

# Place des phages (de la phagothérapie) dans les infections ostéoarticulaires

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Regional referral center for the management of complex bone and joint infection  
Centre de Référence des IOA complexes de Lyon (CRIOAc Lyon)



# Centre de Référence des Infections Ostéo-Articulaires complexes CRIOAc

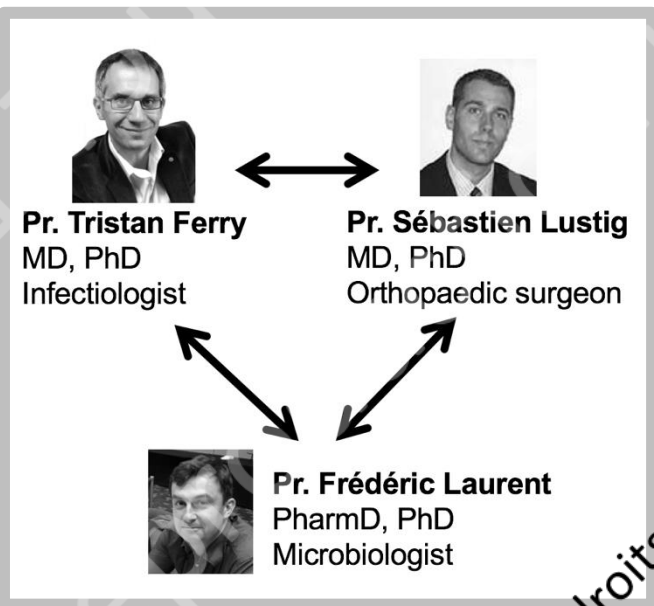


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# Centre de Référence des Infections Ostéo-Articulaires complexes CRIOAc

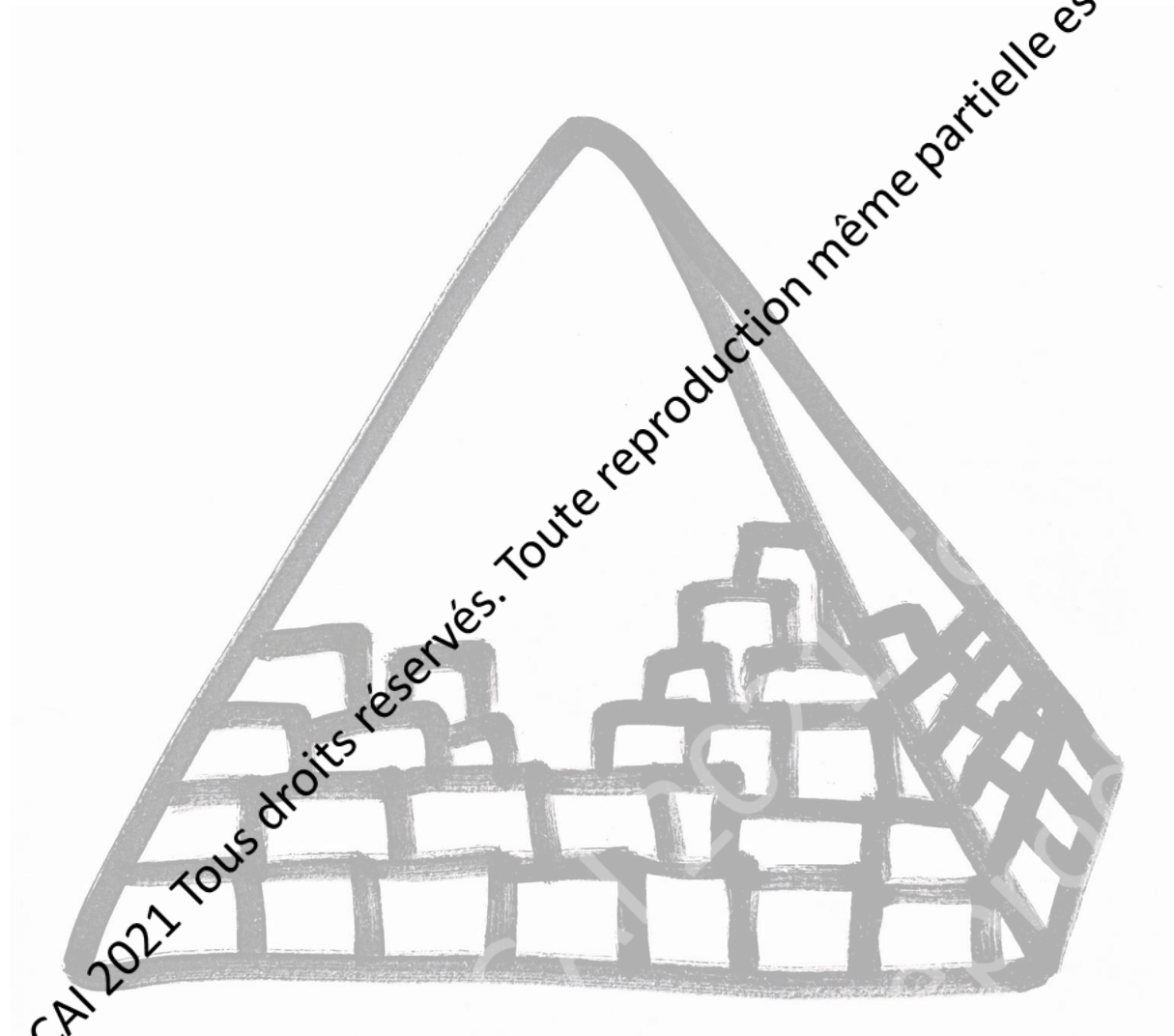


## Réseau des CRIOAc



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# Personalized medicine for BJI



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# Personalized medicine for BJI

**OPTIMAL  
SEPTIC  
SURGERY**



**TARGETED AND  
OPTIMAL  
ANTIMICROBIAL  
THERAPY**

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# Personalized medicine for BJI

**ADJUVANT  
INNOVATIVE ANTI-  
INFECTIVE AGENTS**

Antibiotic-loaded  
PMMA cements

Antibiotic-loaded  
bone  
substitutes

Bacteriophages

Bacteriophage-derived  
lysins

New antibiotics targeting  
the biofilm

**OPTIMAL  
SEPTIC  
SURGERY**

**TARGETED AND  
OPTIMAL  
ANTIMICROBIAL  
THERAPY**

New antibiotics  
usable for SAT

Subcutaneous  
personalized SAT

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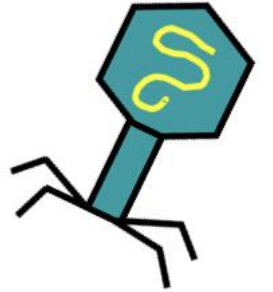
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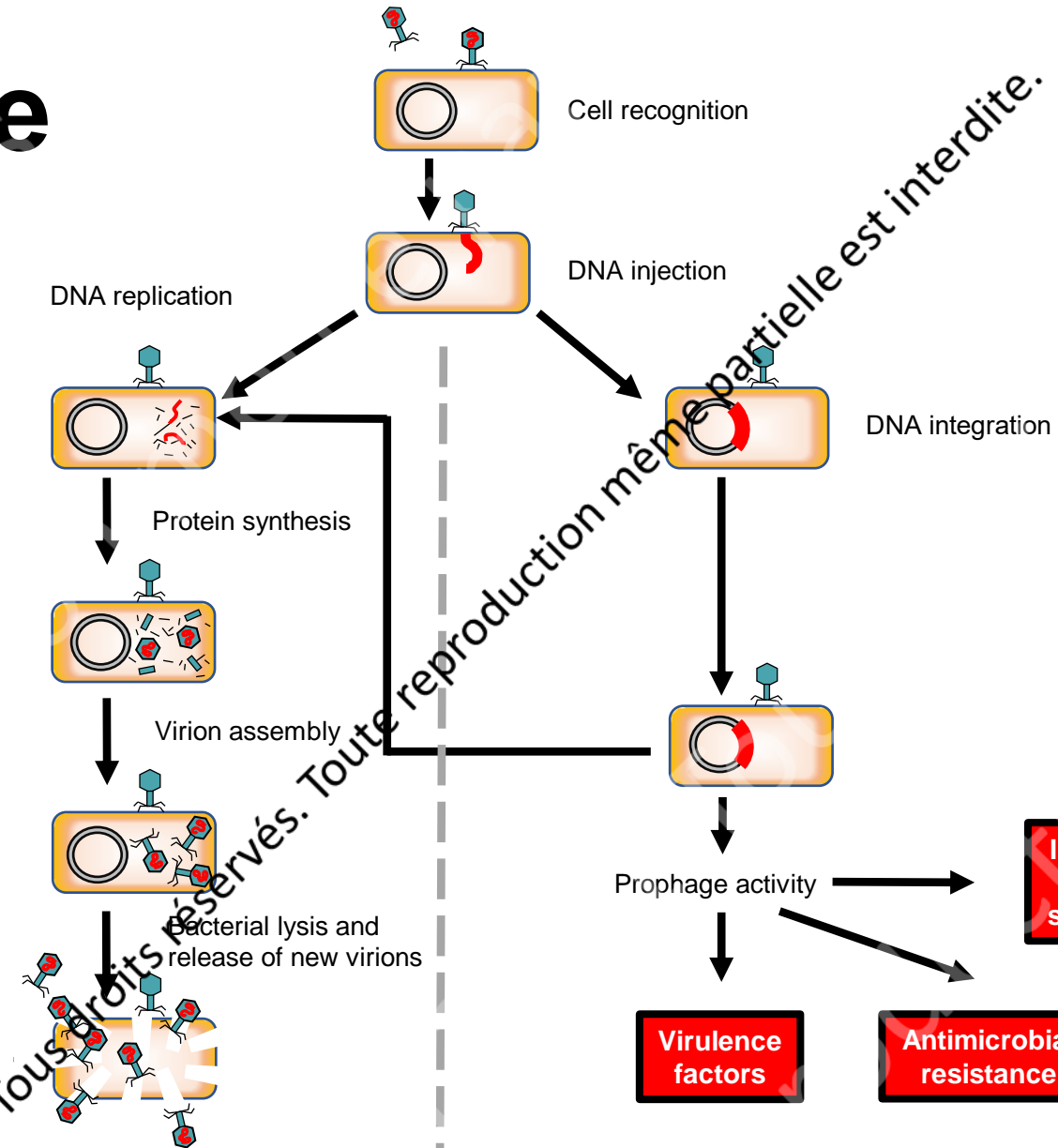
# What is a « bacteriophage » ?

