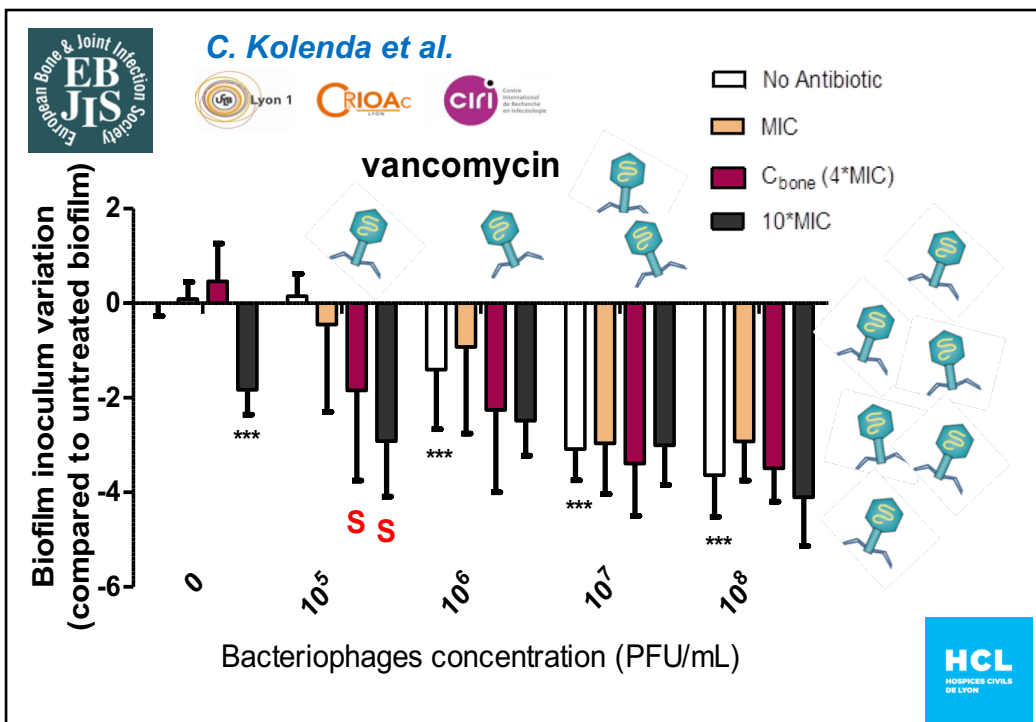
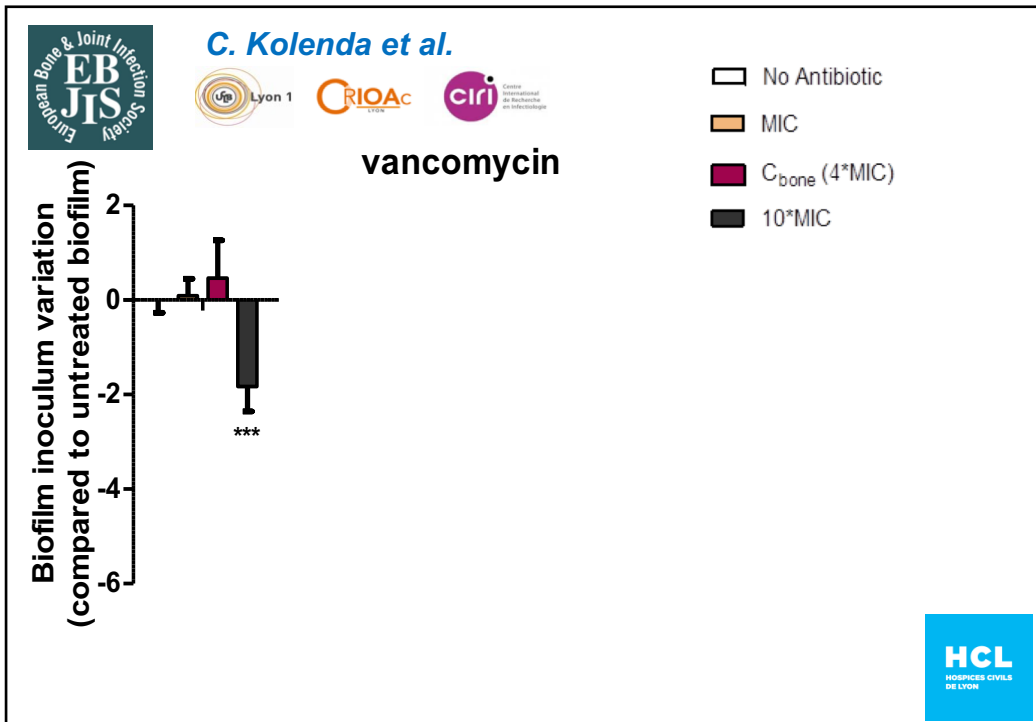
**“Bacterial cells that escape the effects of antibiotics without undergoing genetic change”**



