

# Phage therapy to treat complex bone and joint infections in industrialized countries

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



# 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, les infections cutanées, otitiques, bronchitiques, leur être attribuées semble être en augmentation. Leur caractère rebelle est une de leurs caractéristiques. La phagothérapie, différente de celles que nous connaissons, l'existence de bactériophages, de stock-bactériophages, l'adaptation par sélection à une variété de bactériophage à la souche isolée du malade permet une action thérapeutique nutritif ordinaire. Mais l'emploi contre, l'adaptation indispensable de la phagothérapie sur bouillon intraveineuse, inest par contre in dilué pour arachidiennepportés dans cette publication.

**Antimicrobial resistance**

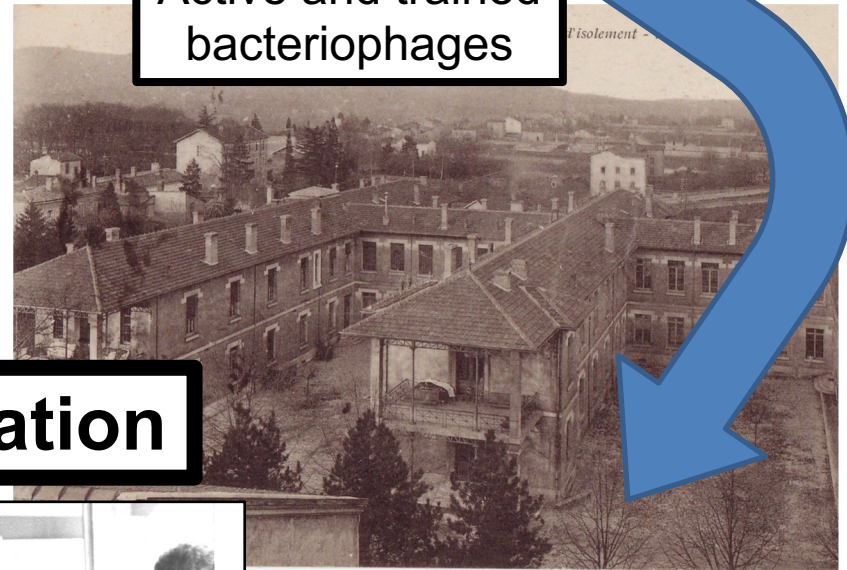
**Phage banking  
Phage training**