- 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.





# The phage life



**Lytic cycle**

Self-maintained bacterial lysis

**Lysogenic cycle**

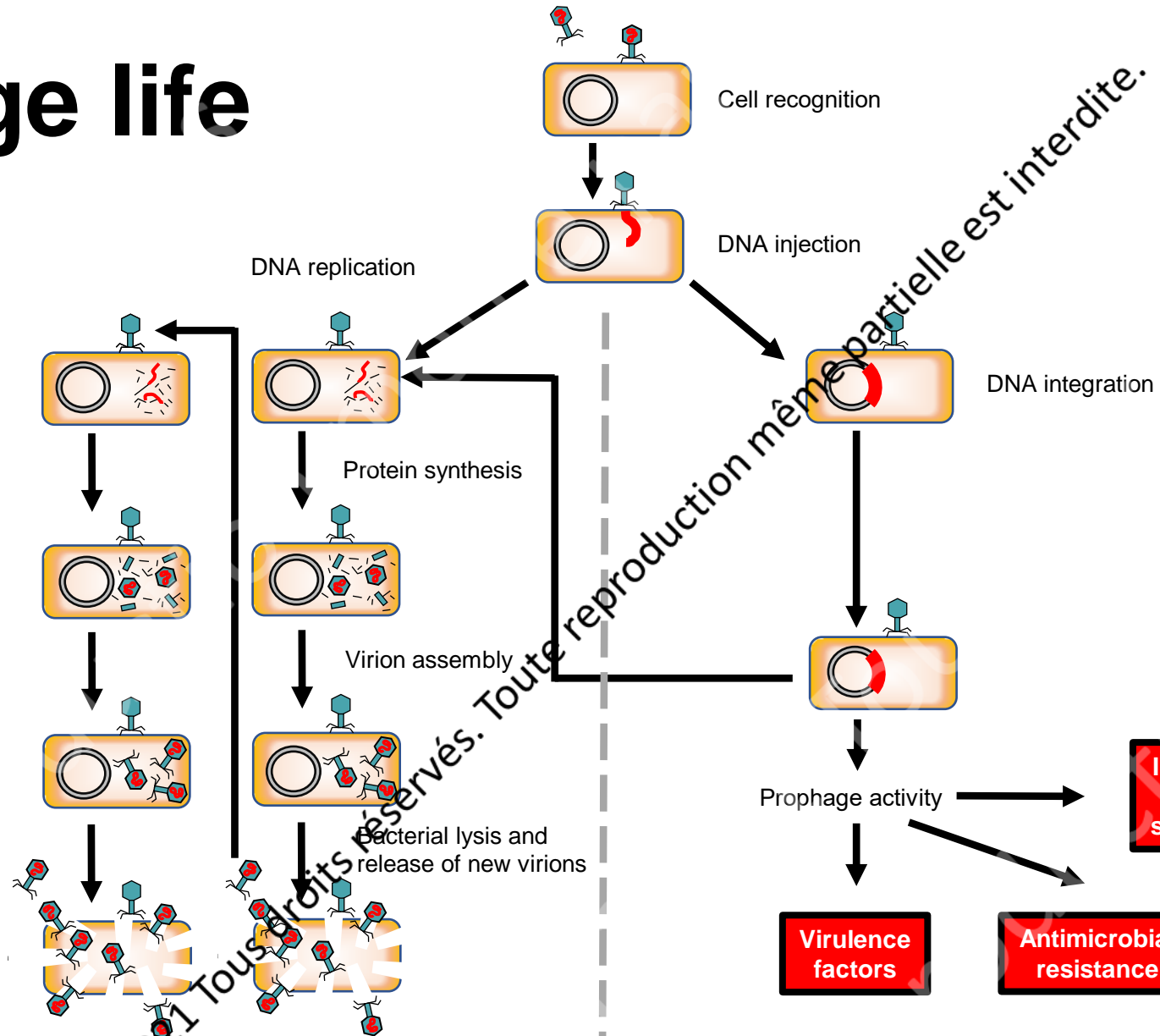
Bacterial genetic remodeling

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# The phage life



## Lytic cycle

Self-maintained bacterial lysis

## Lysogenic cycle

Bacterial genetic remodeling

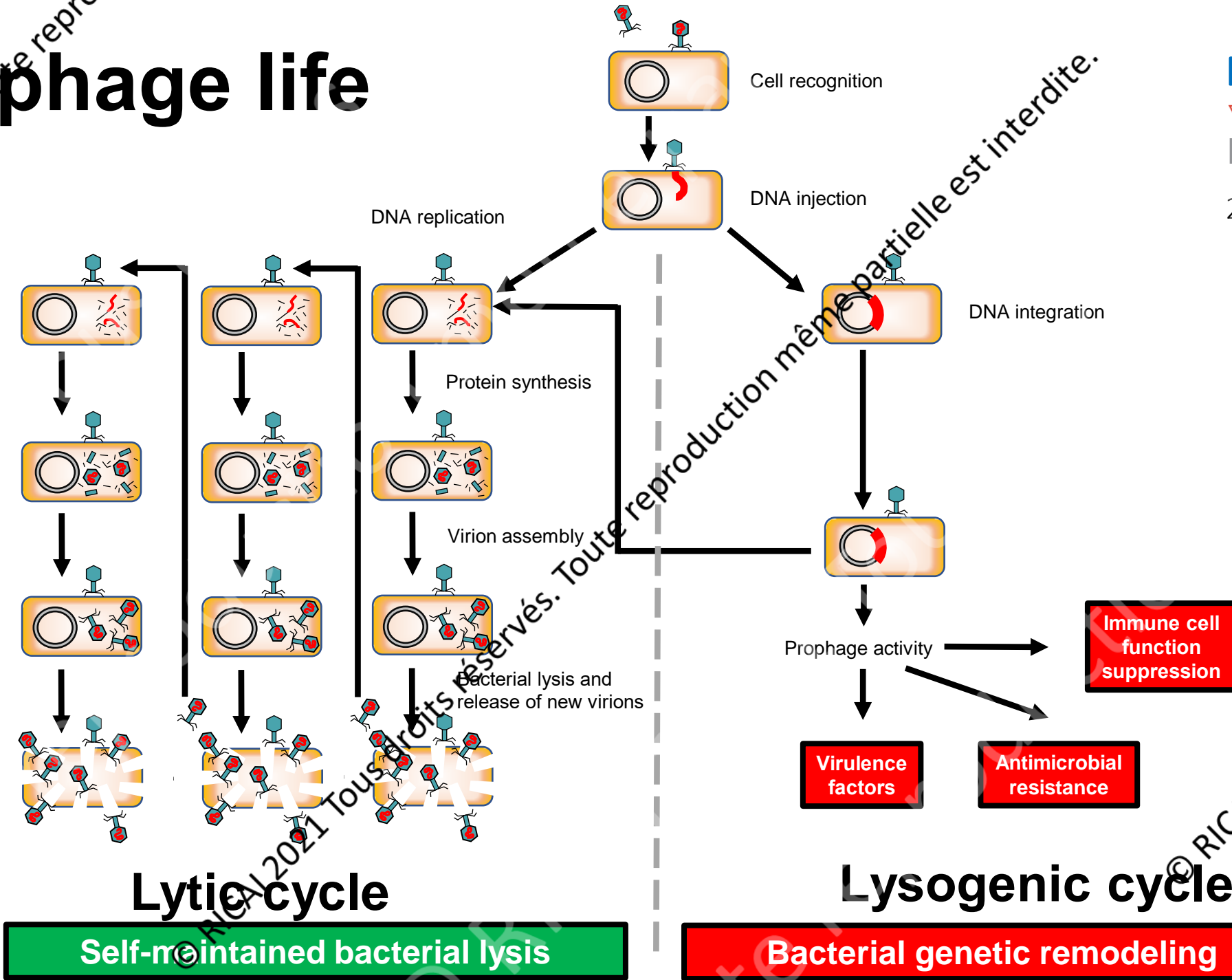
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# The phage life

Ferry T. et al.  
**Virologie**  
2020;24(1):49-56



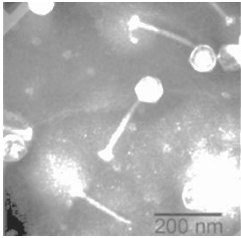
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# Only lytic phages have to be used

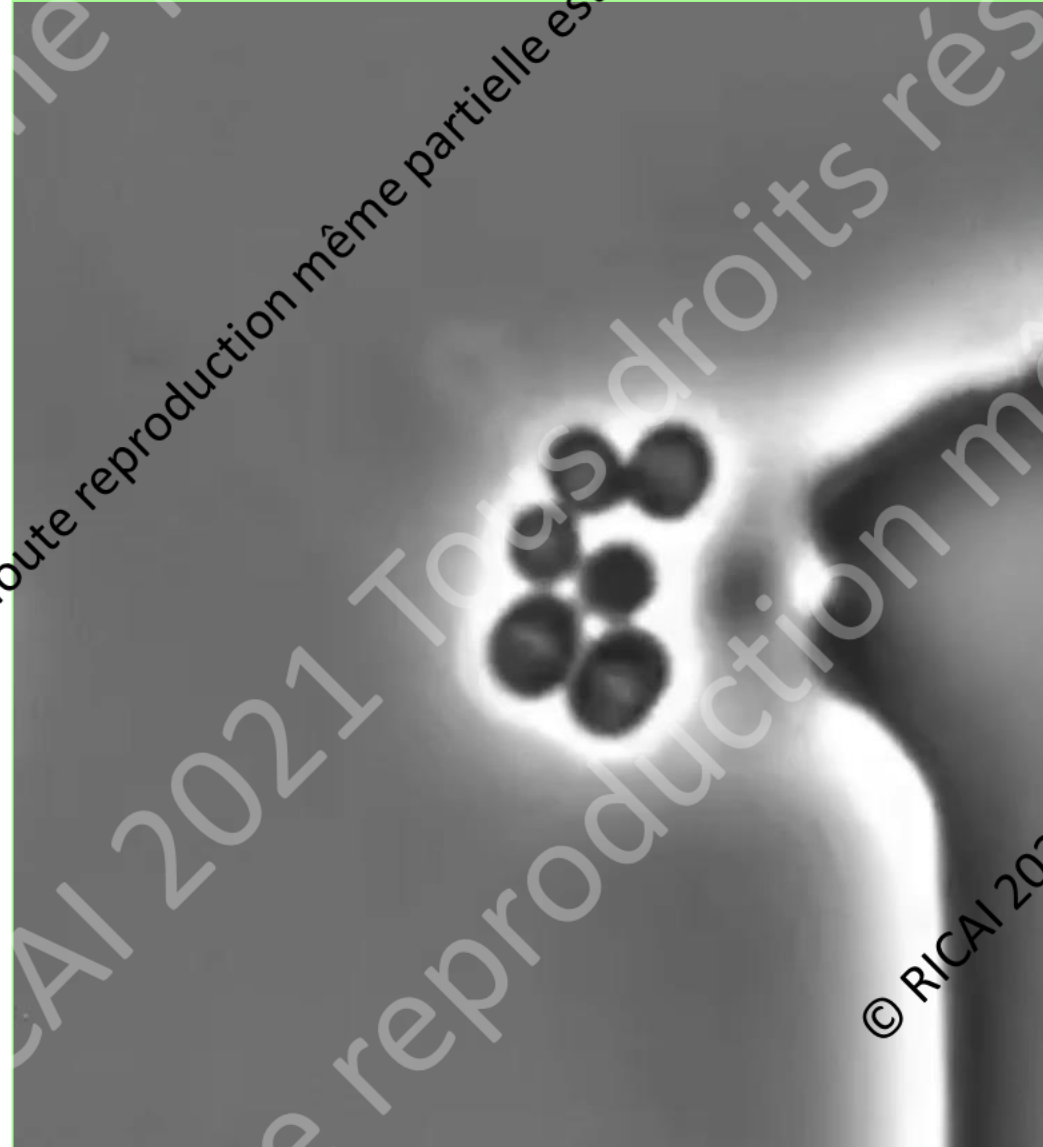
***S. aureus* being lysed  
by the Sa2 phage**