## Persisters in chronic BJI

**“Bacterial cells that escape the effects of antibiotics without undergoing genetic change”**





# Declaration of Helsinki

**Medical Research Involving Human Subjects**

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

World Medical Association



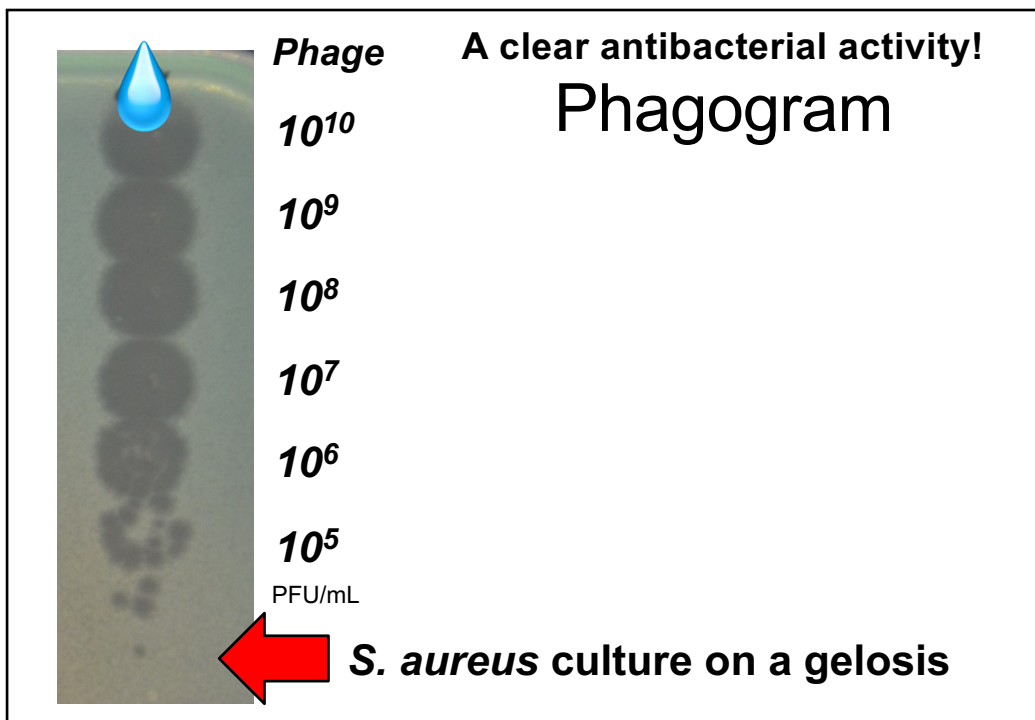
**WMA**

WORLD  
MEDICAL  
ASSOCIATION

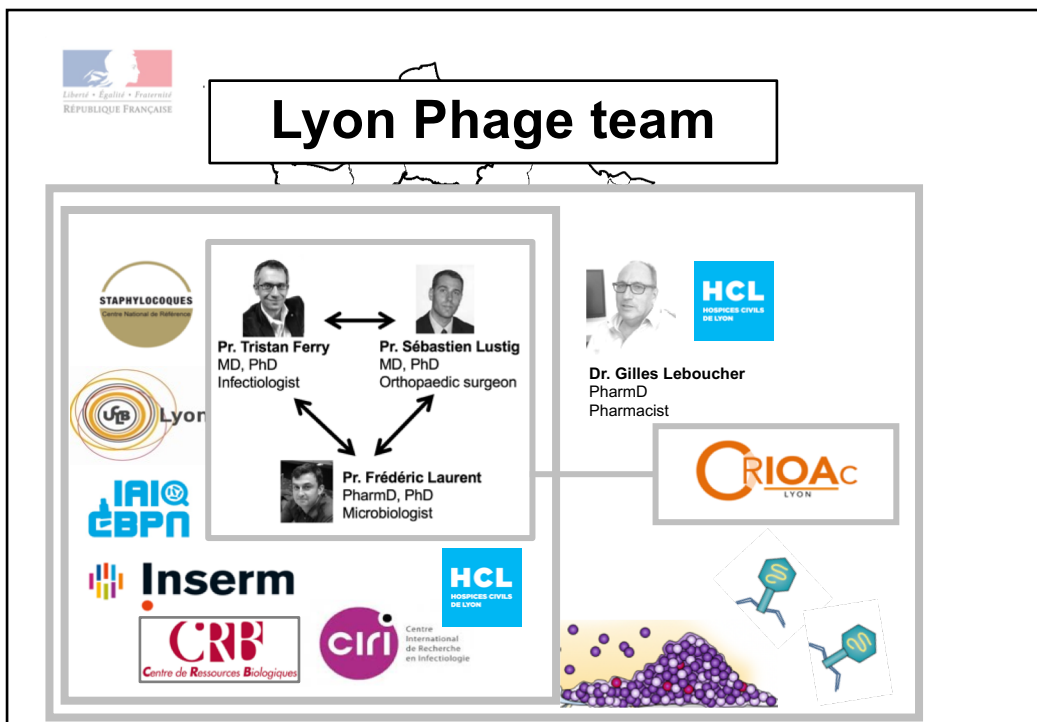
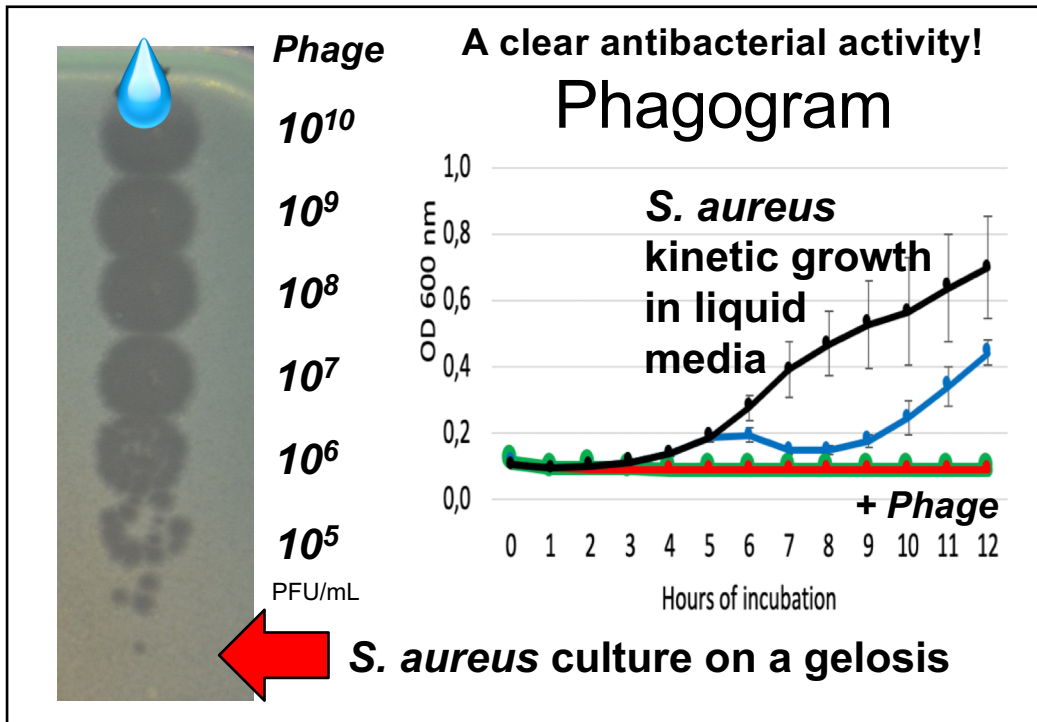


