

DIU « Infection ostéoarticulaire » - Séminaire de Lyon
du mardi 6 et mercredi 7 décembre 2022

Intérêt des bactériophages et des Lysines de bactériophages au cours des infections ostéoarticulaires

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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 (CARIOAc Lyon)

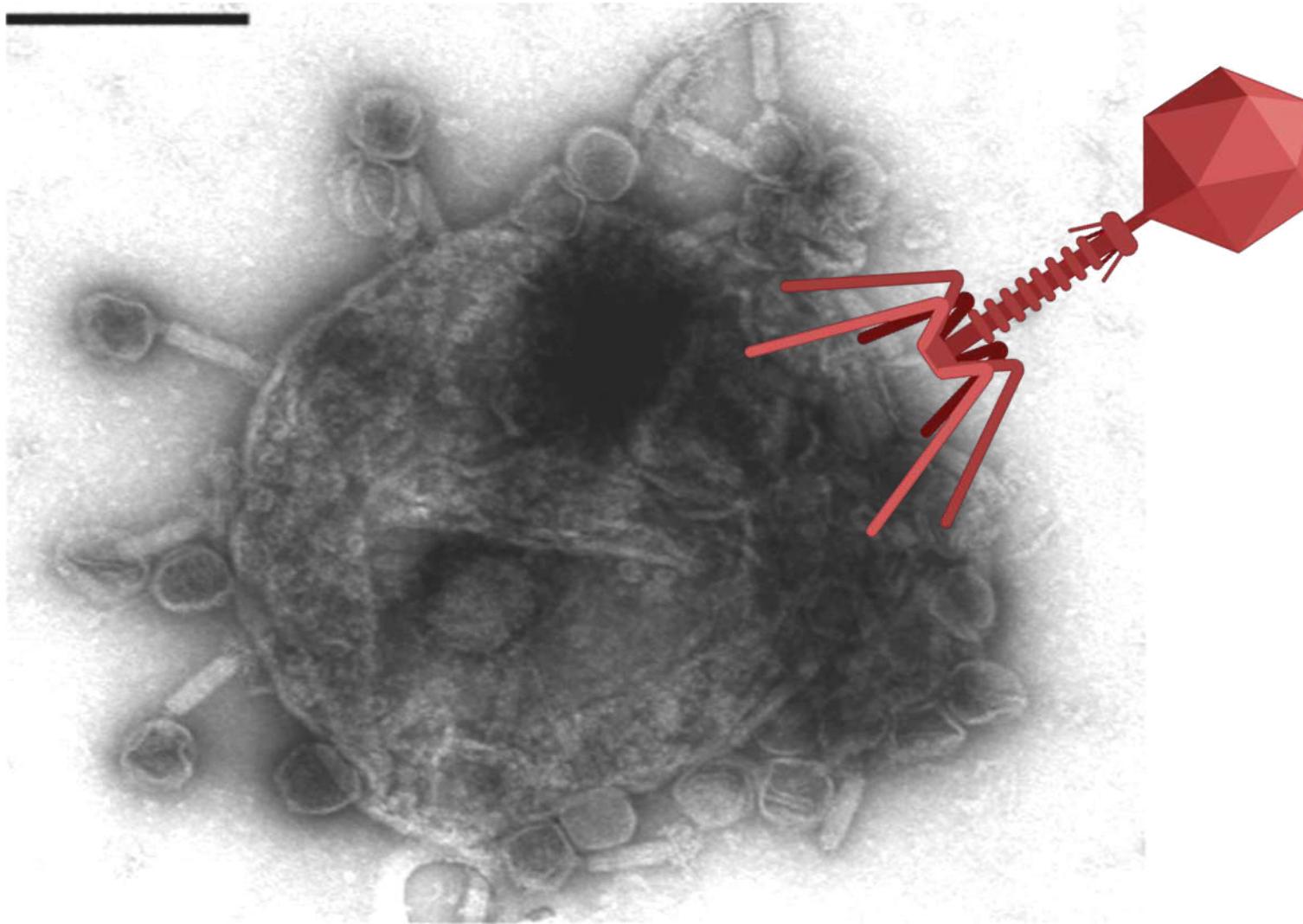
Président du Comité Scientifique des CARIOAc 2017-2022