Bacterial DNA  
appeared in green

Courtesy Pascal Maquin  
Luciano Marraffin Lab

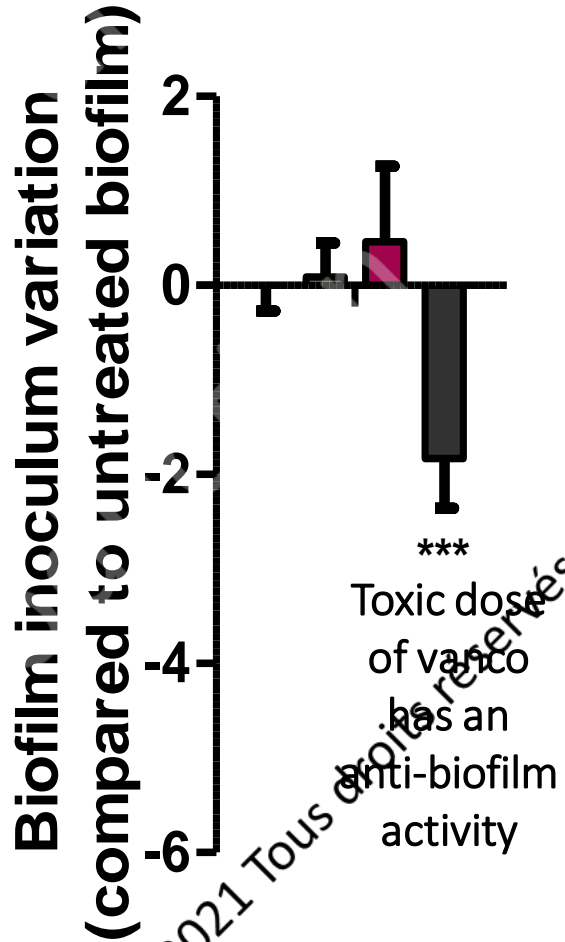
THE ROCKEFELLER UNIVERSITY







# Phages have antibiofilm activity

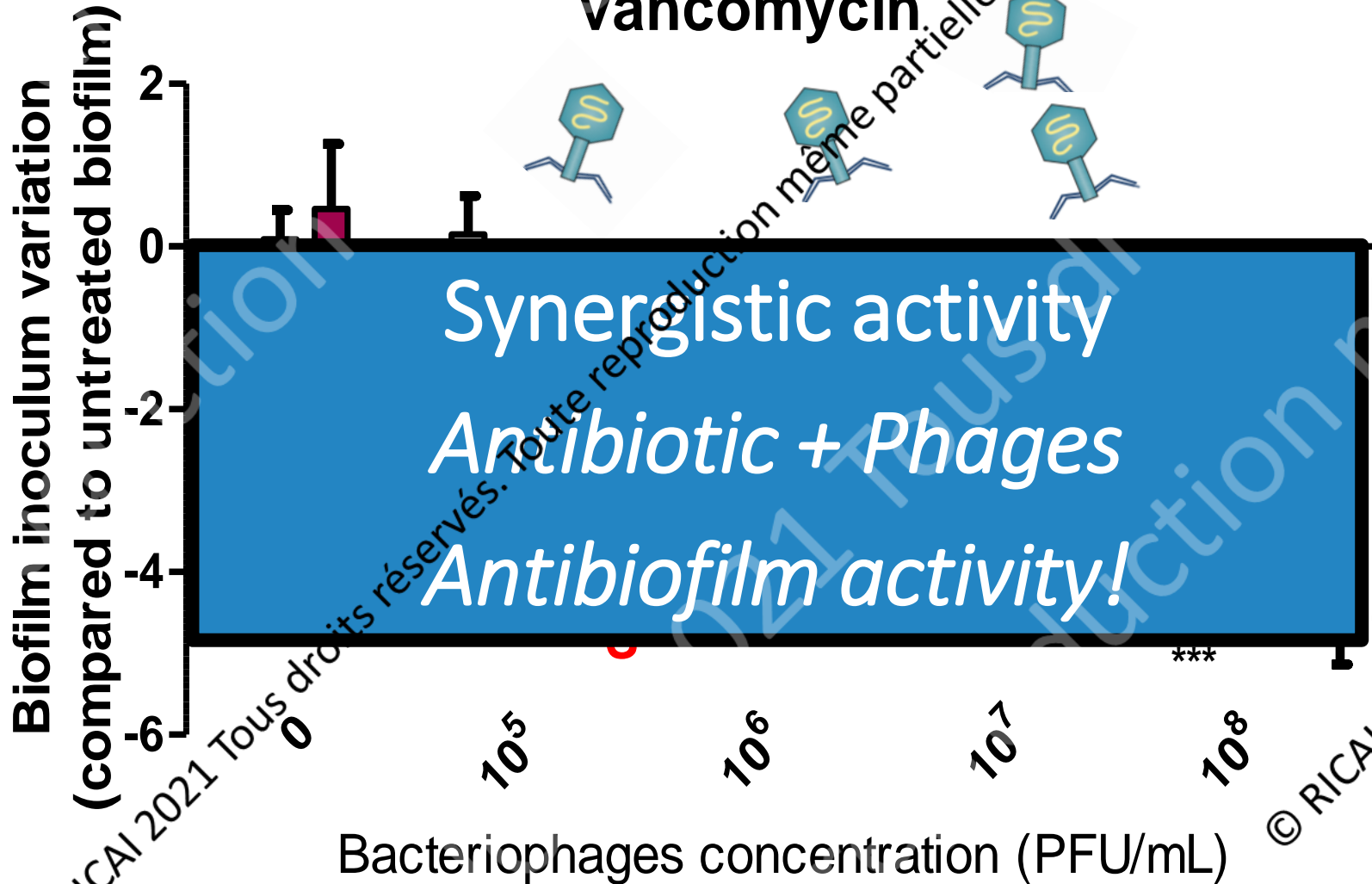
vancomycin

- No Antibiotic
- MIC
- C<sub>bone</sub> (4\*MIC)
- 10\*MIC



# Phages have antibiofilm activity

-  No Antibiotic
-  MIC
-  C<sub>bone</sub> (4\*MIC)
-  10\*MIC



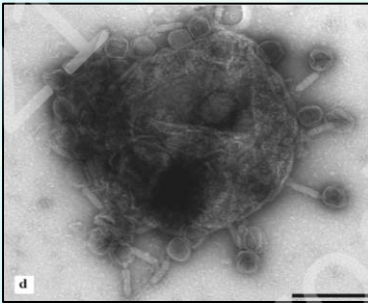
*C. Kolenda et al. Antimicrob Agents Chemother 2019*



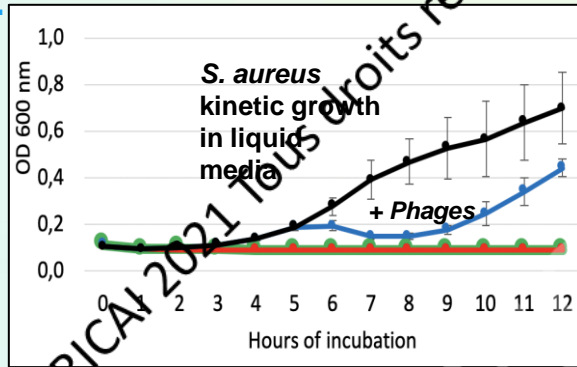
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# Only purified lytic phages have to be used



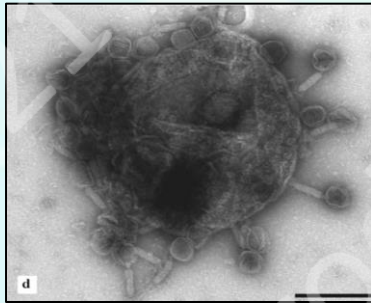
Merabishvili et al.  
*PLoS ONE* 2009



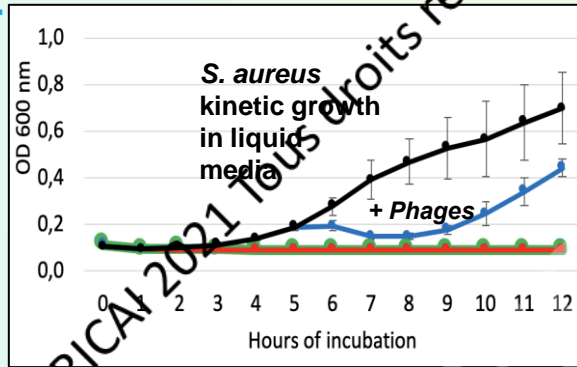
Ferry et al. *OFID* 2018



# Only purified lytic phages have to be used



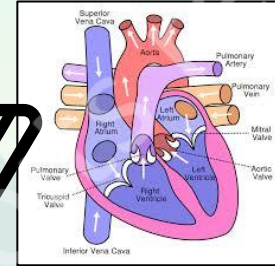
Merabishvili et al.  
PloS ONE 2009



Ferry et al. OFID 2018



# Curing bacterial disease

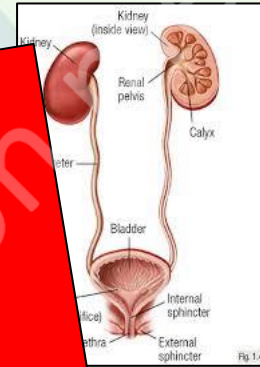


## Prognosis factors

Host  
Comorbidity

**What are the relevant indications for phage therapy?**

Costly ( $\geq 1M\text{€}$ )  
Take time (years)