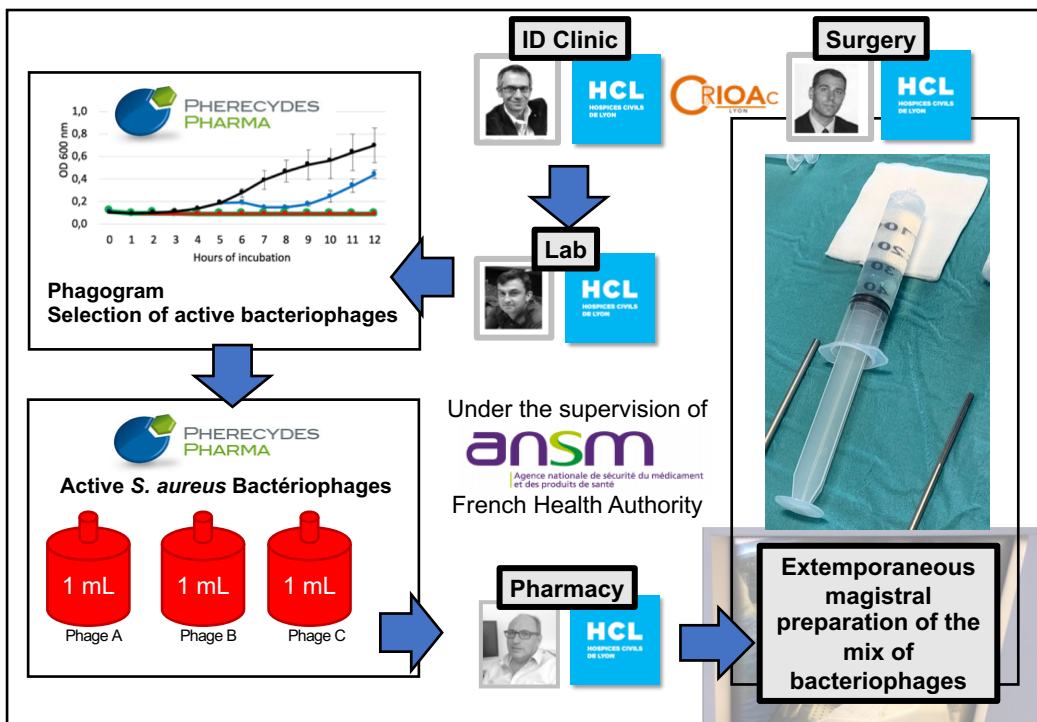
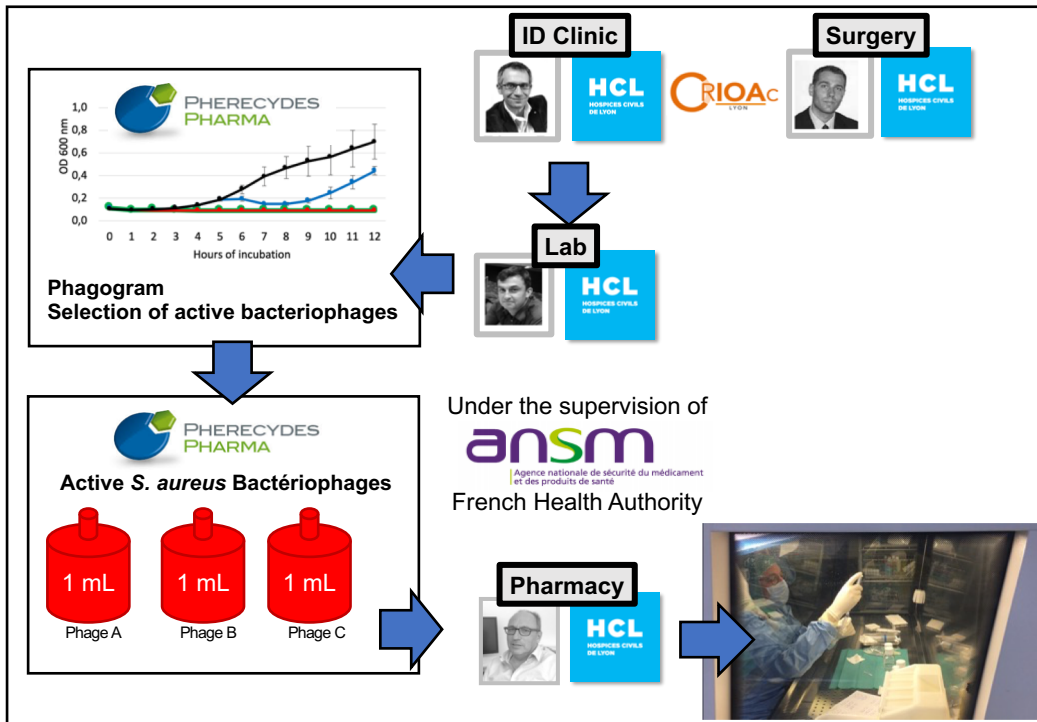
- **Unproven Interventions in Clinical Practice**
- 37. In the treatment of an **individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician**, after seeking expert advice, **with informed consent from the patient** or a legally authorised 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