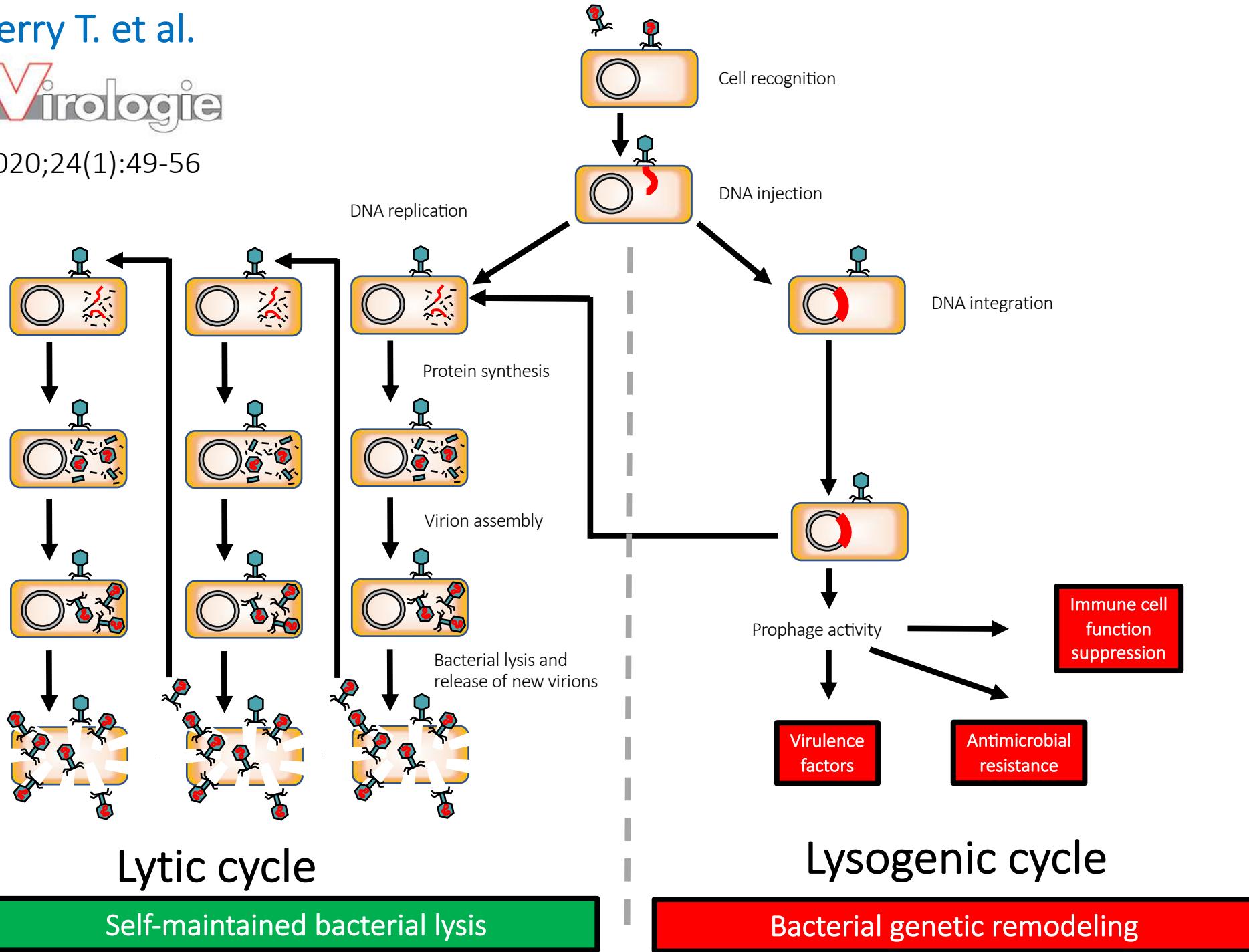
PHAGE*in***LYON**



Bacteria have also their pandemia!

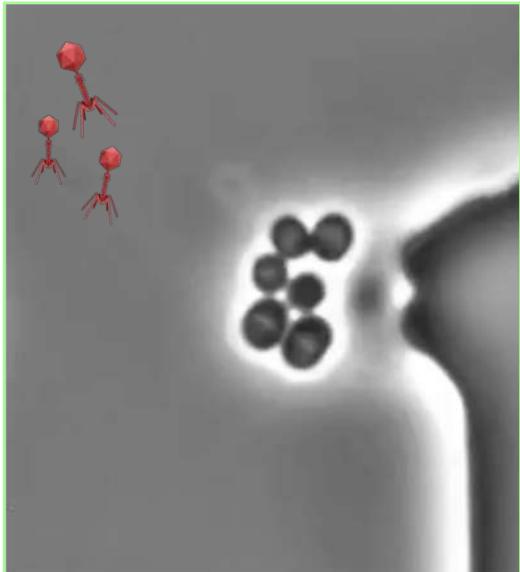
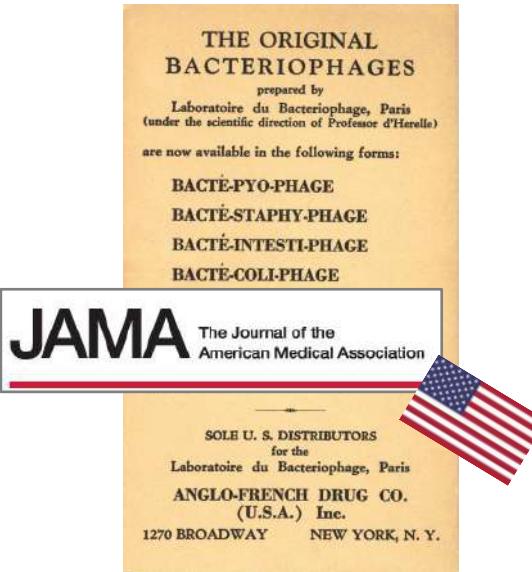