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# Bone and joint infections

Post-trauma  
long-bone  
osteomyelitis



Surgery  
(debridement & reconstruction)  
Antibiotics

Chronic  
prosthetic-joint  
infection



Surgery  
(prosthesis explantation)  
Antibiotics

Spinal infection  
with abscess and  
bone destruction



Surgery  
(debridement & stabilization)  
Antibiotics

# Clinical case #1

**54-year-old man**

**Trauma** with open fracture

Post-trauma tibial *S. aureus*  
**osteomyelitis**

Surgical debridement

Antibiotics

Failure

Management in Georgia for  
receiving **phage therapy**  
bacteriophages 10 years ago

Failure



# Clinical case #1

**54-year-old man**

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Post-trauma tibial *S. aureus*  
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Management in Georgia for  
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bacteriophages 10 years ago

Failure



# Clinical case #1

54-year-old  
Trauma

**Sclerotic bone with biofilm  
requiring surgery**

Post-traumatic  
**osteomyelitis**

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

Surgical debridement

**MAJOR BIOLOGICAL LIMIT:**

**Bacteriophages**

**have not the ability to:**

**perform bone debridement**

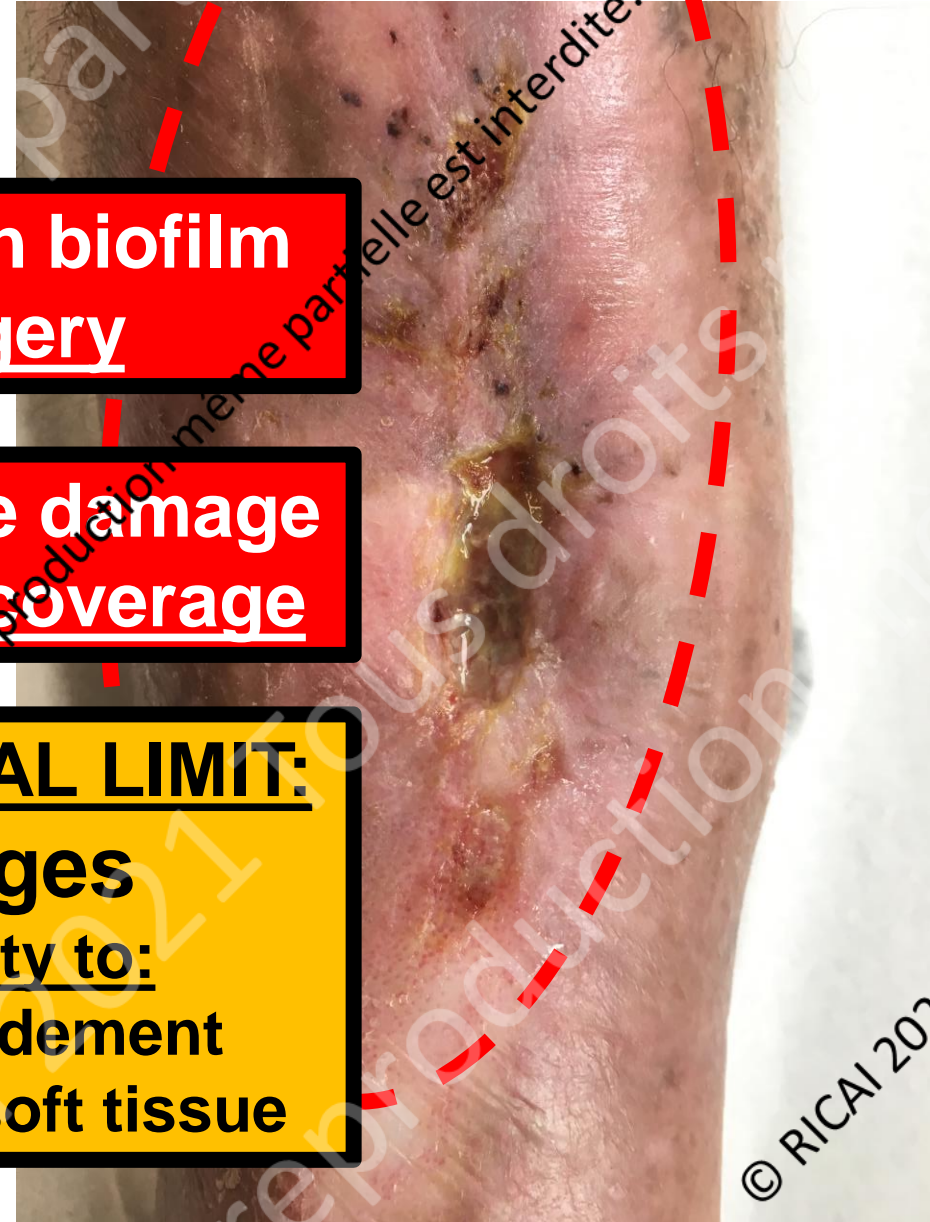
**regenerate skin and soft tissue**

Management

received

bacteriophages 10 years ago

Failure



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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# Bone and joint infections

Post-trauma  
long-bone  
osteomyelitis



Surgery  
(debridement & reconstruction)  
Antibiotics

Chronic  
prosthetic-joint  
infection



Surgery  
(prosthesis explantation)  
Antibiotics

Spinal infection  
with abscess and  
bone destruction



Surgery  
(debridement & stabilization)  
Antibiotics

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# Clinical case #2

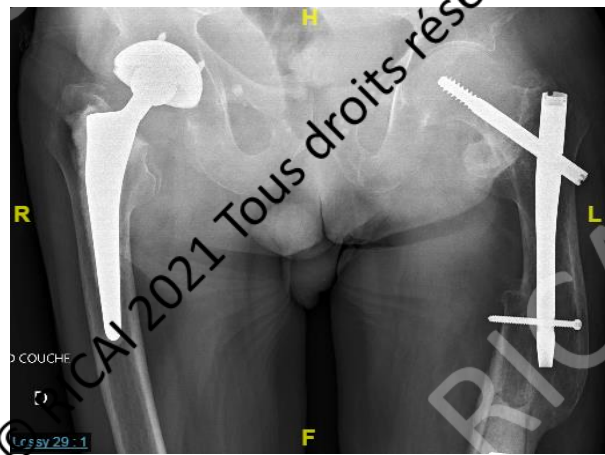
80-year-old man

**Relapsing *S. aureus*** prosthetic left knee infection (past revision)

## **Failure**

Complex orthopaedic situation with past femoral fracture

Impossible to walk (painful knee)



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**Septic arthritis**



**Fistula and purulent discharge**

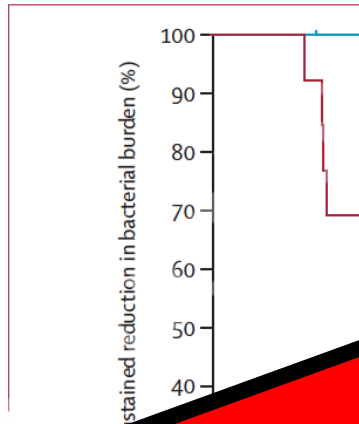


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# Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial

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



**COMPASSIONATE USE**



*Pseudomonas*

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CYDES

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Kaplan-Meier analysis of median time to observe reduction in bacterial burden. HR=hazard ratio. PP1131=cocktail of 12 natural lytic anti-*Pseudomonas aeruginosa* bacteriophages.



# PHOSA

PHARMACIE  
PHERECYDES

PHOSA & Phagothérapie Consortium PHOSA Communication Contact



bpi**france**

**C**RIOAc  
LYON



**Viv**exia  
laboratory



**C**H  
CENTRE HOSPITALIER  
INTERCOMMUNAL  
VILLENEUVE-SAINT-GEORGES  
Lucie & Raymond AUBRAC

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



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

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## “Debridement And Implant Retention” (DAIR)



# “PhagoDAIR”



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

# Clinical case #2

## Post-operative antibiotics:

Daptomycin + Rifampin

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

Levofloxacin + Rifampin

## Then:

Cefalexin as suppressive antimicrobial therapy



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**Favorable outcome  
at 2 years**



*"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.

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**Favorable outcome at 1 year**



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**Favorable outcome  
at 1 year**



# Implementation of a Phage Therapy Center in a CRIOAc

250 km



PHAGEinLYON

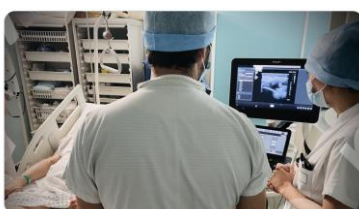


**CMI** CLINICAL MICROBIOLOGY AND INFECTION

FERRY T. et al. 2021

Number of patients	2017	2018	2019	2020	Total
Managed in CRIOAc Lyon	557	594	647	520	2318
For whom a phagogram was performed	7 (1.2%)	10 (1.7%)	17 (2.6%)	23 (4.4%)	57 (2.4%)
For whom phage therapy was done	4 (0.7%)	2 (0.3%)	8 (1.2%)	7 (1.3%)	21 (0.9%)

●○ BJI   ●○ Endocarditis   ●○ Pneumonia



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# Implementation of a Phage Therapy Center in a CRIOAc

250 km



PHAGEinLYON



**CMI** CLINICAL MICROBIOLOGY AND INFECTION

FERRY T. et al. 2021

30 patients in Lyon since 2017

- 27 with phages from



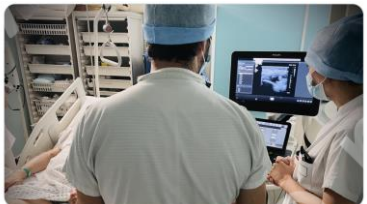
- 3 with phages from



- 26 **BJI** (including 22 **PJI**)
- 3 **endocarditis**
- 1 **PAVM bactériémique**