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



# Institut Pasteur Lyon

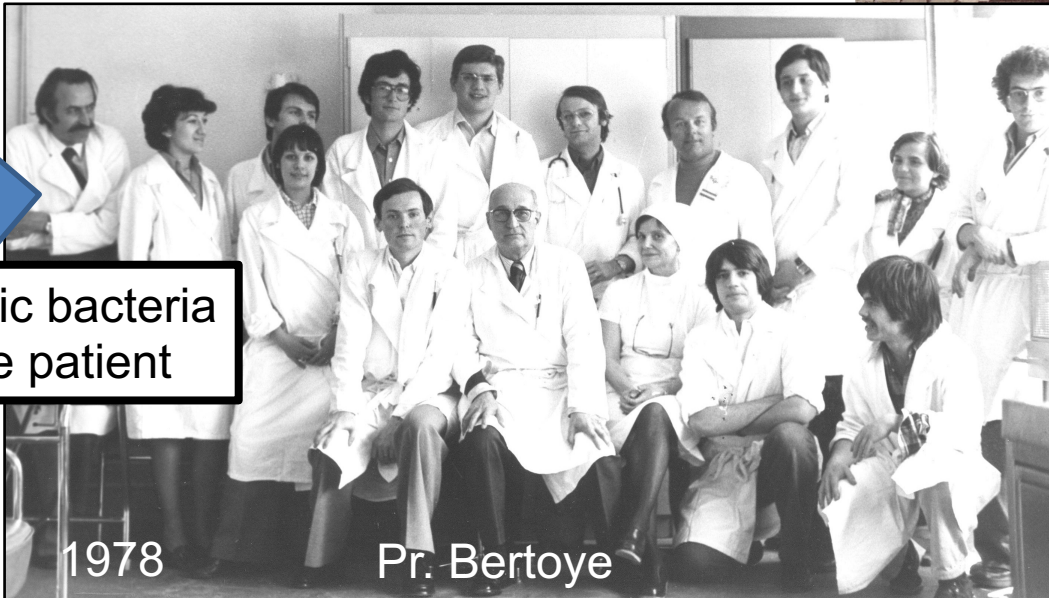
Active and trained  
bacteriophages



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

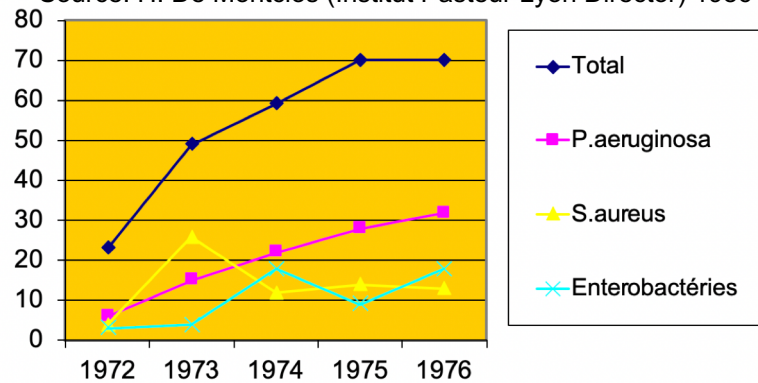
**Academic collaboration**

Pathogenic bacteria  
from the patient



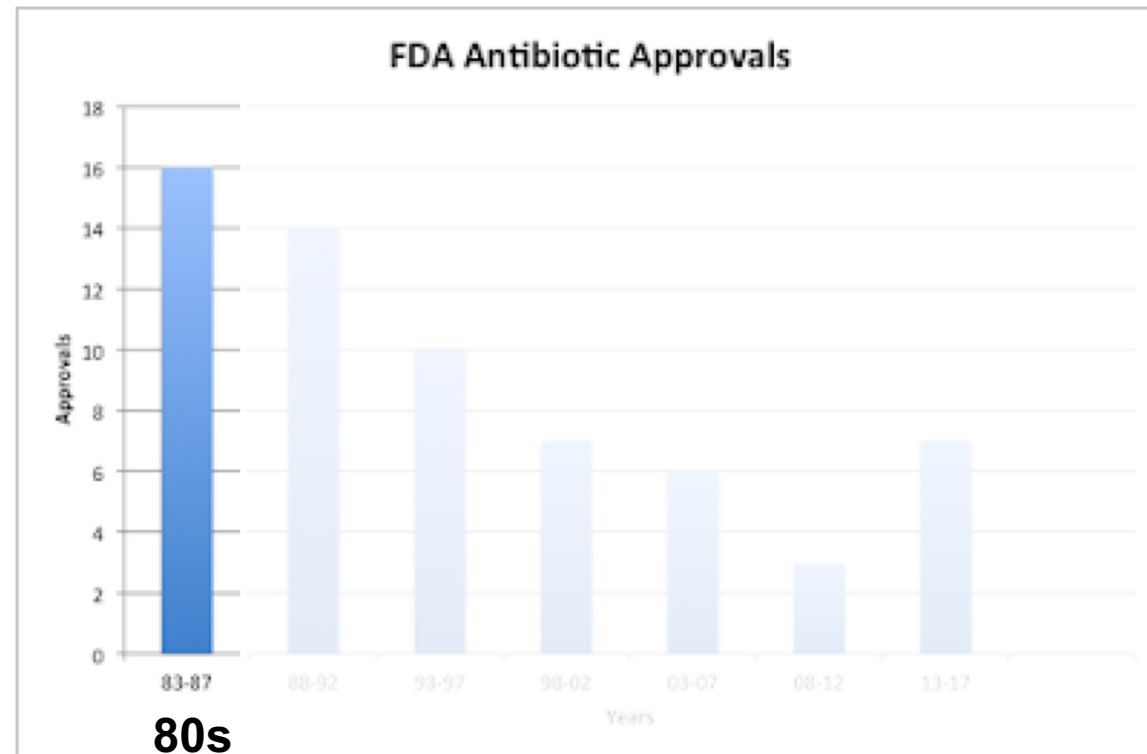
**Infectious  
Disease  
clinic**

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



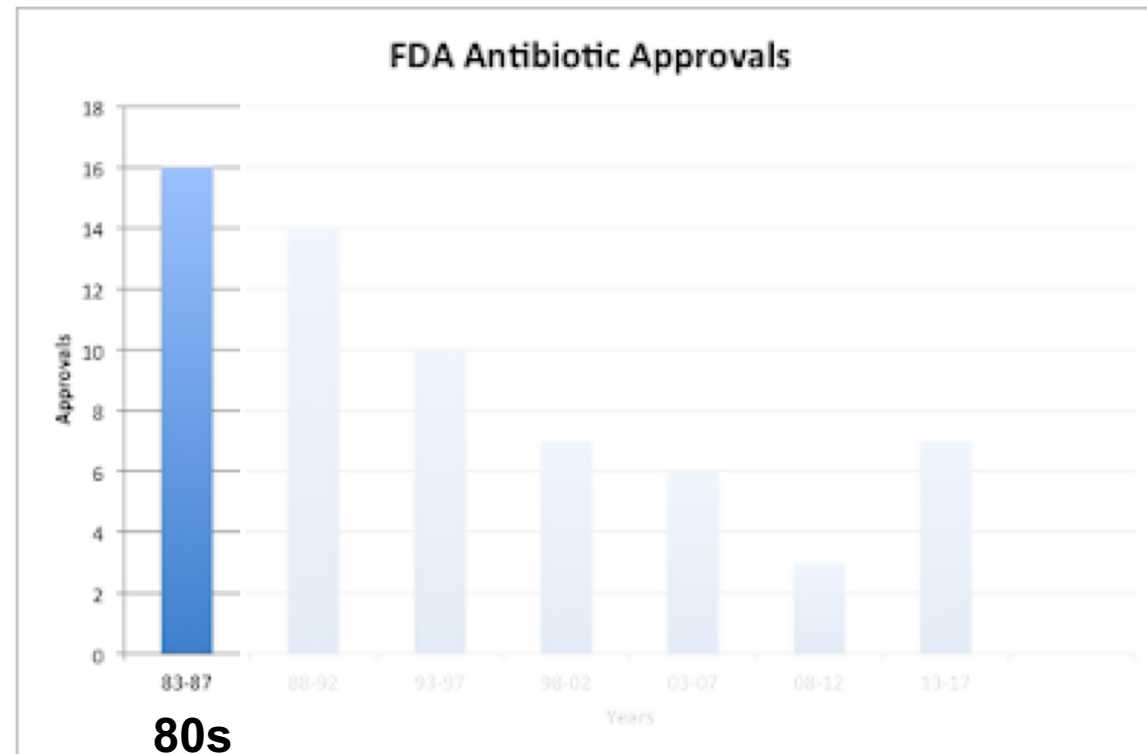
# Large production of antibiotics in 1970-1980 killed the phage therapy

- 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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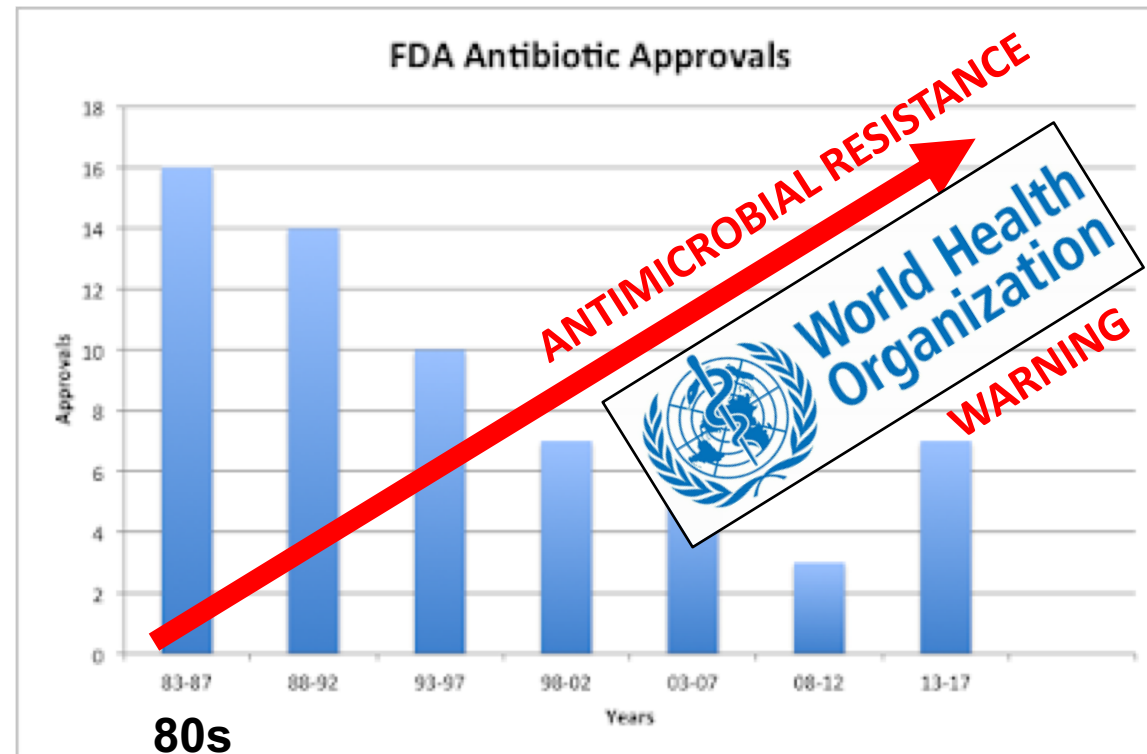
VS.



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

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

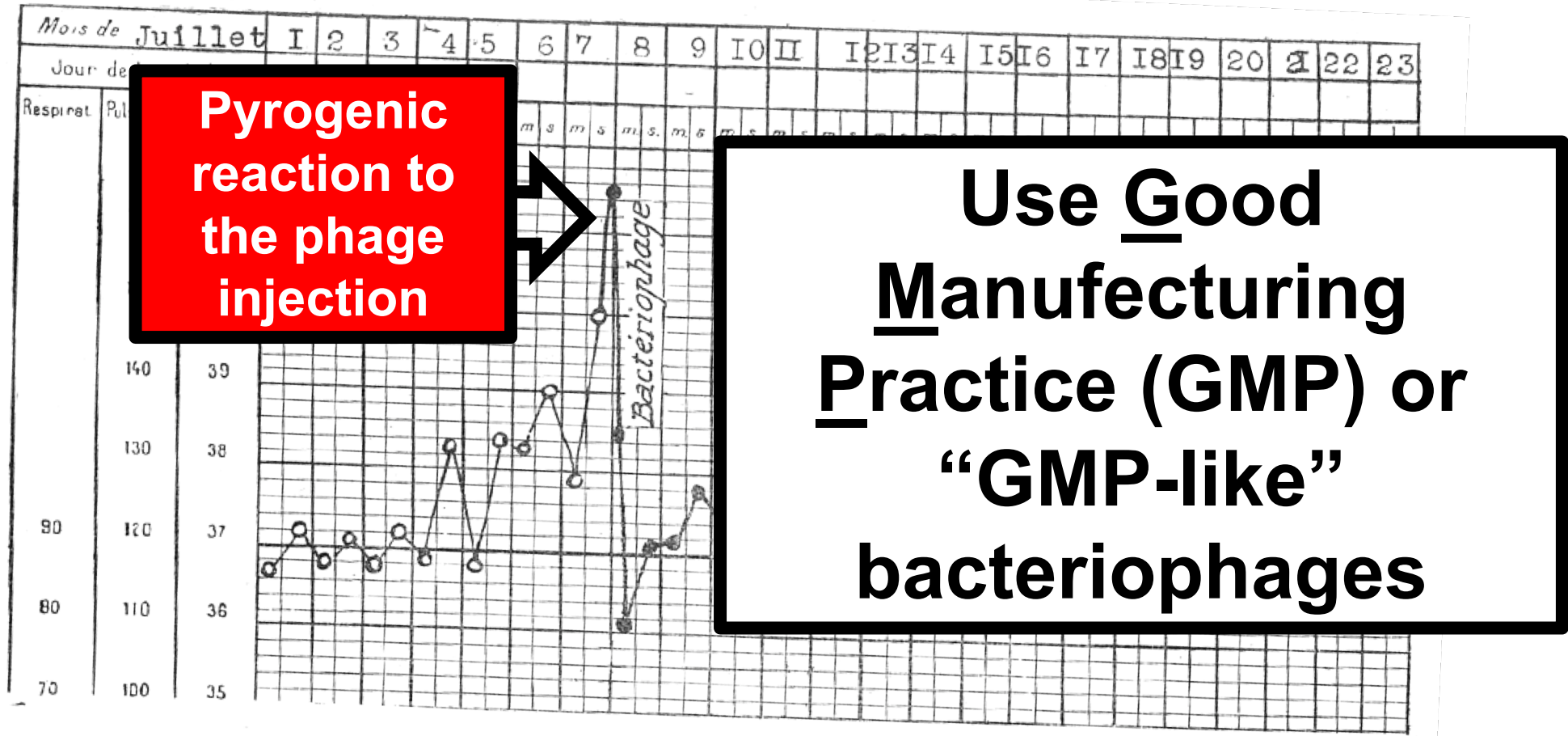
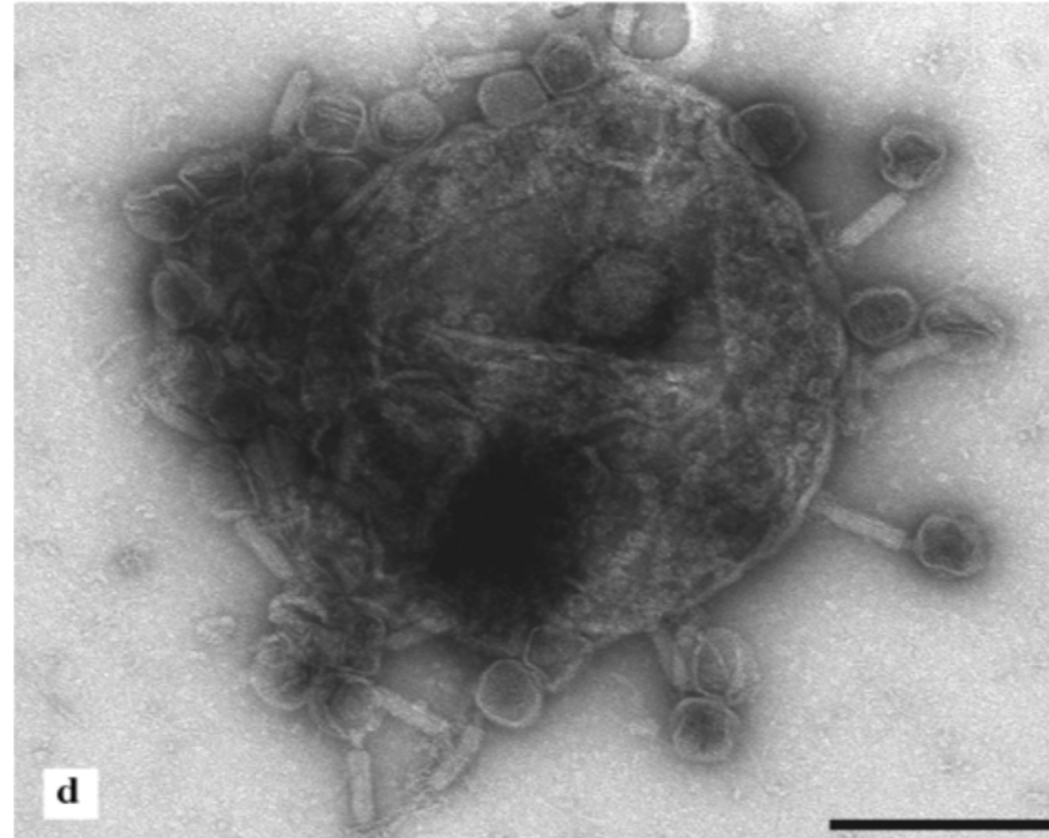