Merabishvili et al. *PLoS ONE* 2009



Phage therapy is fascinating

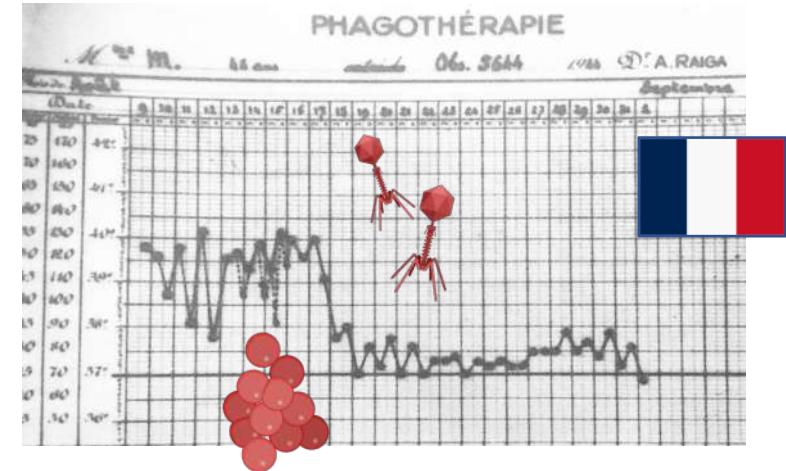
- Viral therapy for bacterial infections
- Story of phage therapy is connected to worldwide geopolitical events
- Potential incredible preclinical efficacy
- Failure to implement phage therapy in the west



S. aureus being lysed
by the Sa2 phage

Bacterial DNA
appeared in green

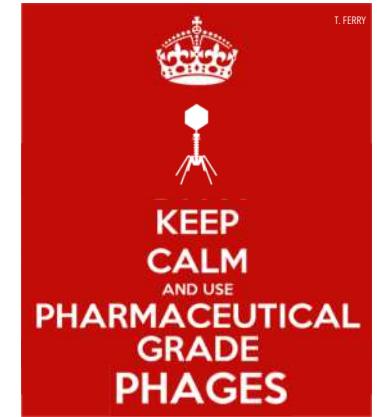
Courtesy Pascal Maguin
Luciano Marraffini Lab
THE ROCKEFELLER UNIVERSITY



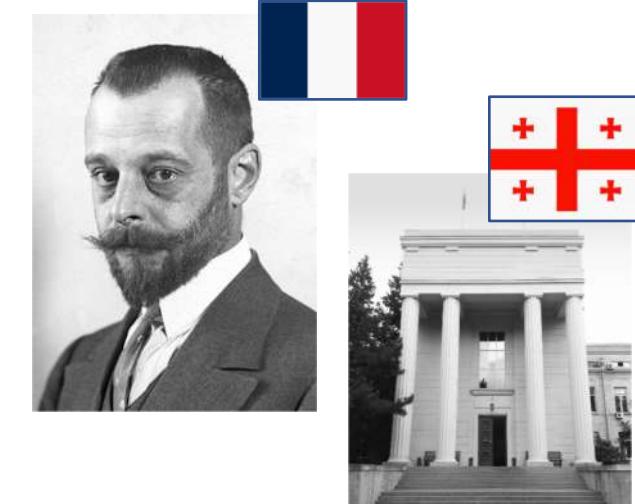
Contemporary

Previous clinical trials have not « failed »

- Most of them were phase I/IIa/IIb and not phase III
- Phages are particular anti-infective agents (\neq antibiotics)
- Need a specific purification process
- Purified phages or phage cocktails are potentially not stable during time
- High specificity of phages
- Potential need for a phagogram (like antibiogram) before treatment



Don't forget the lessons of the past



Respect the experience of the East



T. FERRY



KEEP
CALM
AND USE
**PHARMACEUTICAL
GRADE
PHAGES**



ESCMID STUDY GROUP
FOR NON-TRADITIONAL
ANTIBACTERIAL THERAPY

European Society of Clinical Microbiology and Infectious Diseases

Elected Executive Committee:

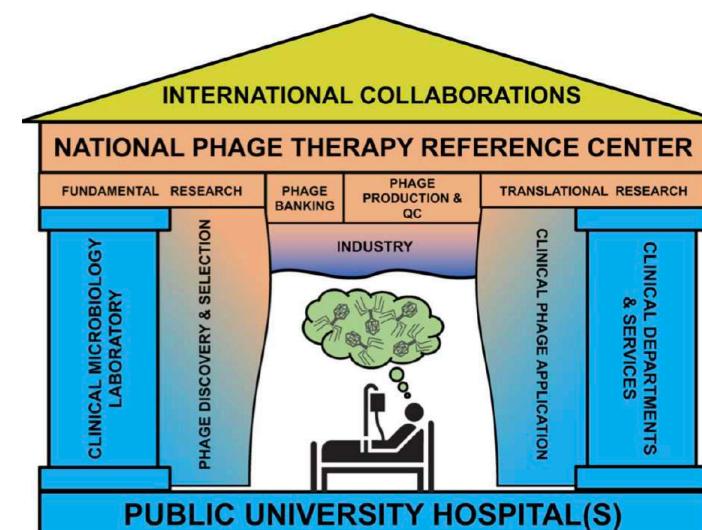
Ran Nir-Paz, Israël

Jean-Paul Pirnay, Belgium

Clinical officer: Tristan Ferry, France

Shawna Mc Callin, Switzerland

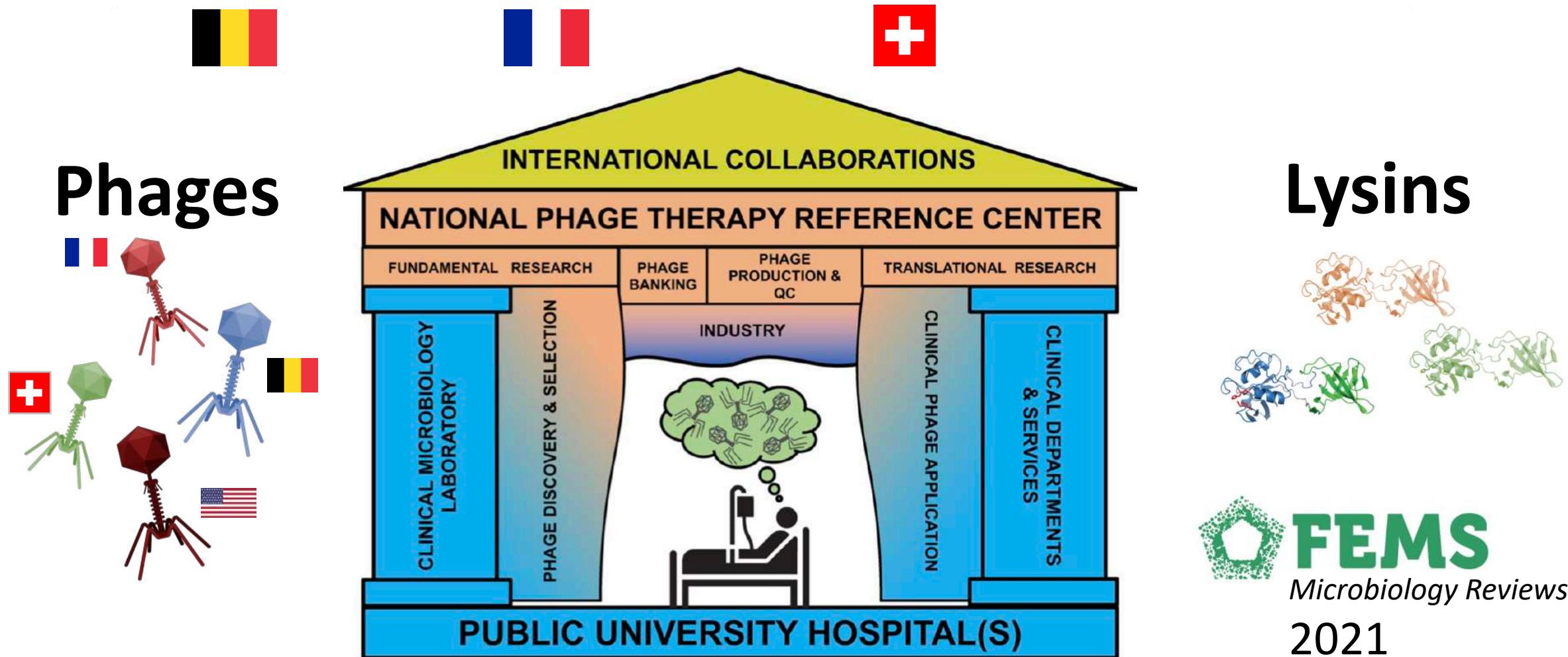
Zuzanna Drulis-kawa, Poland



REVIEW ARTICLE

Recent progress toward the implementation of phage therapy in Western medicine

Jean-Paul Pirnay^{1,†}, Tristan Ferry^{2,3,†} and Grégory Resch^{4,*†}



**THE MYTHOLOGY
OF PHAGE THERAPY**



T. FERRY

vs.



T. FERRY

Développement de la phagothérapie à Lyon

HCL
HOSPISES CIVILS
DE LYON

PHAGE*in*LYON

FONDATION
HCL
HOSPISES CIVILS
DE LYON



PHAGE*in*LYON
Lab



F. Laurent



Recherche et développement
Production de phages publics
Développement du phagogramme