+ 3 patients managed outside Lyon

●○ BJI   ●○ Endocarditis   ●○ Pneumonia

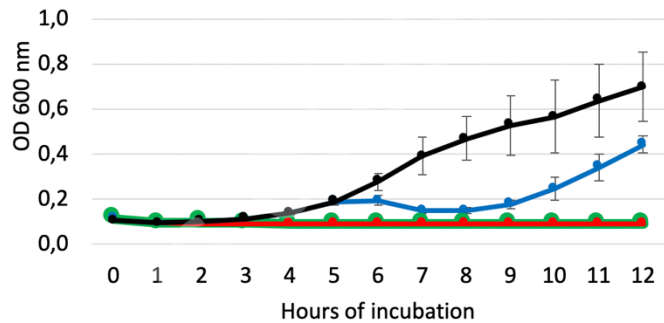


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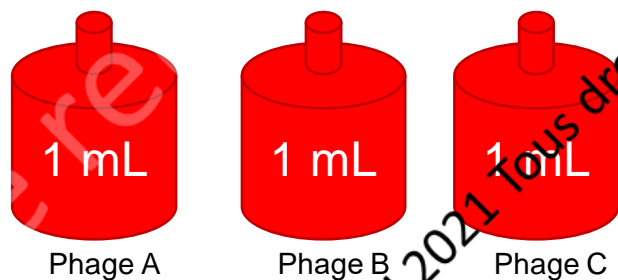
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# PHAGE<sub>in</sub>LYON team



Phagogram  
Selection of active bacteriophages

## Active GMP *S. aureus* Bactériophages



**ID Clinic**  
HCL HOSPICES CIVILS DE LYON

**Surgery**  
HCL HOSPICES CIVILS DE LYON

CRIOAC LYON  
ADJUVANT INNOVATIVE ANTI-INFECTIVE AGENTS  
OPTIMAL SEPTIC SURGERY MULTIDISCIPLINARY TEAM  
TARGETED AND OPTIMAL ANTIMICROBIAL THERAPY

**Lab**  
HCL HOSPICES CIVILS DE LYON

Under the supervision of  
  
 Agence nationale de sécurité du médicament et des produits de santé  
 French Health Authority

**Pharmacy**  
HCL HOSPICES CIVILS DE LYON

Extemporaneous magistral preparation of the mix of bacteriophages



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# Bone and joint infections

Post-trauma  
long-bone  
osteomyelitis



Surgery  
(debridement & reconstruction)  
Antibiotics

Chronic  
prosthetic-joint  
infection



Clinical trial  
**PhagoDAIR**  
Janvier 2022

Spinal infection  
with abscess and  
bone destruction



Surgery  
(debridement & stabilization)  
Antibiotics

# Clinical case #3

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 #3

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> 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)
Meropenème	R (> 8)
Gentamicine	R (> 8)
Tobramycine	R (> 8)
Amikacine	R (> 32)
Ciprofloxacine	R (> 2)
Lévofloxacine	R (> 4)
Cotrimoxazole	R
Colistine	S (8) ⇒ R
Colistine (Etest)	S E-test : 1 ⇒ R
Ceftolozane-tazobactam (Etest)	R E-test : > 256
Ceftazidime-Avibactam (Etest)	R E-test : 64

 MARECYDES  
PHARMA

 AMPLI PHI  
BIOSCIENCES CORPORATION

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

# Potential European academic collaborations



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# Potential European academic collaborations

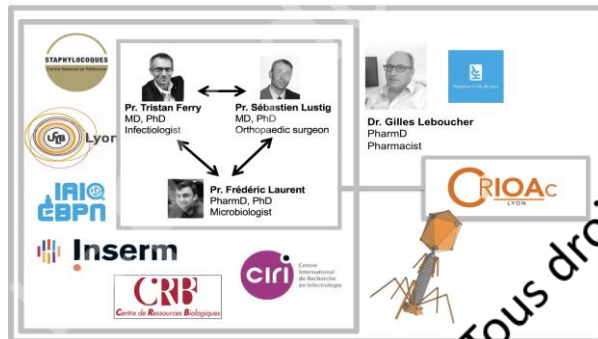
Under the supervision of



Agence nationale de sécurité du médicament et des produits de santé

French Health Authority

## Lyon Phage team



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# Potential European academic collaborations

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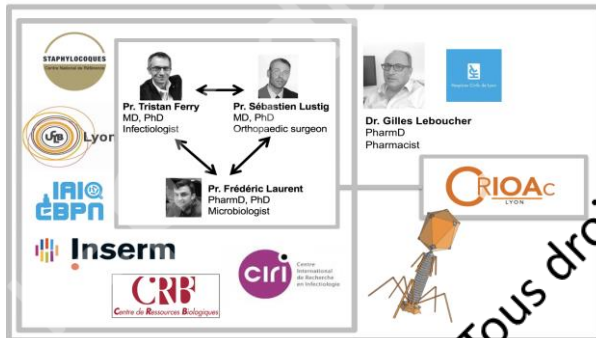


Jean-Paul Pirnay



Gregory Resch

Lyon Phage team



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# Potential European academic collaborations

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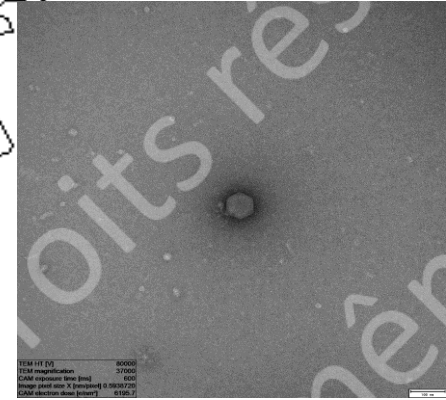


Agence nationale de sécurité du médicament et des produits de santé

French Health Authority

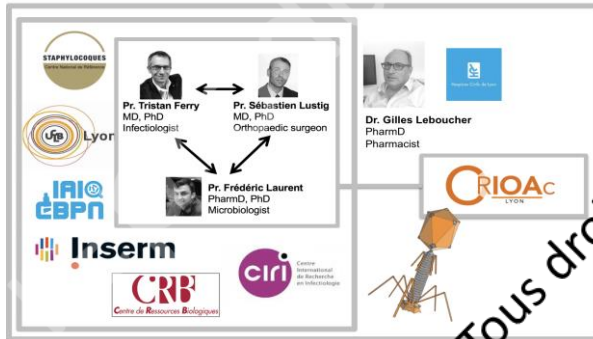


Jean-Paul Pirnay

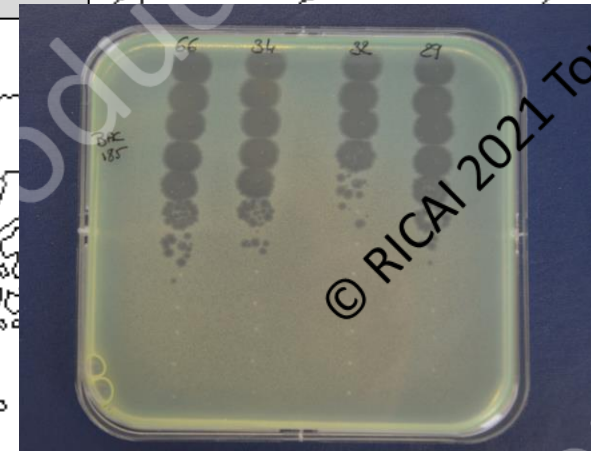


Gregory Resch

Lyon Phage team



UNIL | Université de Savoie

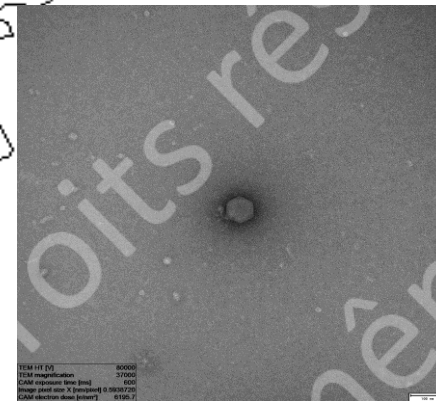


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# Potential European academic collaborations

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Agence nationale de sécurité du médicament  
et des produits de santé  
French Health Authority

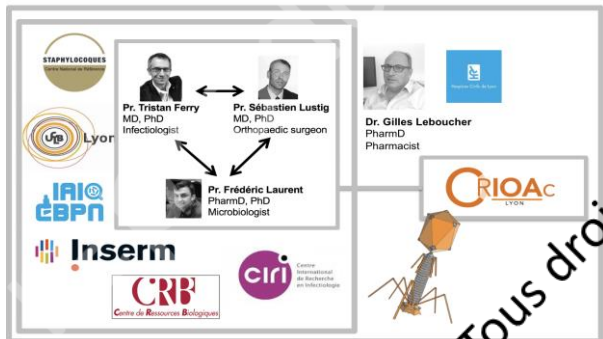


Jean-Paul Pirnay

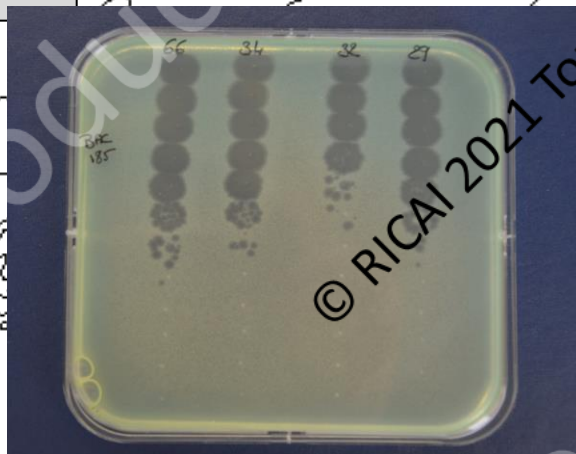


Gregory Resch

Lyon Phage team



The diagram shows the Lyon Phage team structure. At the top, Pr. Tristan Ferry (MD, PhD, Infectiologist) and Pr. Sébastien Lustig (MD, PhD, Orthopaedic surgeon) are connected by a double-headed arrow. Below them, Pr. Frédéric Laurent (PharmD, PhD, Microbiologist) is connected to both. To the right, Dr. Gilles Leboucher (PharmD, Pharmacist) is also connected. The team is affiliated with several institutions: STAPHYLOCOQUES, UFR Lyon, IRI EBPN, Inserm, CRB (Centre de Ressources Biologiques), and CIRI (Centre International de Recherche en Infectiologie).