**‘Debridement And Implant Retention’ (DAIR) with local administration of personalized cocktail of bacteriophages (PhagoDAIR) followed by suppressive antibiotherapy as salvage therapy in patients with relapsing prosthetic knee infection**

**Phago DAIR**

**CRIOAc LYON**

**30th ECCMID**  
Paris, France  
18 –21 April 2020

**PHERECYDES PHARMA**

**HCL**  
HOSPICES CIVILS DE LYON

**Conclusions: Personalized bacteriophage therapy has the potential to be used as salvage therapy during DAIR in patients with relapsing *S. aureus* and *P. aeruginosa* prosthetic knee infection, to improve the efficacy of suppressive antibiotics, and to avoid considerable loss of function.**

**Ultrasound guided local administration of personalized cocktail of bacteriophages followed by suppressive antibiotherapy as salvage therapy in patients with relapsing total femur prosthesis infection**

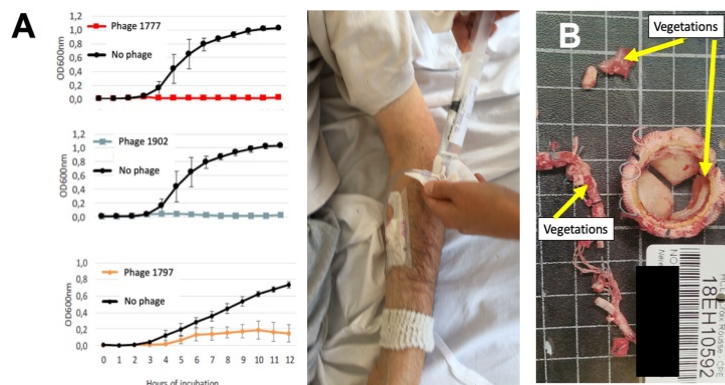
**30th ECCMID**  
Paris, France  
18 –21 April 2020

**PHERECYDES PHARMA**

**HCL**  
HOSPICES CIVILS DE LYON

**Conclusions: Ultrasound-guided local administration of personalized cocktail of GMP bacteriophages followed by suppressive antibiotherapy in patients with relapsing total femur PJI has the potential to be used as salvage therapy to control the infection and avoid disarticulation. Dramatic superinfection could be diagnosed at the time of phage administration.**