Fig. 1.  
Obs. 841, Mme D..., 7, 8 Juillet 1930. Septicémie à staphylocoque.  
o—o—o Température avant }  
●—●—● Température après } l'injection intra-veineuse de Bactériophage.

# Cocktails produced in 2019 by the Eliava Institute

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

Bacteriophage ISP (*Myoviridae*)



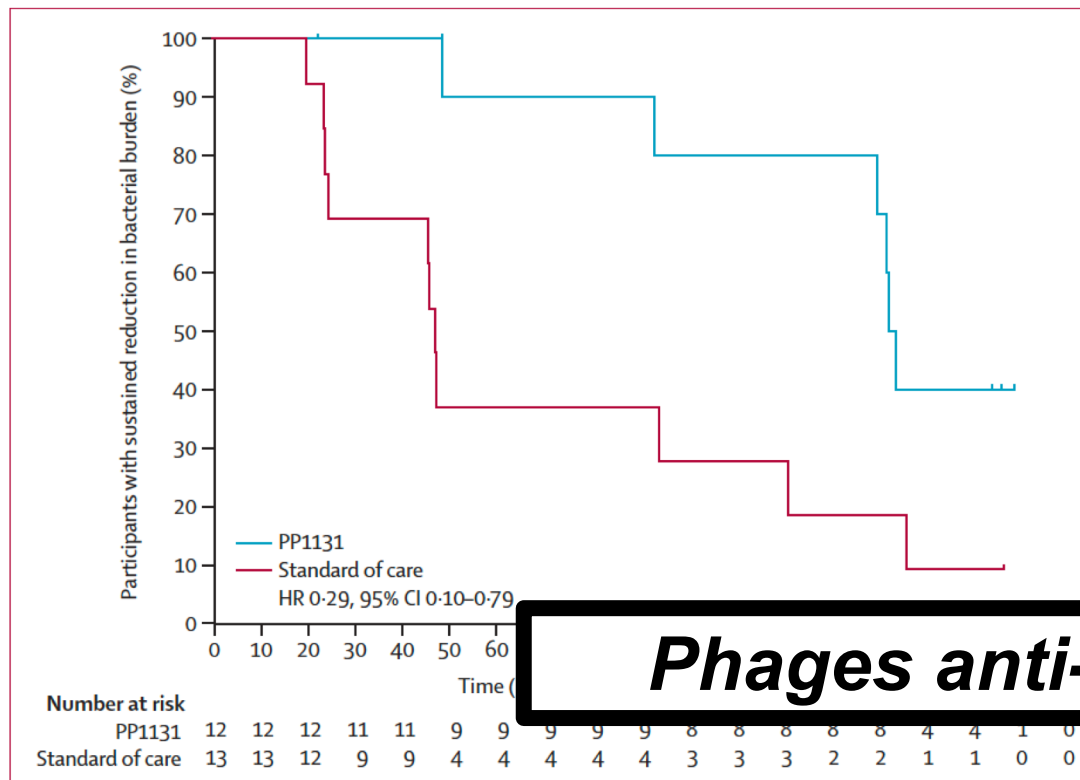
Merabishvili et al. PloS ONE 2009



T. Ferry

# 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 Jennes, Jean Paul Pirnay, Yok-Ai Que, Gregory Resch, Anne Françoise Rousseau, François Ravat, Hervé Carsin, Ronan Le Floch, Jean Vivien Schaal, Charles Soler, Cindy Fevre, Isabelle Arnaud, Laurent Bretaudeau, Jérôme Gabard



**Phages anti-*P. aeruginosa***

**Figure 2:** Time to observe reduction in bacterial burden in the most infected wound  
Kaplan-Meier analysis of median time to sustained semi-quantitative reduction of two or more quadrants of highest daily bacterial burden compared with day 0. HR=hazard ratio. PP1131=cocktail of 12 natural lytic anti-*Pseudomonas aeruginosa* bacteriophages.



PHOSA & Phagothérapie

Consortium PHOSA

Communication

Contact



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



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





## 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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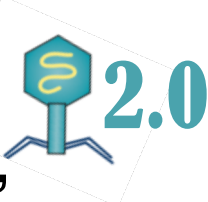
**Partial bone necrosis  
requiring surgery**

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

**MAJOR BIOLOGICAL LIMIT:**

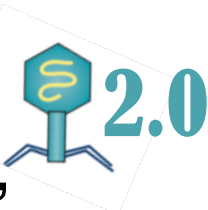

**Bacteriophages have not the capacity to perform bone debridement nor to regenerate skin and soft tissue**

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

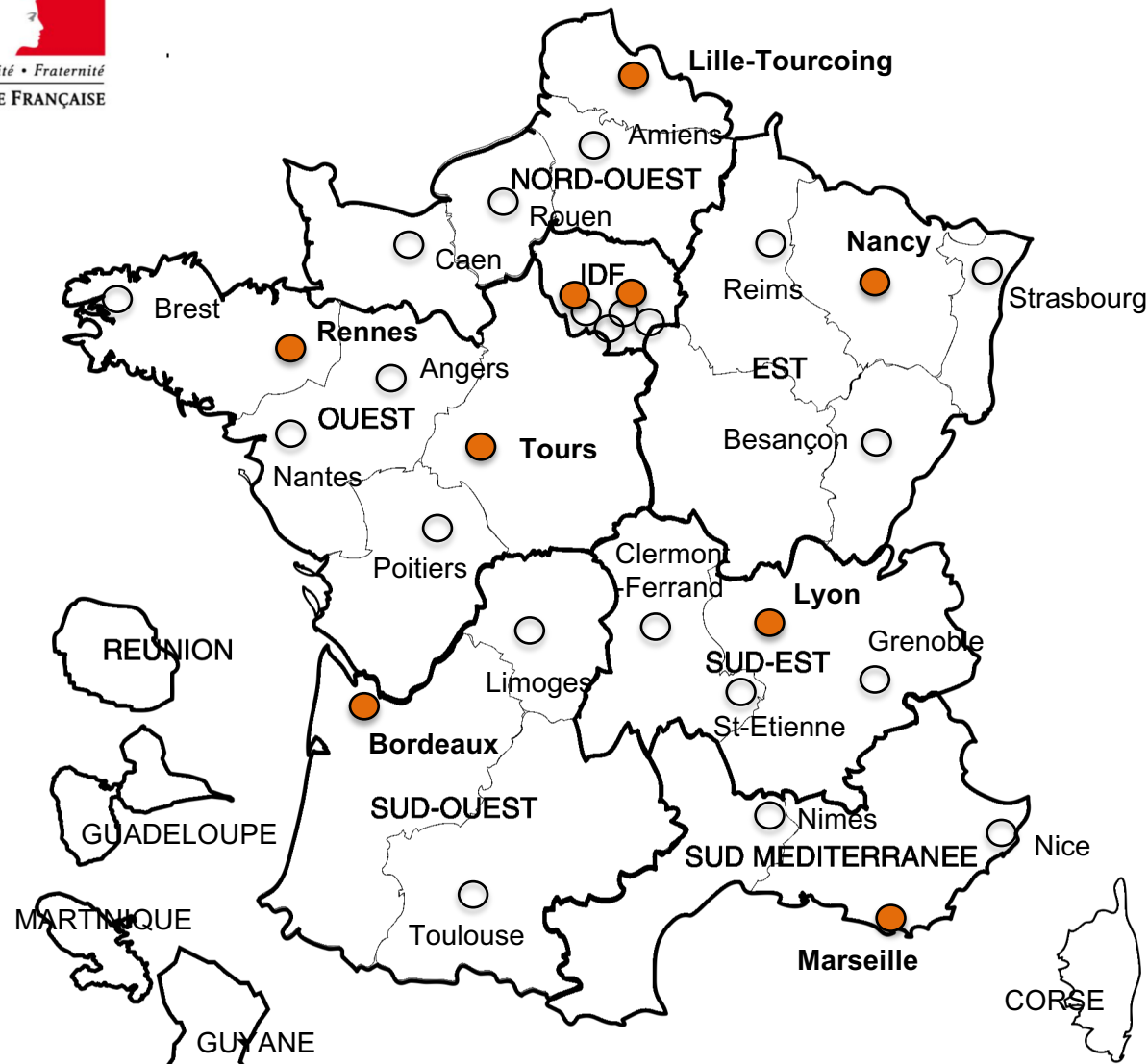
- Use GMP or 'GMP-like' bacteriophages (IV use) 
- “Ready-to-use” phage cocktails for “easy-to-treat” bacterial infections (commercial use) Prêt-à-porter
- Personalize phage therapy in patients with severe bacterial infection Sur-mesure