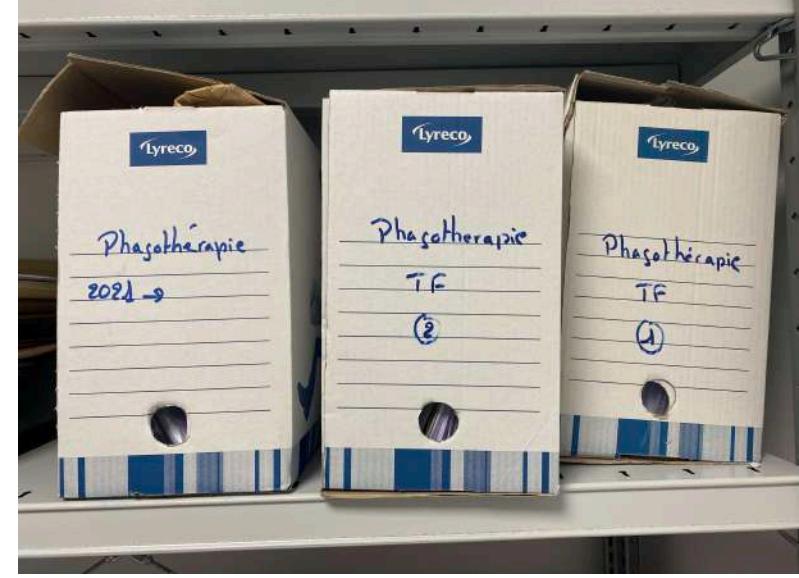
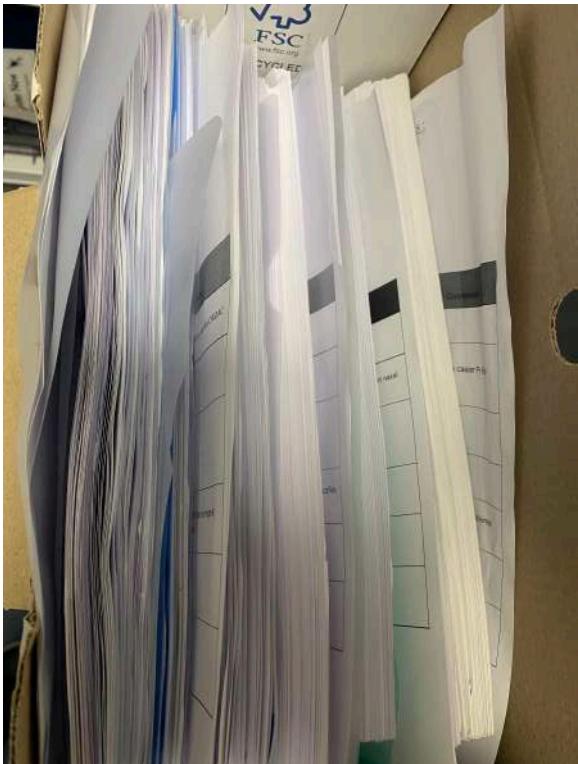
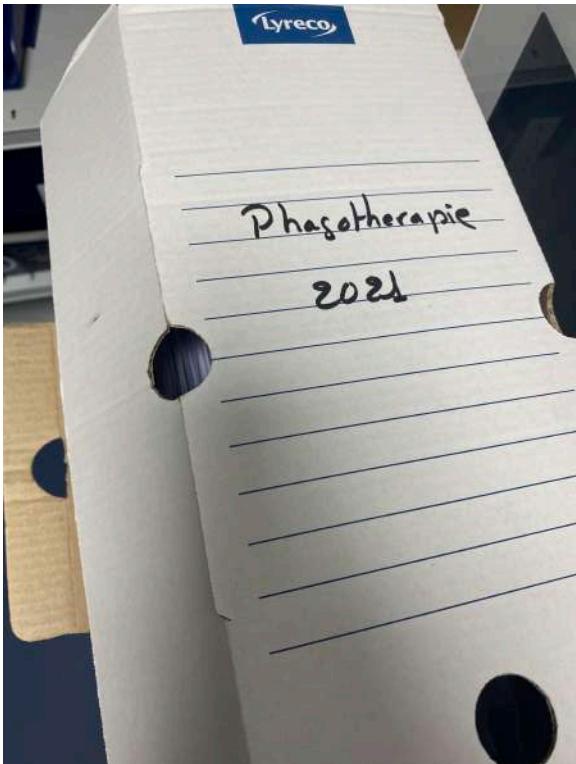
PHAGE*in*LYON
Clinic



T. Ferry

Développement clinique
RCP Crioac Thérapies innovantes
RCP Phagothérapie
Validation des indications
Prise en charge des patients
Etudes de cohortes
Essais thérapeutiques

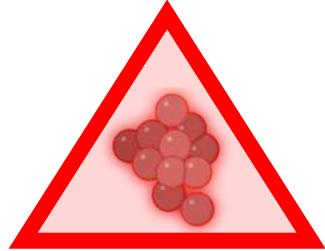
PHAGE *in* LYON Clinic



**Infections ostéoarticulaires ?
Autres indications ?
Infections en réanimation ?
Infections pulmonaires ?
Infections cardiovasculaires ?
Infections en réanimation ?
Pédiatrie ?