**Intravenous administration of personalized cocktail of bacteriophages as salvage therapy in combination with ceftazidime/avibactam in patients with relapsing *P. aeruginosa* bacteremia: Lesson learned from two cases**



30th  
ECCMID

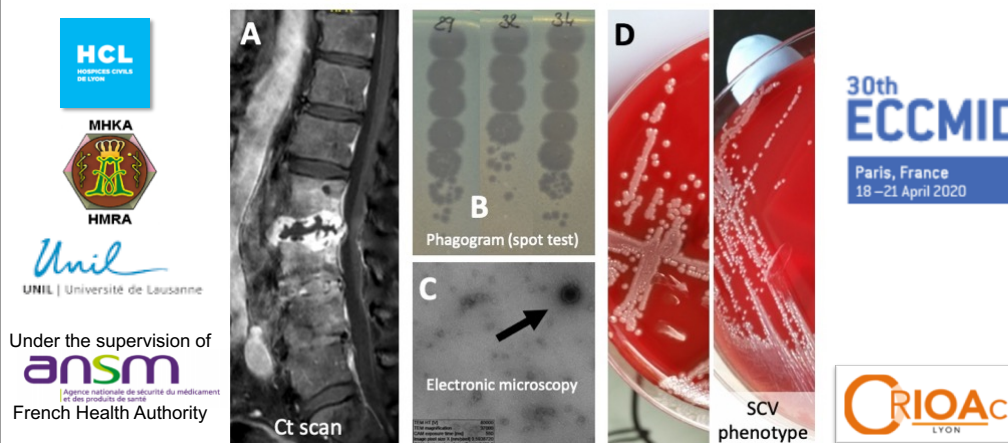
Paris, France  
18–21 April 2020

PHERECYDES  
PHARMA

HCL  
HOSPICES CIVILS  
DE LYON

**Conclusions:** The type of filter used for the magistral preparation and the duration of the perfusion influenced the phage titer, as the titer in the patient's blood. Personalized GMP bacteriophage therapy has the potential to be used as salvage therapy of *P. aeruginosa* intravascular implant infections.

**Personalized production and administration of bacteriophages: lessons learned from a unique European academic collaboration to treat a patient with pandrug-resistant spinal *P. aeruginosa* infection**



30th  
ECCMID

Paris, France  
18–21 April 2020

CRIOAC  
LYON

**Conclusions:** Personalized phage therapy is a potential adjunct treatment for patients with complex BJI due to pandrug-resistant bacteria. **In addition to industrial phages under development, academic collaborative research is crucial to develop personalized phage therapy.**

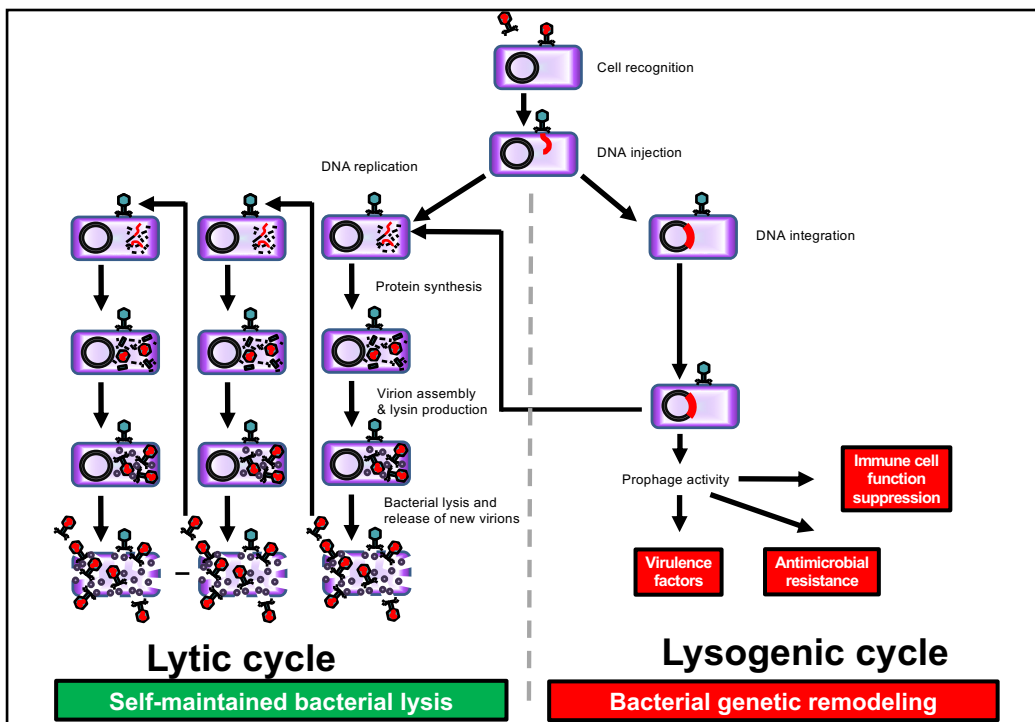
**Personalized production and administration of bacteriophages: lessons learned from a unique European academic collaboration to treat a patient with pandrug-resistant spinal *P. aeruginosa* infection**