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

- Use GMP or 'GMP-like' bacteriophages (IV use) 
- “Ready-to-use” phage cocktails for “easy-to-treat” bacterial infections (commercial use) Prêt-à-porter
- Personalize phage therapy in patients with severe bacterial infection Sur-mesure 
- Academic collaborations (lab. and clinic) to phage banking, susceptibility, training and administration
- Particular interest for patients infected with antibiotic-resistant bacteria
- Do not use it alone in bone and joint infection in patients with bone necrosis

# REFERENCE CENTERS FOR THE MANAGEMENT OF BONE AND JOINT INFECTION



● CRIOAc coordonateur ○ Centres correspondants

## “CRIOAc” Network



Adapté de l'article Ferry T, et al.  
Orthop Traumatol Surg Res. 2019 Feb;105(1):185-190.

## CRIOAc Lyon



**Pr. Tristan Ferry**  
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Infectiologist



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



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



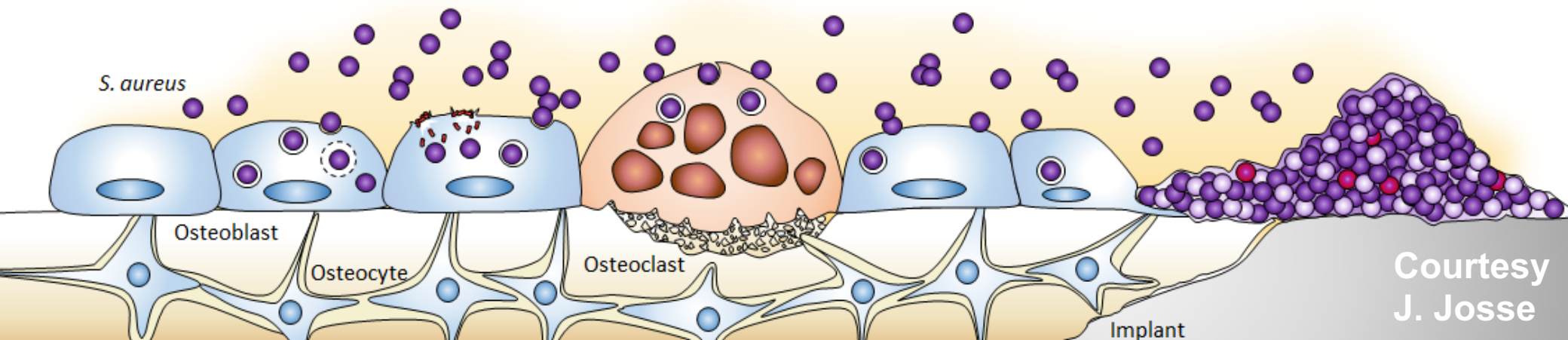
Multidisciplinary management of the patient

Better understanding of the pathophysiology of BJI

Promotion of innovative treatments

# Persisters in chronic BJI

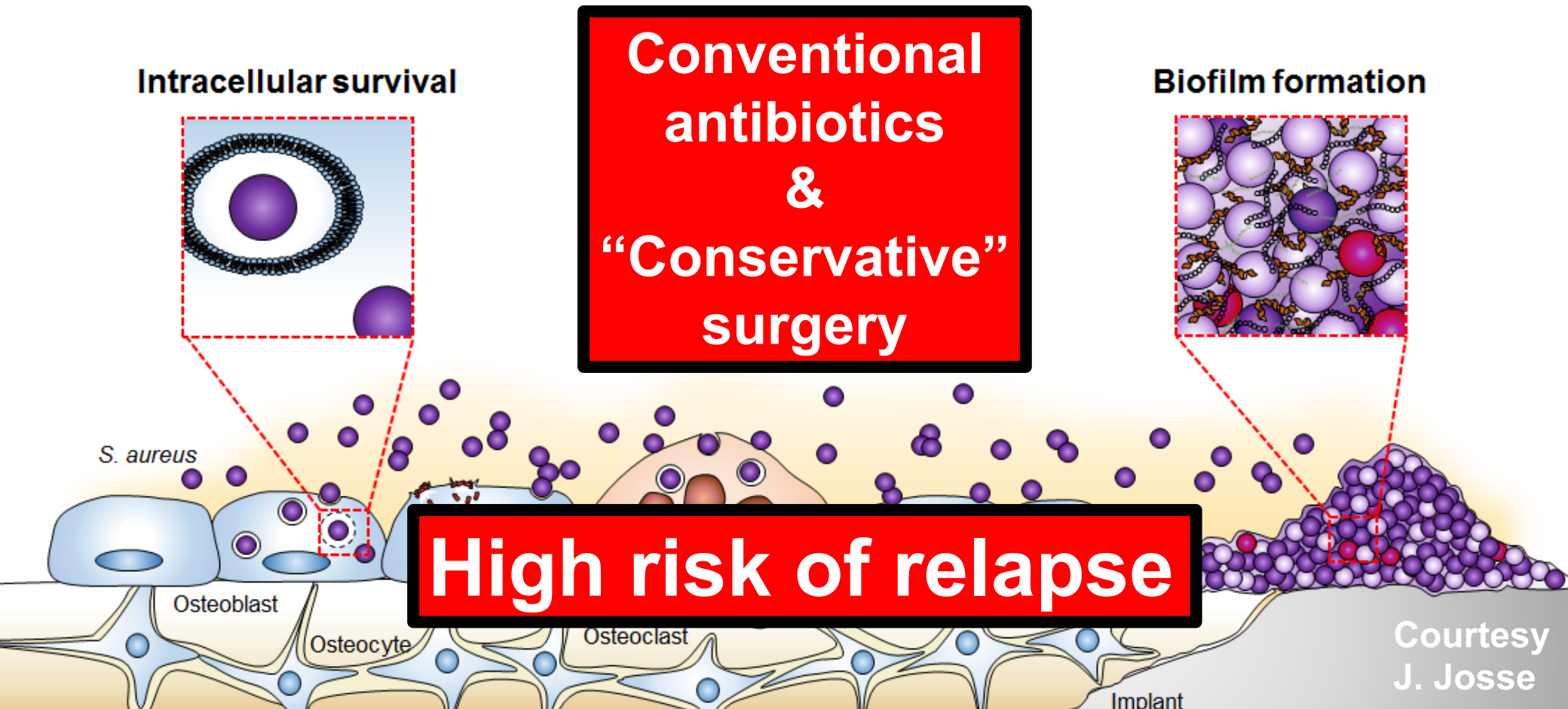
**“Bacterial cells that escape the effects of antibiotics without undergoing genetic change”**