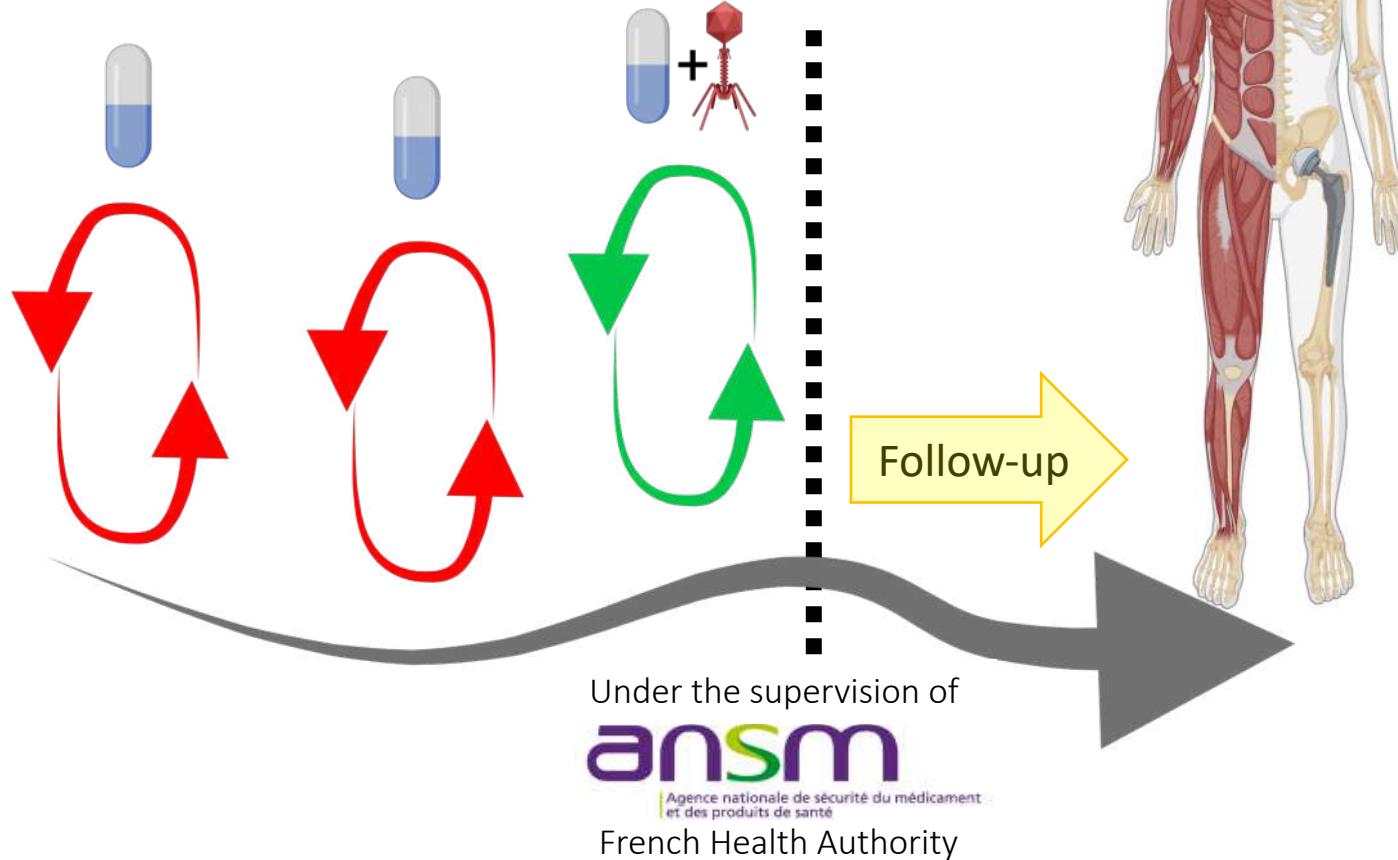
Se limiter aux infections à BMR ?**

A large panel of severe bacterial infections

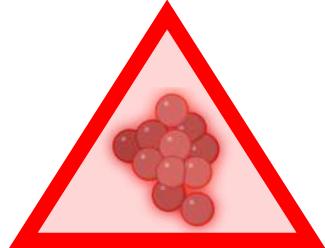


Some positive signals
in these infections

The patient is his “own control”



A large panel of severe bacterial infections



Central nervous system infections

Implant-associated meningitis

Lung infections

Ventilator-associated pneumonia
Exacerbation in cystic fibrosis
Exacerbations in bronchiectasis

Urinary tract infections

Pyelonephritis
Ureteral stent-associated infection



Cardiovascular infections

Endocarditis
Cardiac electronic device infection
Prosthetic-valve endocarditis
Vascular graft infection