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# Potential European academic collaborations

Under the supervision of



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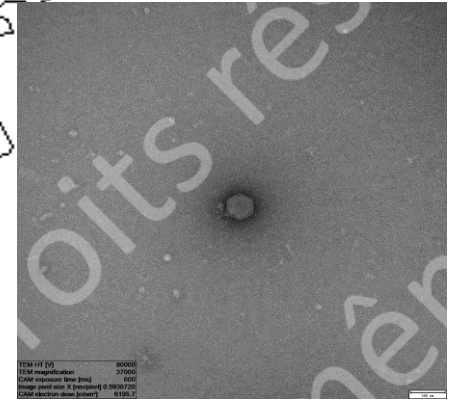
French Health Authority



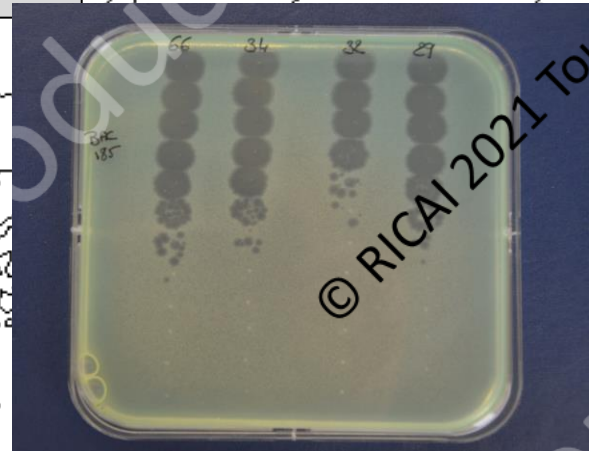
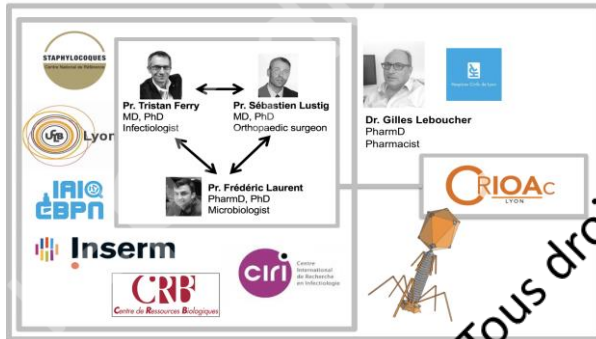
Lyon Phage team



Jean-Paul Pirnay



Gregory Resch



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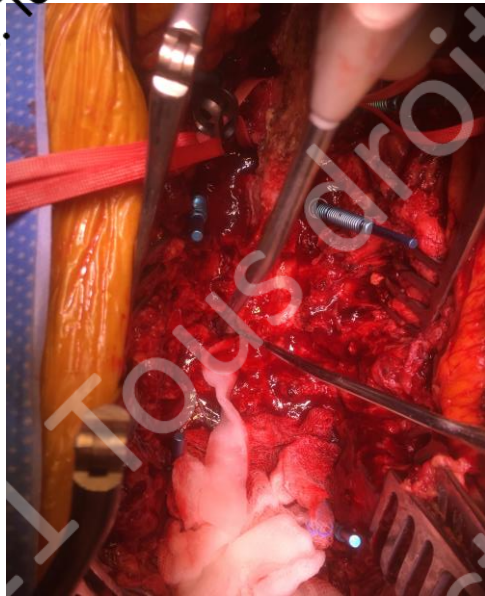
# Potential European academic collaborations

Under the supervision of



Agence nationale de sécurité du médicament et des produits de santé

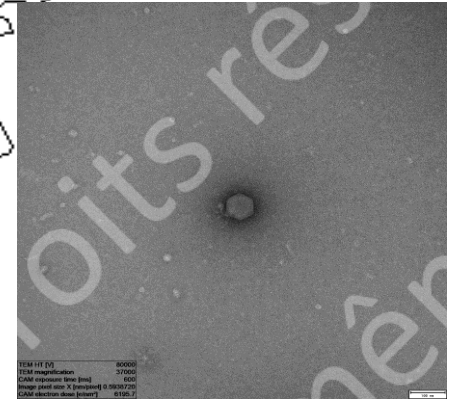
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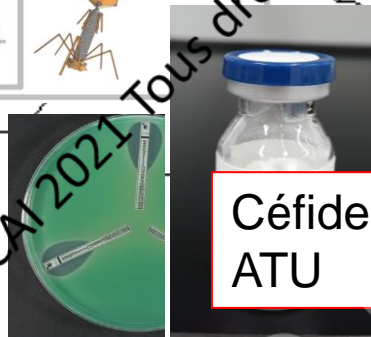
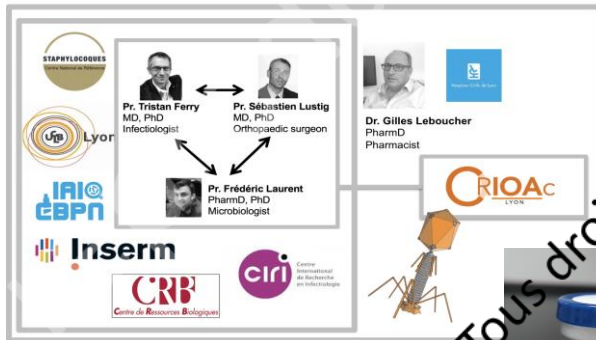
Lyon Phage team



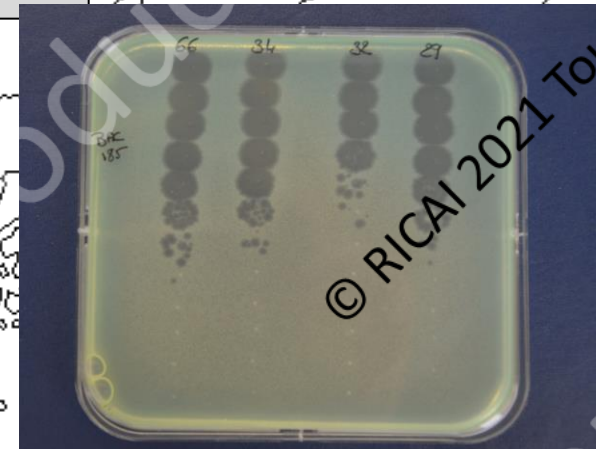
Jean-Paul Pirnay



Gregory Resch



Céfiderochol  
ATU



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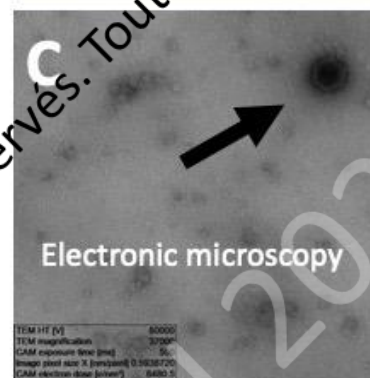
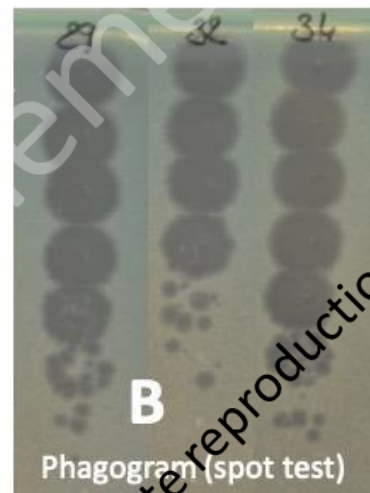
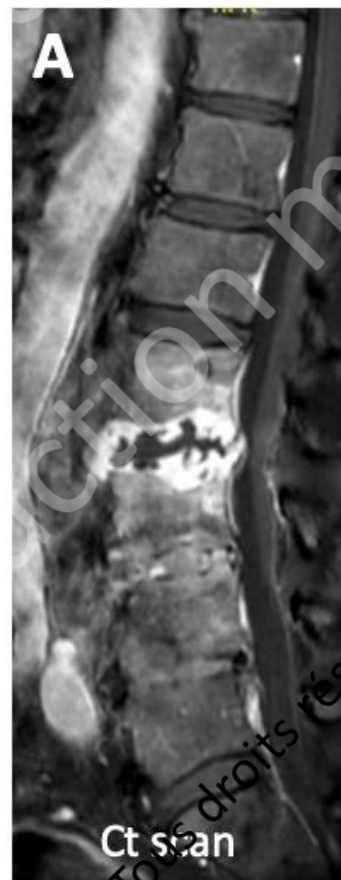
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# Personalized production and administration of bacteriophages: lessons learned from a unique European academic collaboration to treat a patient with pandrug-resistant spinal *P. aeruginosa* infection



Under the supervision of



**Conclusions:** Personalized phage therapy is a potential adjunct treatment for patients with complex BUI 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



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Favorable outcome at 18 months



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

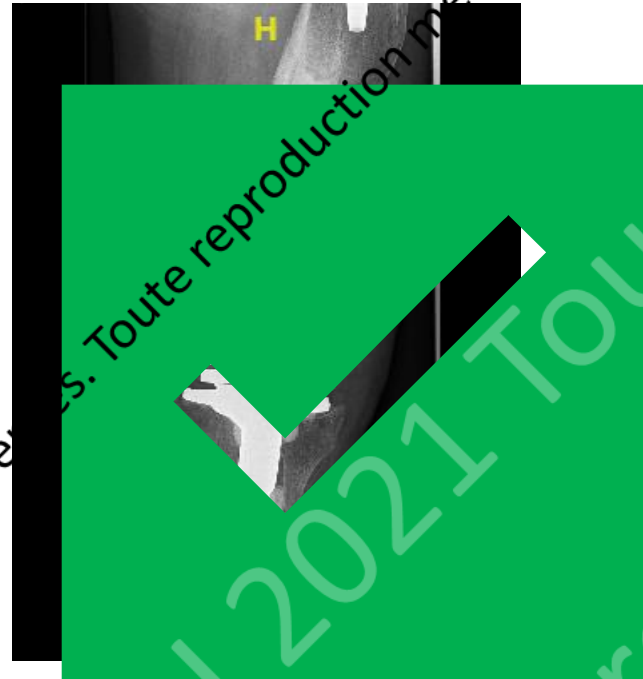
# Bone and joint infections

Post-trauma  
long-bone  
osteomyelitis



Surgery  
(debridement & reconstruction)  
Antibiotics

Chronic  
prosthetic-joint  
infection



Surgery  
(prosthesis explantation)  
Antibiotics

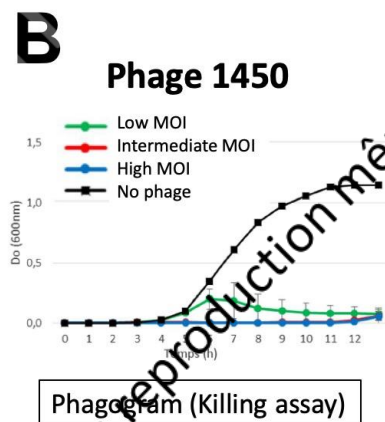
Spinal infection  
with abscess and  
bone destruction