Courtesy  
J. Josse

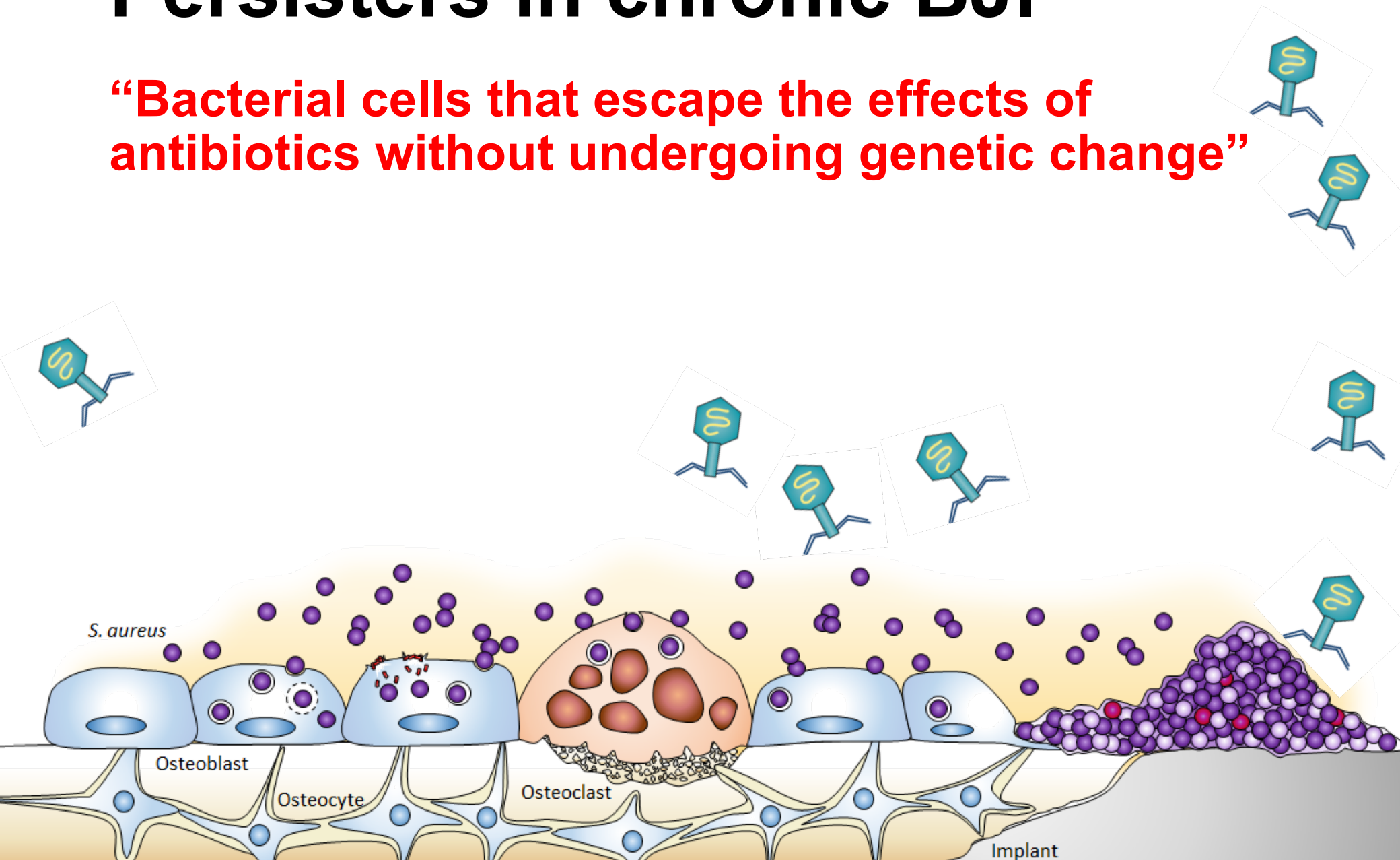
# Persisters in chronic BJI

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# Persisters in chronic BJI

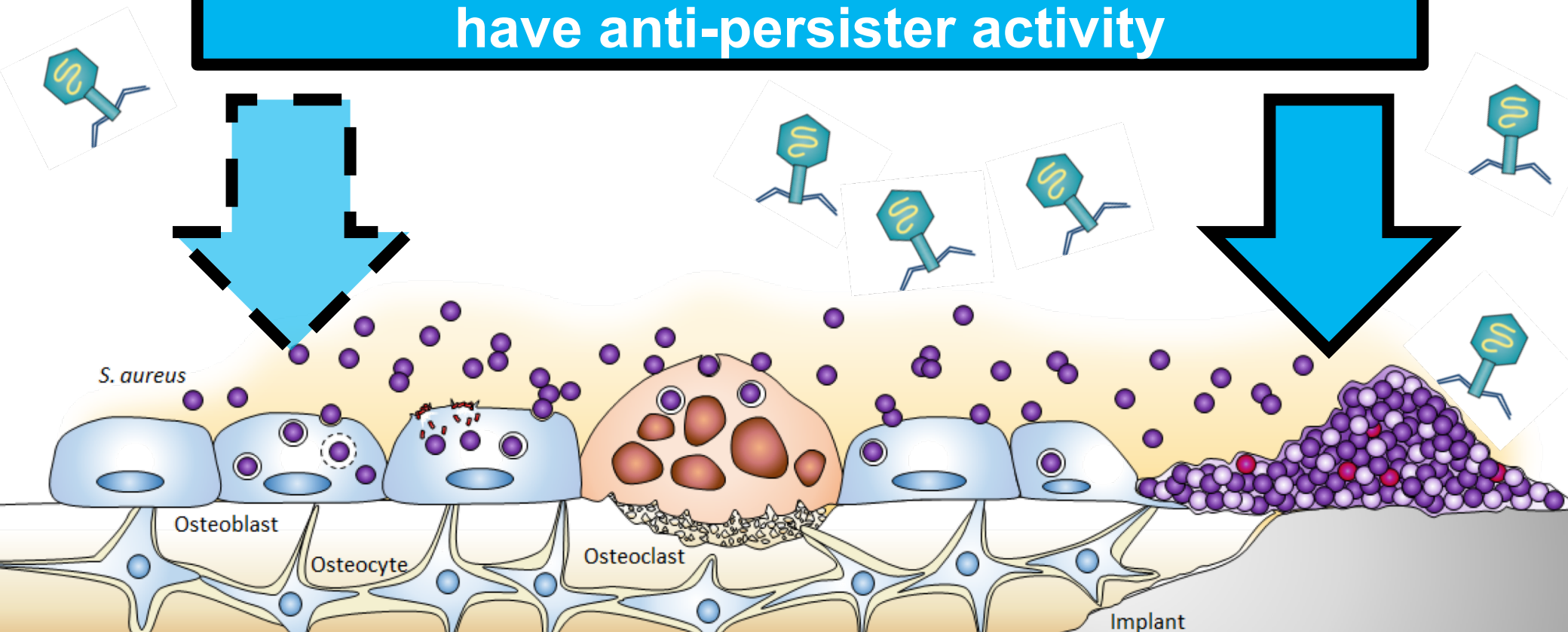
**“Bacterial cells that escape the effects of antibiotics without undergoing genetic change”**