Muskuloskeletal infections

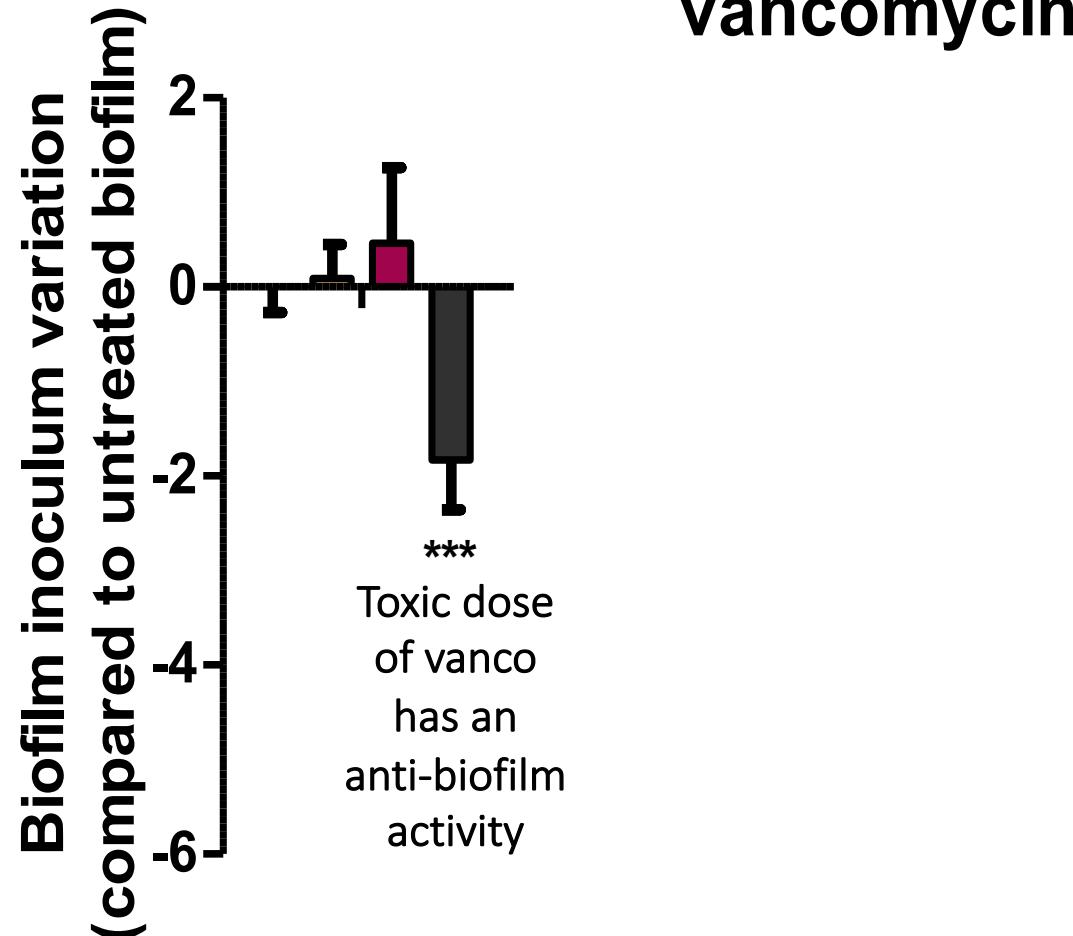
Wound infection
Osteomyelitis, fracture-related infection
Implant-associated bone and joint infection
Prosthetic joint infection