Surgery  
(debridement & stabilization)  
Antibiotics

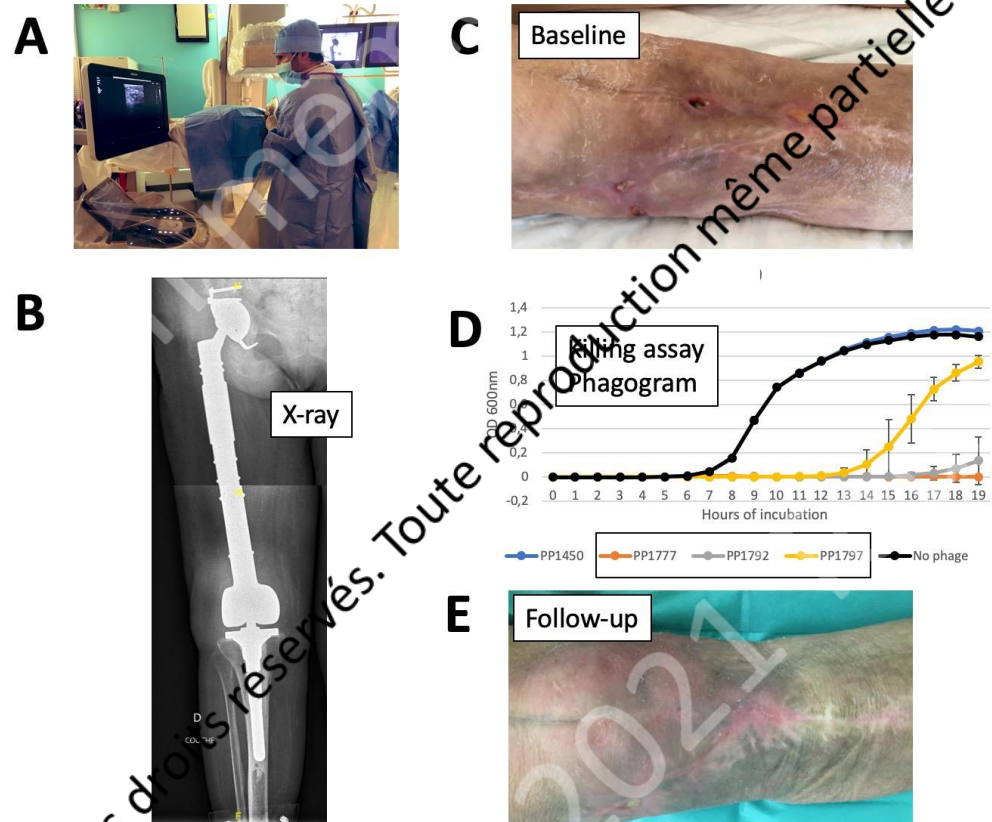
# Debridement And Implant Retention' (DAIR) with local administration of personalized cocktail of bacteriophages (PhagoDAIR) followed by suppressive antibiotherapy as salvage therapy in patients with relapsing prosthetic knee infection

Phago  
DAIR



**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.

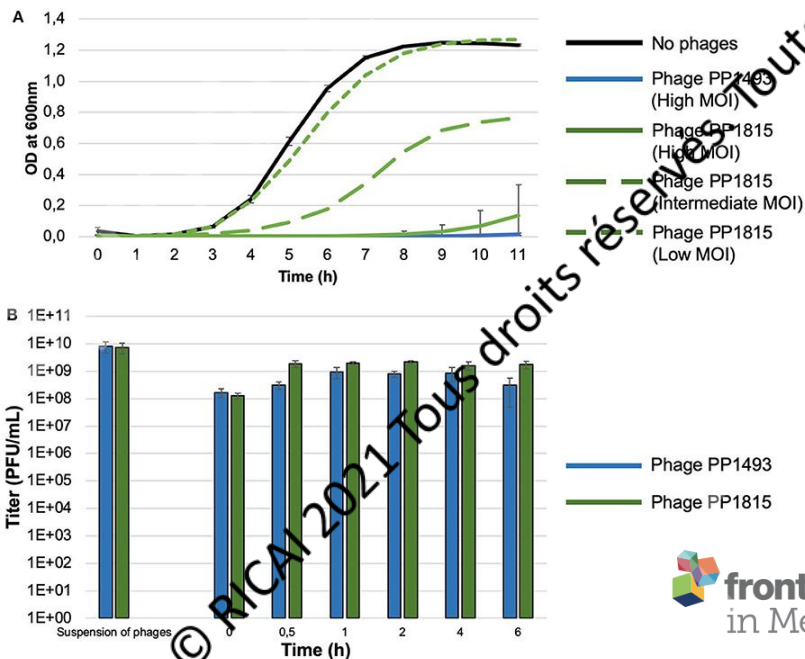
# Ultrasound guided local administration of personalized cocktail of bacteriophages followed by suppressive antibiotherapy as salvage therapy in patients with relapsing total femur prosthesis infection



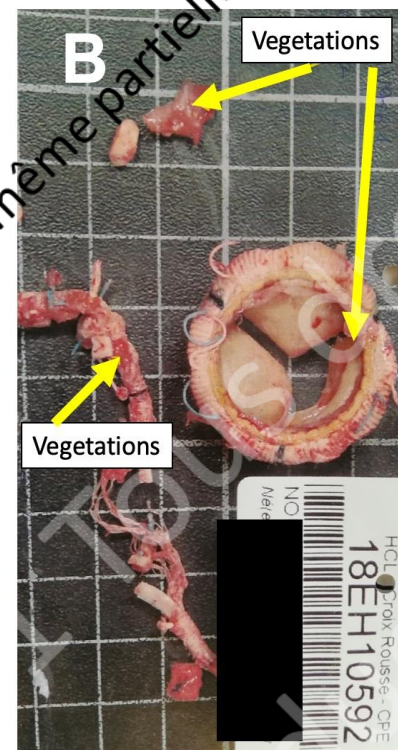
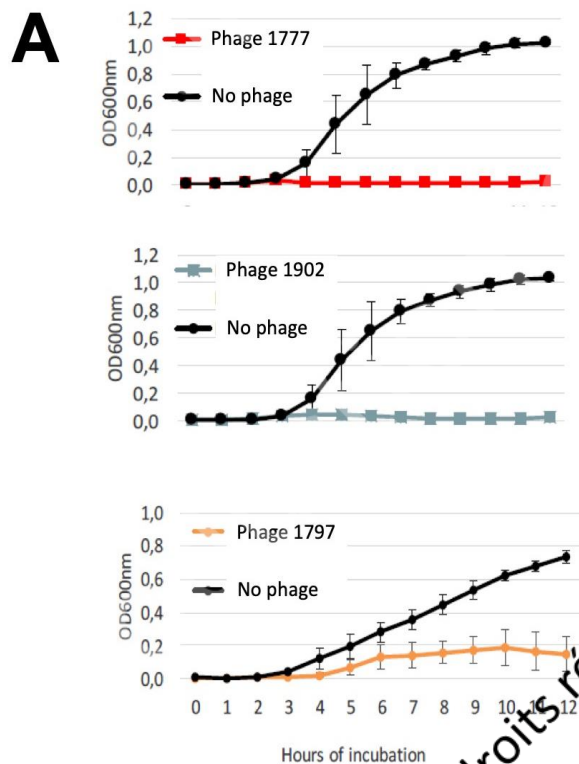
**Conclusions:** **Ultrasound-guided local administration** of personalized cocktail of GMP bacteriophages followed by suppressive antibiotherapy in patients with relapsing total femur PJI **has the potential to be used as salvage therapy** to control the infection and avoid disarticulation. Dramatic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

# The Potential Innovative Use of Bacteriophages Within the DAC<sup>®</sup> Hydrogel to Treat Patients With Knee Megaprosthesis Infection Requiring “Debridement Antibiotics and Implant Retention” and Soft Tissue Coverage as Salvage Therapy

Tristan Ferry<sup>1,2,3,4\*</sup>, Cécile Batailler<sup>2,3,5</sup>, Charlotte Petitjean<sup>6</sup>, Joseph Chateau<sup>7</sup>, Cindy Fevre<sup>6</sup>, Emmanuel Forestier<sup>8</sup>, Sophie Brosset<sup>7</sup>, Gilles Leboucher<sup>9</sup>, Camille Kolenda<sup>2,3,4,10</sup>, Frédéric Laurent<sup>2,3,4,10</sup> and Sébastien Lustig<sup>2,3,5</sup> on behalf of the Lyon BJI Study Group



# 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



**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.

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Open Forum Infectious Diseases

BRIEF REPORT



# Case Report: Arthroscopic “Debridement Antibiotics and Implant Retention” With Local Injection of Personalized Phage Therapy to Salvage a Relapsing *Pseudomonas Aeruginosa* Prosthetic Knee Infection

frontiers in Medicine

2021

Tristan Ferry<sup>1,2,3,4\*</sup>, Camille Kolenda<sup>2,3,4,5</sup>, Cécile Batailler<sup>2,3,6</sup>, Romain Gaillard<sup>3,6</sup>, Claude-Alexandre Gustave<sup>2,3,4,5</sup>, Sébastien Lustig<sup>2,3,6</sup>, Cindy Fevre<sup>7</sup>, Charlotte Petitjean<sup>7</sup>, Gilles Leboucher<sup>8</sup>, Frédéric Laurent<sup>2,3,4,5</sup> and the Lyon BJI Study group

Ferry T.

Salvage De  
Implant Re  
Local Injec  
of Bacterio  
an Elderly  
Staphyloco  
Infection?



# The Potential Innovative Use of Bacteriophages Within the DAC<sup>®</sup> Hydrogel to Treat Patients With Knee Infection Requiring Antibiotics and Soft Tissue Surgery

frontiers in Medicine

Charlotte Petitjean<sup>6</sup>, Joseph Chateau<sup>7</sup>, Romain Gosset<sup>7</sup>, Gilles Leboucher<sup>9</sup>, and the Lyon BJI Study Group

2020

ction

bone and joint infection including local application of a selected cocktail of bacteriophages

Tristan Ferry ✉, Fabien Boucher, Cindy Fevre, Thomas Perpoint, Joseph Chateau, Charlotte Petitjean, Jérôme Josse, Christian Chidiac, Guillaume L’hostis, Gilles Leboucher, ... Show more

Journal of Antimicrobial Chemotherapy, Volume 73, Issue 10, 1 October 2018, Pages 2901–2903, doi: 10.3389/jm.2020.570372

# #PhagoDAIR

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# Where to find phages for clinical use?