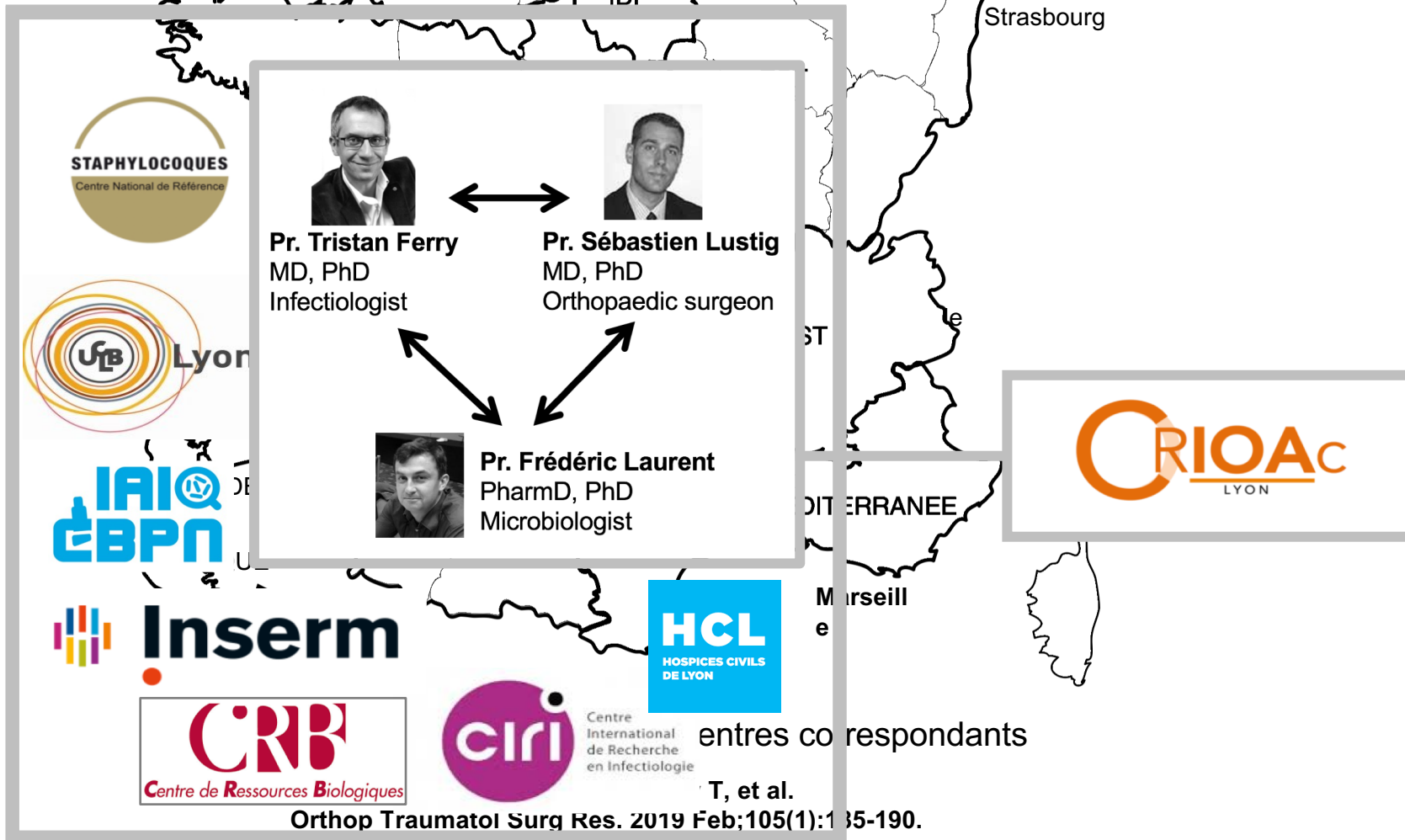
# Persisters in chronic BJI

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

**Bacteriophages and lysins  
have anti-persister activity**



# Lyon Phage team



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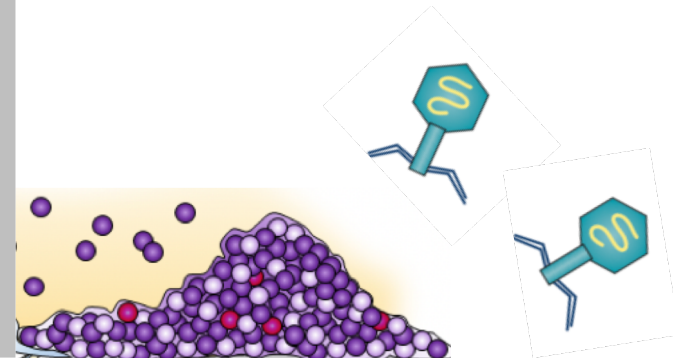
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# Clinical case #4

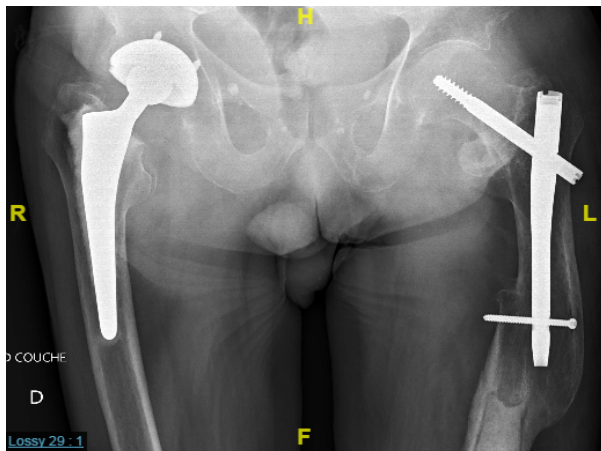
80-year-old man

**Relapsing MSSA** prosthetic  
knee infection

**Failure** under suppressive oral  
antimicrobial therapy

Complex orthopaedic situation  
with past femoral fracture

Impossible to walk (painful knee)





Fistula and  
purulent discharge

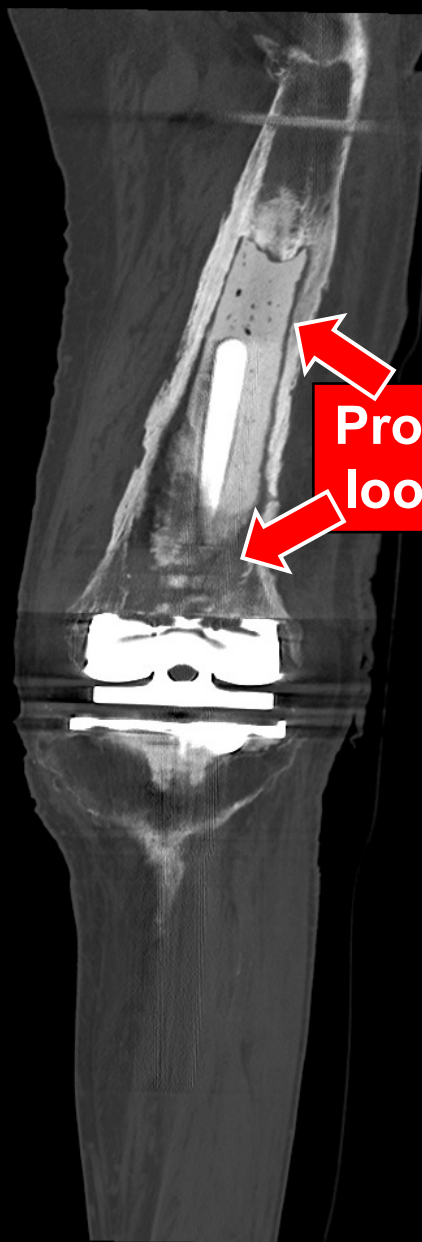


HAL

HAL

HLP

HLP



Prosthesis  
loosening

FPR

FPR

FRA

FRA

# Clinical case #4

Amputation  
(but not feasible !) ?



VS.



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

New DAIR + innovative approach to disrupt biofilm + suppressive antimicrobial therapy ?

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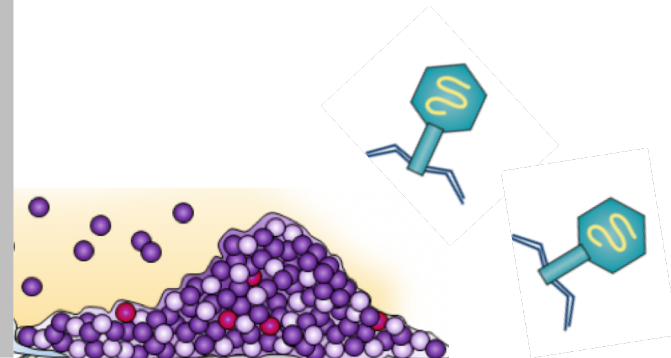
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ID Clinic



**HCL**  
HOSPICES CIVILS  
DE LYON



Surgery



**HCL**  
HOSPICES CIVILS  
DE LYON

Lab



**HCL**  
HOSPICES CIVILS  
DE LYON

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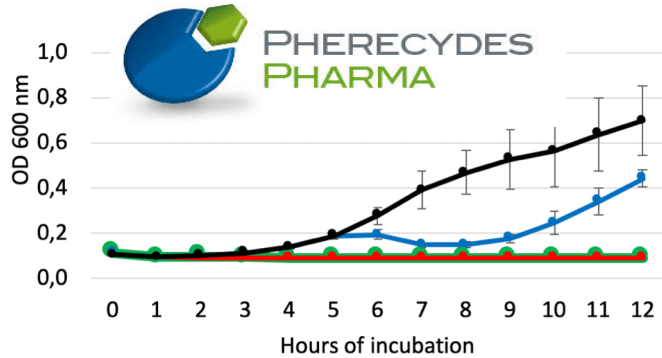
Agence nationale de sécurité du médicament  
et des produits de santé

French Health Authority

Pharmacy



**HCL**  
HOSPICES CIVILS  
DE LYON



Phagogram  
Selection of active bacteriophages



Active *S. aureus* Bactériophages



1 mL

Phage A



1 mL

Phage B



1 mL

Phage C



ID Clinic

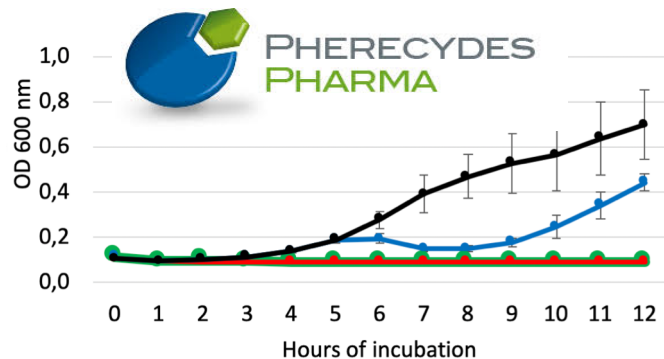


**HCL**  
HOSPICES CIVILS  
DE LYON

Surgery



**HCL**  
HOSPICES CIVILS  
DE LYON



Lab



**HCL**  
HOSPICES CIVILS  
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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

# 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.

# Clinical case #5

74-year-old man

Melanoma treated with anti-PD1

Catheter-related ***P. aeruginosa***  
**bacteriemia** in January 2018

Spinal pain summer 2018

**Spondylodiscitis** with **spinal**  
**abscess**

**Pandrug-resistant** ***P. aeruginosa***  
**in culture!**



# Clinical case #5

74-year-old man

Melanoma treated with anti-PD1

Catheter-related *P. aeruginosa*  
bacteriemia in January 2018

Spinal pain summer 2018

Spondylodiscitis with spinal  
abscess

Pandrug-resistant *P. aeruginosa*  
in culture!