Paris, France  
18–21 April 2020





**Conclusions:** Personalized phage therapy is a potential adjunct treatment for patients with complex BJI due to pandrug-resistant bacteria. **In addition to industrial phages under development, academic collaborative research is crucial to develop personalized phage therapy.**





# Bacteriophage Lysins



**Vincent A. Fischetti**  
@microbepheg


**Tristan Ferry** Lyon University Hospitals  
@FerryLyon

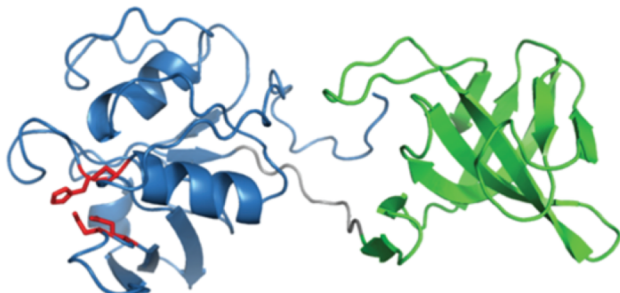
Incredible talk of Pr. Vincent A. Fischetti @microbepheg @IDWeek2019 about the great potential of #bacteriophage #lysins to induce bacterial explosion... and disappearance! It's good to hear that he discovered lysins that are active against #multidrugresistant #ESKAPE pathogens!

## Combination Therapy With Lysin CF-301 and Antibiotic Is Superior to Antibiotic Alone for Treating Methicillin-Resistant *Staphylococcus aureus*-Induced Murine Bacteremia


Raymond Schuch,<sup>1</sup> Han M. Lee,<sup>1</sup> Brent C. Schneider,<sup>1</sup> Karen L. Sauve,<sup>1</sup> Christina Law,<sup>1</sup> Babar K. Khan,<sup>1</sup> Jimmy A. Rotolo,<sup>1</sup> Yuki Horiuchi,<sup>1</sup> Daniel E. Couto,<sup>1</sup> Assaf Raz,<sup>2</sup> Vincent A. Fischetti,<sup>2</sup> David B. Huang,<sup>1</sup> Robert C. Nowinski,<sup>1</sup> and Michael Wittekind<sup>1</sup>

<sup>1</sup>ContraFact Corporation, Yonkers, NY, and <sup>2</sup>Department of Bacterial Pathogenesis and Immunology, The Rockefeller University, New York, New York