- Pherecydes Pharma
- Phage community



Under the supervision of



# Where to find phages for clinical use?

- Pherecydes Pharma
- Phage community



Under the supervision of



## PHAGÉ in LYON



Purified academic phages  
Usable in the next 5 years

# Where to find phages for clinical use?

- Pherecydes Pharma
- Phage community



European Society of Clinical Microbiology and Infectious Diseases

Inauguration Committee Members:

Ran Nir-Paz, Israël

Tristan Ferry, France

Patrick Soentjens, Belgium

Zuzanna Drulis-kawa, Poland

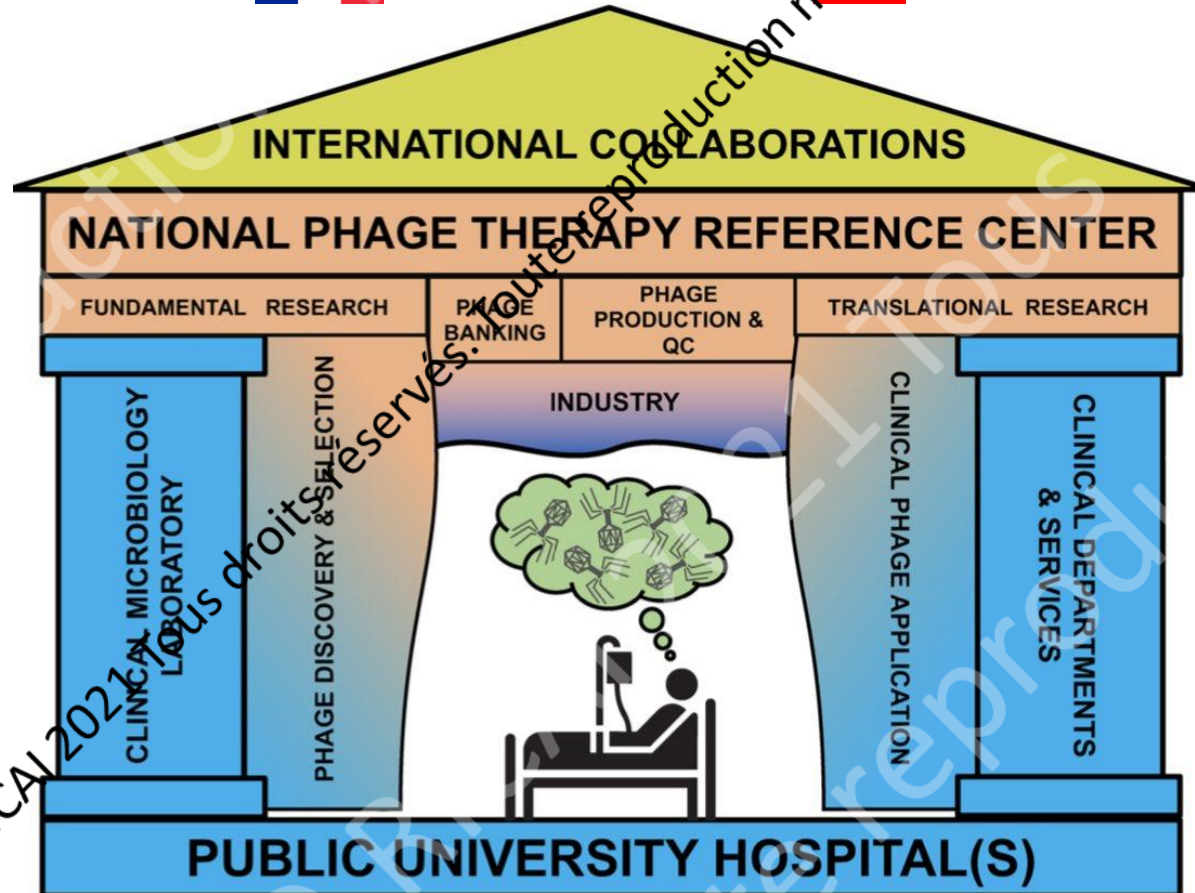
Joana Azeredo, Portugal



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# Recent progress toward the implementation of phage therapy in Western medicine

Jean-Paul Pirnay<sup>1,†</sup>, Tristan Ferry<sup>2,3,†</sup> and Grégory Pasch<sup>4,\*†</sup>

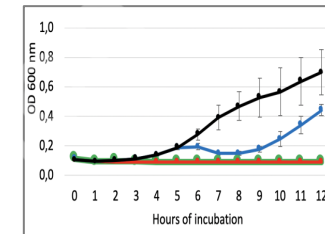


# Conclusion

- There is a real place for phage therapy to maximize clinical success in complex bacterial infections
- Need to identify relevant clinical indications
- Expertise of referral clinical centers
- Don't forget Lessons from 20<sup>th</sup> century
- Develop and use purified bacteriophages
  - ▶ 30 patients treated since 2017
- Industry / health authority / academic collaborations
- Need for Phage discovery, banking, susceptibility, to personalize the therapy
- Need for national phage
- Clinical trials have to be potential benefit in severe



Centre International de Recherche en Infectiologie



Clinical trial  
**PhagoDAIR**  
Janvier 2022



# Lyon BJI Study group

## Coordinator: Tristan Ferry

**Infectious Diseases Specialists – Tristan Ferry**, Florent Valour, Thomas Perpoint, Florence Ader, Sandrine Roux, Agathe Becker, Claire Triffault-Fillit, Anne Conrad, Cécile Poudroux, Pierre Chauvelot, Paul Chabert, Johanna Lippman, Evelyne Braun

**Surgeons – Sébastien Lustig**, Elvire Servien, Cécile Batailler, Stanislas Gunst, Axel Schmidt, Elliot Sappey-Marinier, Quentin Ode, Michel-Henry Fessy, Anthony Viste, Jean-Luc Besse, Philippe Chaudier, Lucie Louboutin, Adrien Van Haecke, Marcelle Mercier, Vincent Belgaid, Aram Gazarian, Arnaud Walch, Antoine Bertani, Frédéric Rongieras, Sébastien Martres, Franck Trouillet, Cédric Barrey, Ali Mojallal, Sophie Brosset, Camille Hanriat, Hélène Person, Philippe Céruse, Carine Fuchsmann, Arnaud Gleizer,

**Anesthesiologists – Frédéric Aubrun**, Mikhail Dziadzko, Caroline Macabéo, Dana Patrascu;

**Microbiologists – Frederic Laurent**, Laetitia Beraud, Tiphaine Roussel-Gaillard, Céline Dupieux, Camille Kolenda, Jérôme Josse;

**Imaging – Fabien Craighero**, Loic Bousel, Jean-Baptiste Pialat, Isabelle Morelec;

**PK/PD specialists – Michel Tod**, Marie-Claude Gagnieu, Sylvain Goutelle;

**Clinical research assistant and database manager – Eugénie Mabrut**

## PHAGE *in* LYON

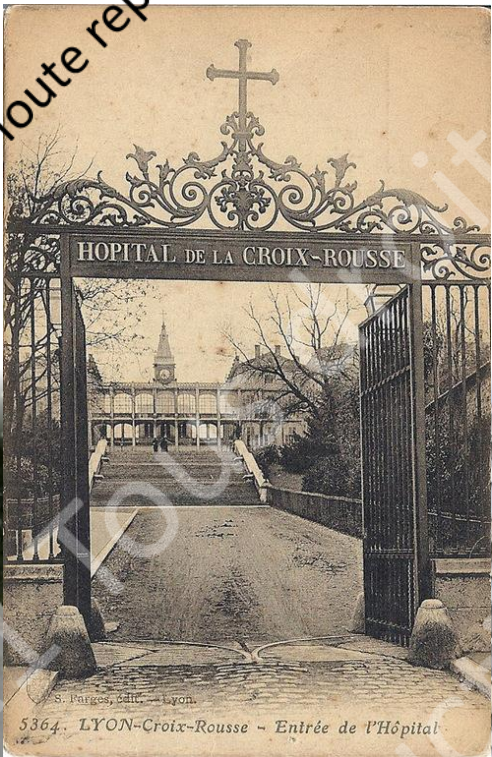


## Coordinators: Tristan Ferry and Frédéric Laurent

Mathieu Medina, Camille kolenda, Floriane Launay, Melanie Bonhomme, Leslie Blazere, Tiphaine Legendre, Eline Terrazzoni, Fabrice Pirot, Camille Merienne, Samira Filali, Benjamine Lapras, Gilles Leboucher, Thomas Briot.



# Croix-Rousse Hospital



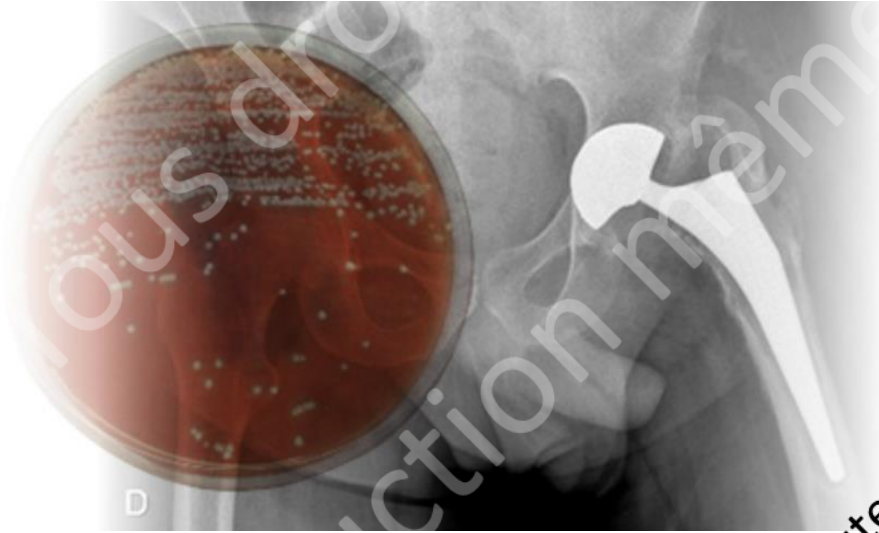
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