|                                | <i>Pseudomonas aeruginosa</i><br>CMI (mg/l) |
|--------------------------------|---|
| Ticarcilline + Ac. Clav        | R (> 64)                                    |
| Pipéracilline                  | R (> 64)                                    |
| Pipéracilline + Tazobactam     | R (> 64)                                    |
| Ceftazidime                    | R (> 32)                                    |
| Céfépime                       | R (> 32)                                    |
| Aztréonam                      | R (> 32)                                    |
| Imipénème                      | R (> 8)                                     |
| Meropeneme                     | R (> 8)                                     |
| Gentamicine                    | R (> 8)                                     |
| Tobramycine                    | R (> 8)                                     |
| Amikacine                      | R (> 32)                                    |
| Ciprofloxacin                  | R (> 2)                                     |
| Lévofloxacin                   | R (> 4)                                     |
| Cotrimoxazole                  | R   |
| Colistine                      | S (8) ⇒ R                                   |
| Colistine (Etest)              | S<br>E-test : 1 ⇒ R                         |
| Ceftolozane-tazobactam (Etest) | R<br>E-test : > 256                         |
| Ceftazidime-Avibactam (Etest)  | R<br>E-test : 64                            |



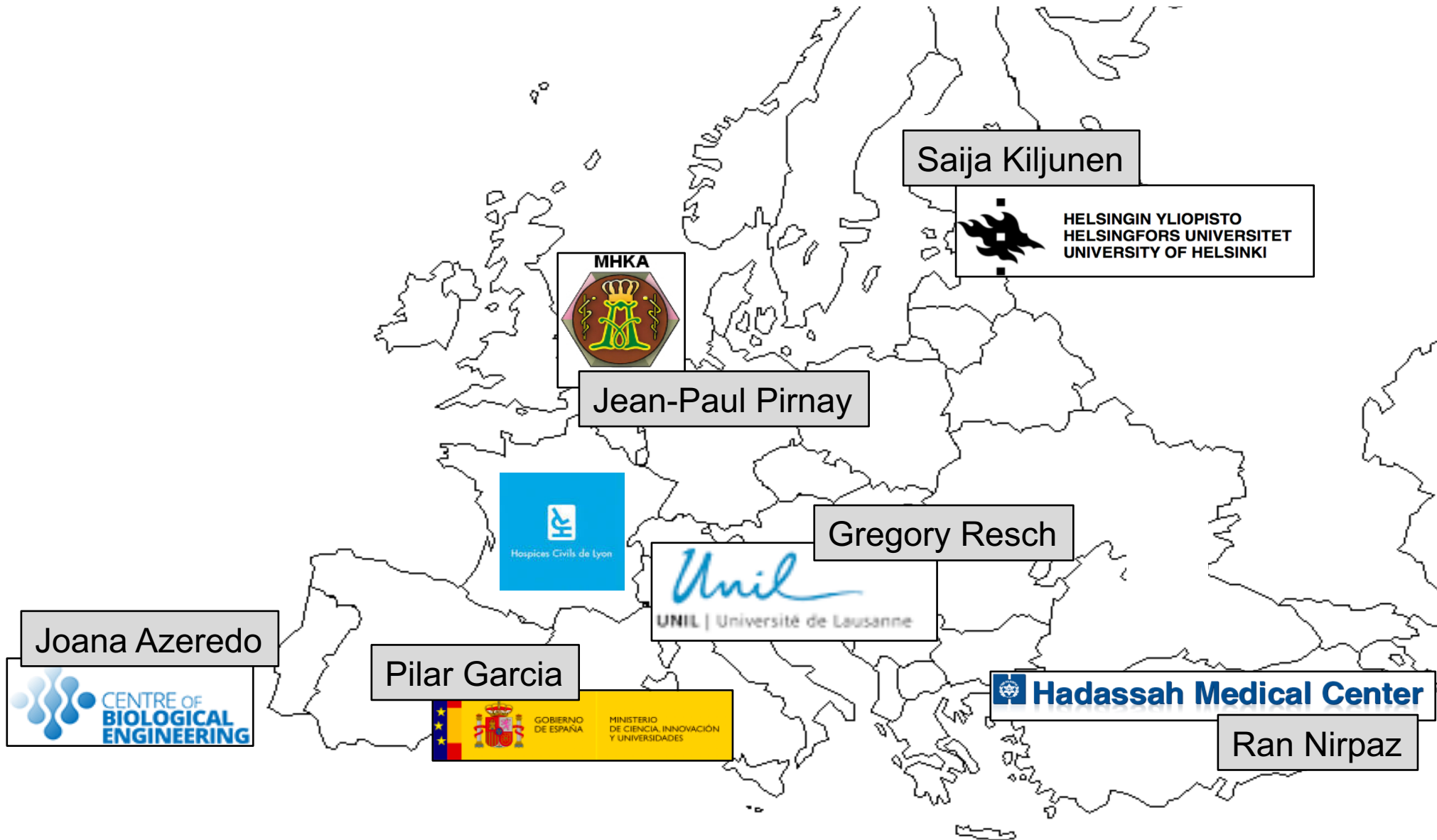
PHERECYDES  
PHARMA



AMPLIPHI  
BIOSCIENCES CORPORATION

The strain was also **spontaneously**  
**resistant to GMP bacteriophages !!!**

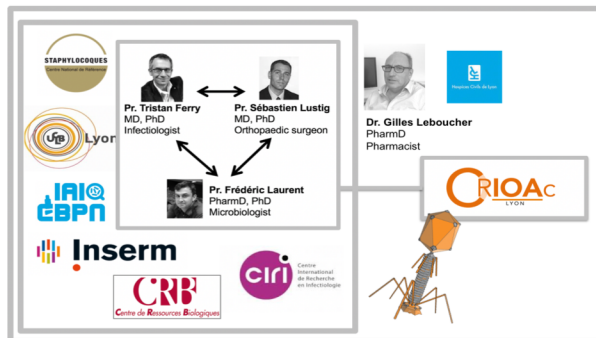
# Potential European academic collaborations



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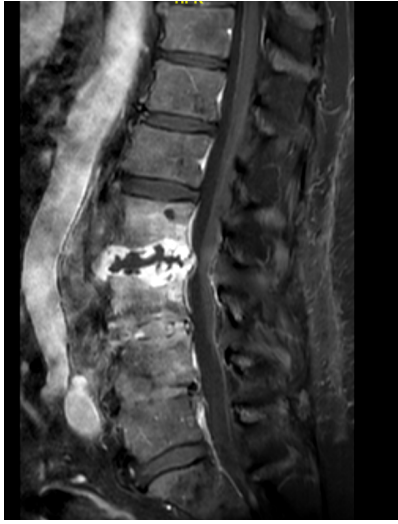
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French Health Authority

## Lyon Phage team



# Potential European academic collaborations

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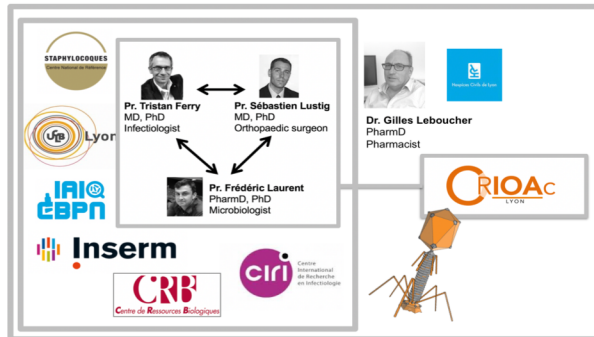


Jean-Paul Pirnay



Gregory Resch

## Lyon Phage team

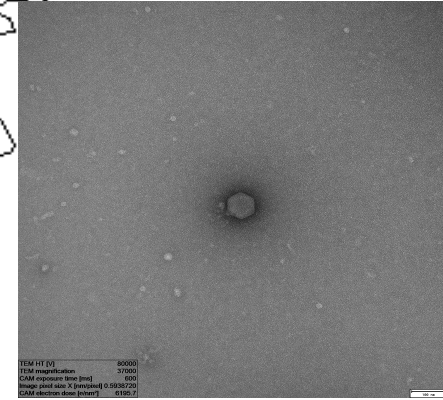


# Potential European academic collaborations

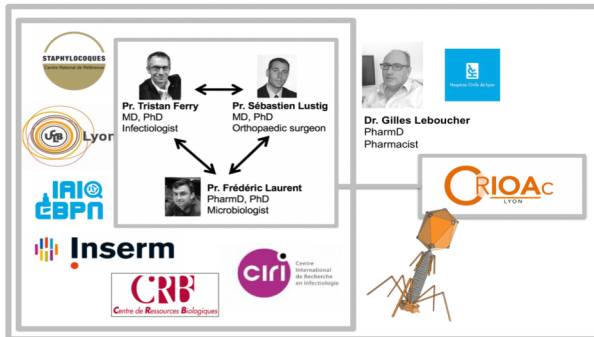
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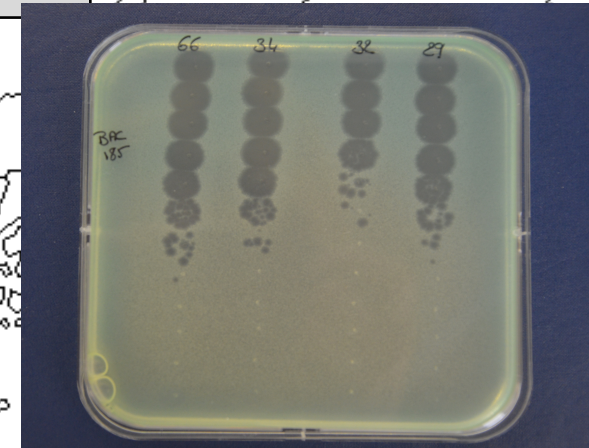
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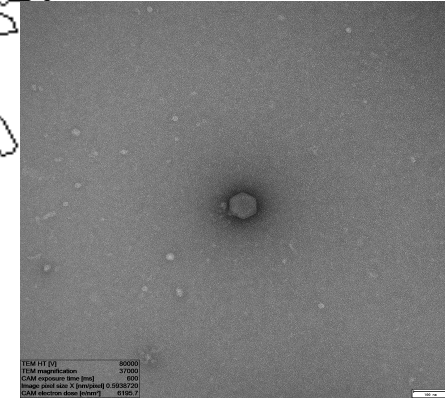