**CF-301**

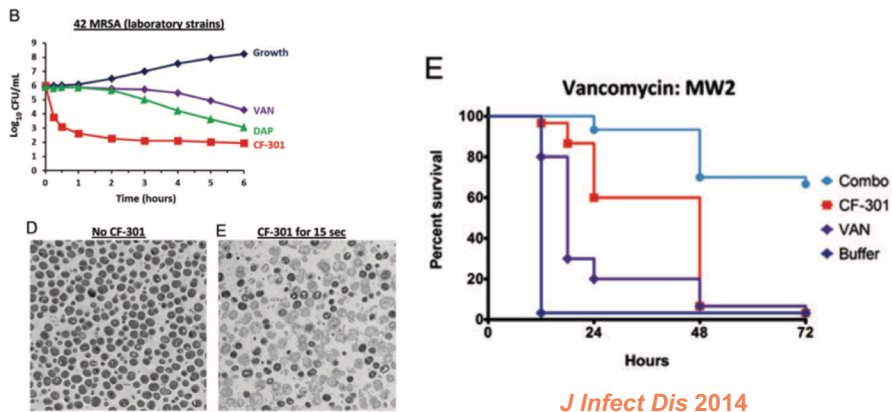


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## Arthroscopic debridement, antibiotic and implant retention (DAIR) with local administration of Exebacase (Lysin CF-301) (LysinDAIR) followed by suppressive tedizolid as salvage therapy in elderly patients for relapsing multidrug-resistant *Staphylococcus epidermidis* prosthetic knee infection



30th  
ECCMID

Paris, France  
18–21 April 2020


ContraFect




**Conclusions:** Exebacase has the potential to be used as salvage therapy during arthroscopic DAIR in patients with relapsing MDR *S. epidermidis* PKI, to improve the efficacy of suppressive antibiotics, and to avoid considerable loss of function.




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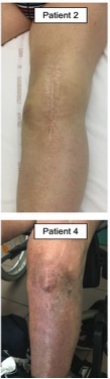
**A**





**B**



**C**

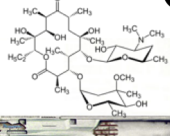



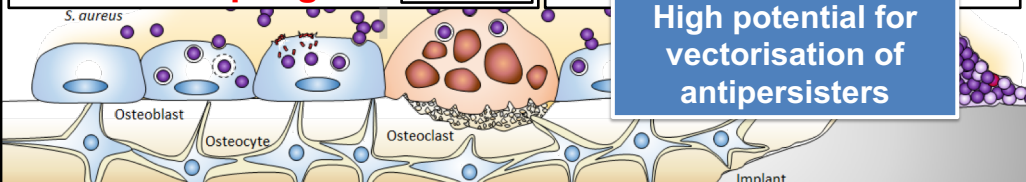



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# Potential anti-Persisters

Basic science > Pre-clinical > Clinical > Market approval > Marketing

<p><u>New small molecules</u></p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td>NH125</td> <td>Nitroxoline</td> <td>TN-5</td> <td>ADEP4S</td> <td>SAR2</td> </tr> <tr> <td>2D-24</td> <td>NCK-10</td> <td>Piscidin p3</td> <td>XF-73</td> <td></td> </tr> <tr> <td>SPI009</td> <td>IDR1018</td> <td>QAC-10</td> <td>PLGP-0206</td> <td></td> </tr> </table>	NH125	Nitroxoline	TN-5	ADEP4S	SAR2	2D-24	NCK-10	Piscidin p3	XF-73		SPI009	IDR1018	QAC-10	PLGP-0206		<p><b>CE</b></p> <p><u>Carriers of conventional drugs</u></p>   <p><b>Local high doses and prolonged exposure</b></p> <ul style="list-style-type: none"> <li>Nanotools</li> <li>Liposomal carriers</li> <li>Antibiotic-loaded hydrogel</li> <li>Antibiotic-loaded ceramic tailored implants</li> <li>Antibiotic-loaded bone substitutes (CaSO4)</li> </ul>
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High potential for vectorisation of antipersisters

## Conclusion



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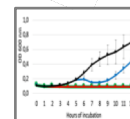
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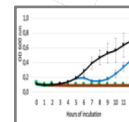
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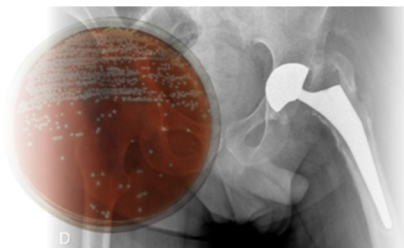
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**2020**



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