Gregory Resch

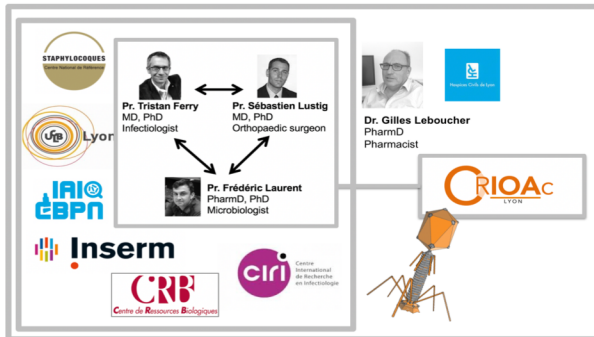


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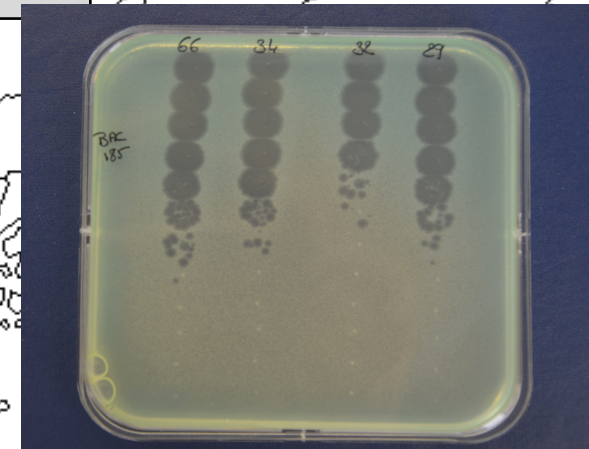
**Lyon Phage team**



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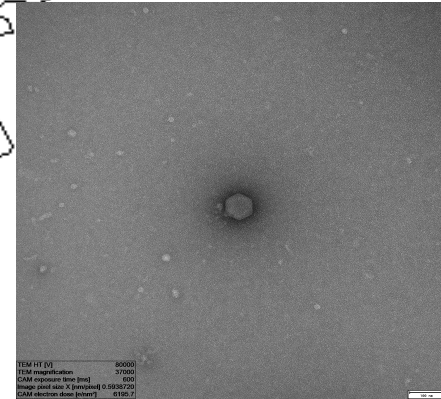
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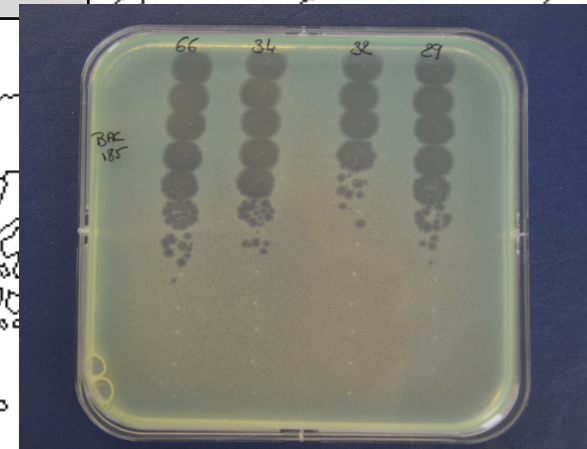
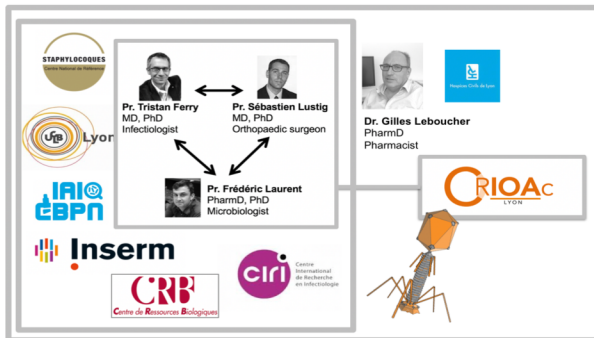
Lyon Phage team



Jean-Paul Pirnay



Gregory Resch



# 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



**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.

# Lyon Phage team



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Infectiologist



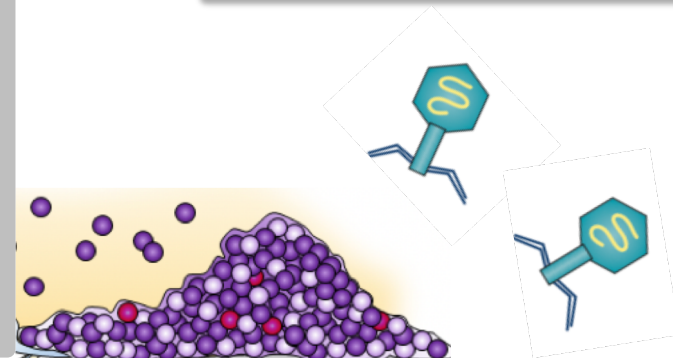
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# Conclusion



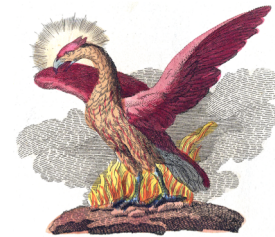
- Crucial need for (alternatives) **additional therapies to antibiotics** to maximise clinical success in complex bacterial infections



# Conclusion



- Crucial need for (alternatives) **additional therapies to antibiotics** to maximise clinical success in complex bacterial infections
- Phage therapy is a **Phoenix**
- Don't forget **Lessons from 20<sup>th</sup> century**



# Conclusion



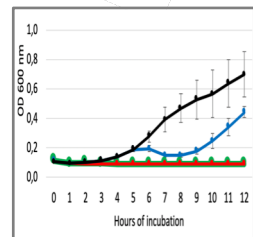
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- Phage therapy is a **Phoenix**
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- Develop and use **GMP bacteriophages** (phages 2.0)
- Industry / health authority / academic **collaborations**



# Conclusion



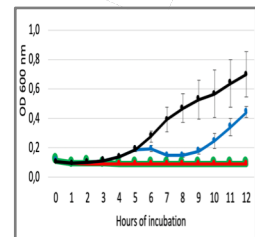
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- Don't forget **Lessons from 20<sup>th</sup> century**
- Develop and use **GMP bacteriophages** (phages 2.0)
- Industry / health authority / academic **collaborations**
- Reference (regional or national) clinical centers to determine **relevant indications**
- Need for **Phage discovery**, **banking**, **susceptibility**, to personalized the therapy



# Conclusion



- Crucial need for (alternatives) **additional therapies to antibiotics** to maximise clinical success in complex bacterial infections
- Phage therapy is a **Phoenix**
- Don't forget **Lessons from 20<sup>th</sup> century**
- Develop and use **GMP bacteriophages** (phages 2.0)
- Industry / health authority / academic **collaborations**
- Reference (regional or national) clinical centers to determine **relevant indications**
- Need for **Phage discovery**, **banking**, **susceptibility**, to personalized the therapy
- **Need for national phage platform**



# *Lyon BJI Study group*

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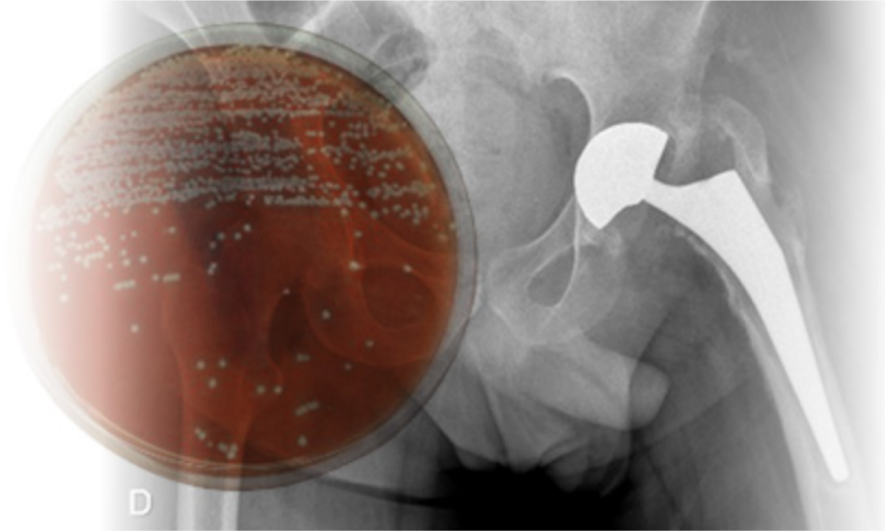
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