Digestive-tract infections

Typhoid fever, shigellosis
Cholera

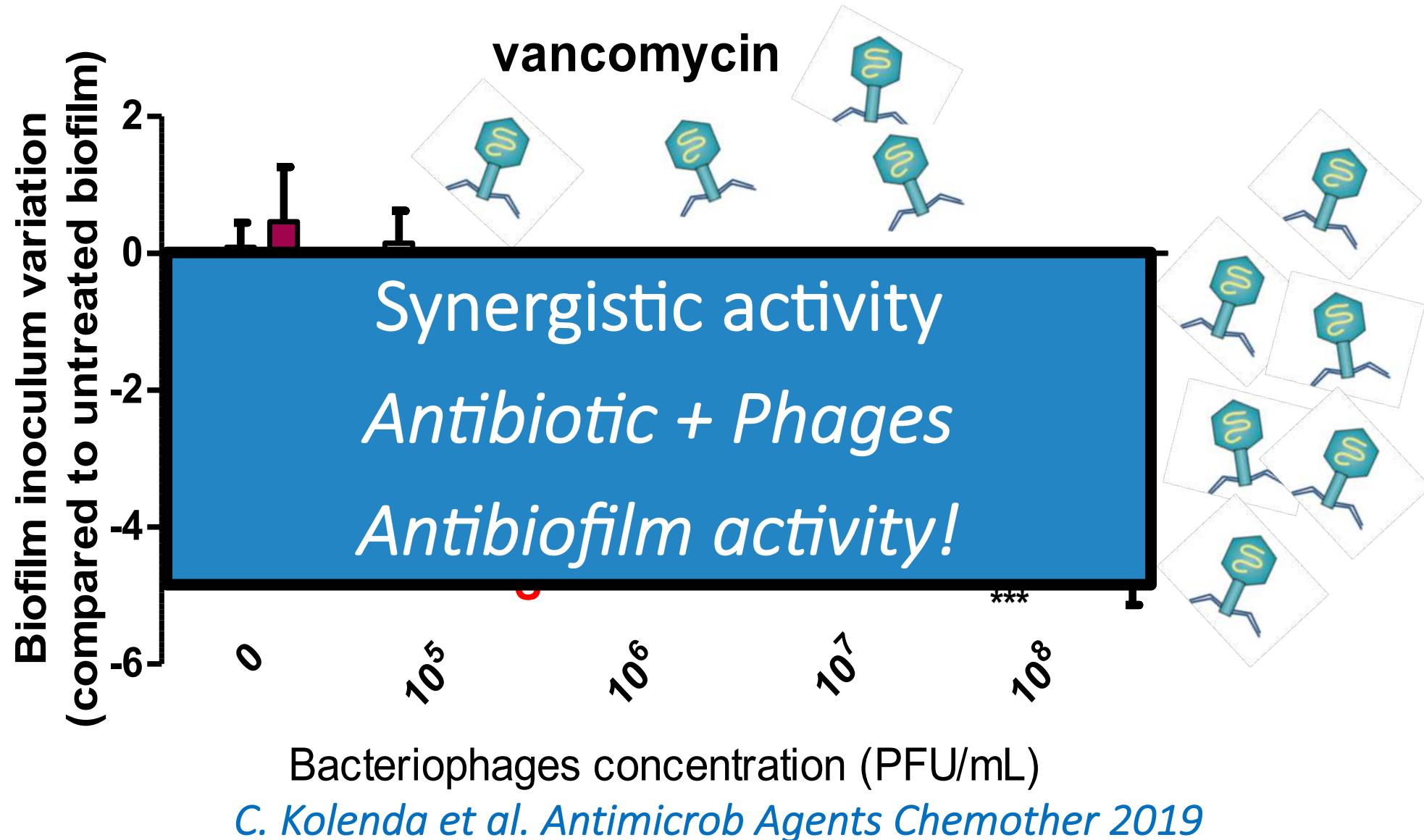
Phages have antibiofilm activity

- No Antibiotic
- MIC
- C_{bone} (4^*MIC)
- 10^*MIC



Phages have antibiofilm activity

- No Antibiotic
- MIC
- C_{bone} (4^*MIC)
- 10^*MIC





viruses

Lyon BJI
study CRIA^{Ac}_{LYON} group

PHAGEinLYON



Review

Past and Future of Phage Therapy and Phage-Derived Proteins in Patients with Prosthetic Joint Infection

REVIEW ARTICLE

OPEN ACCESS

Tristan Ferry,
Jérôme Josse,
Frédéric Laurent
on behalf of

Medical innovations to maintain the function in patients with chronic PJI for whom explantation is not desirable: a pathophysiology-, multidisciplinary-, and experience-based approach

Tristan Ferry^{1,2,3,4,*}, Cécile Batailler^{2,3,5}, Sophie Brosset^{2,3,6}, Camille Kolenda^{2,3,4,7},
Sylvain Goutelle^{2,3,8,9}, Elliot Sappey-Marinier^{2,3,5}, Jérôme Josse^{2,3,4,7}, Frédéric Laurent^{2,3,4,7},
Sébastien Lustig^{2,3,5}, On Behalf of the Lyon BJI Study Group,^a

Virologie

Phage therapy in bone and joint infection : une infection ostéoarticulaire : historique, fondements, faisabilité et perspectives en France

Phage therapy in bone and joint infection: history, rationale, feasibility and perspectives in France

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

Tristan Ferry^{1,2,3,4*}, Camille Kolenda^{2,3,4,5}, Cécile Batailler^{2,3,6}, Romain Gaillard^{3,6}, Claude-Alexandre Gustave^{2,3,4,5}, Sébastien Lustig^{2,3,6}, Cindy Fevre⁷, Charlotte Petitjean⁷, Gilles Leboucher⁸, Frédéric Laurent^{2,3,4,5} and the Lyon BJI Study group

3,743
TOTAL VIEWS



20

Open Forum Infectious Diseases

BRIEF REPORT

Salvage Debridement, Antibiotics and Implant Retention (“DAIR”) With Local Injection of a Selected Cocktail of Bacteriophages: Is It an Option for an Elderly Patient With Relapsing *Staphylococcus aureus* Prosthetic-Joint Infection?

Tristan Ferry,^{1,2,3,4} Gilles Leboucher,⁵ Cindy Fevre,⁶ Yannick Herry,^{2,4,7} Anne Conrad,^{1,2,3,4} Jérôme Josse,^{2,3,4,8} Cécile Batailler,^{2,4,7} Christian Chidiac,^{1,2,3,4} Mathieu Medina,⁶ S. Lustig,⁷ and Frédéric Laurent^{2,3,4,8}; on behalf of the Lyon BJI Study Group

Phage Therapy as Adjuvant to Conservative Surgery and Antibiotics to Salvage Patients With Relapsing *S. aureus* Prosthetic Knee Infection

Tristan Ferry^{1,2,3,4*}, Camille Kolenda^{2,3,4,5}, Cécile Batailler^{2,3,6}, Claude-Alexandre Gustave^{2,3,4,5}, Sébastien Lustig^{2,3,6}, Matthieu Malatray^{3,6}, Cindy Fevre⁷, Jérôme Josse^{2,3,4,5}, Charlotte Petitjean⁷, Christian Chidiac^{1,2,3,4}, Gilles Leboucher⁸ and Frédéric Laurent^{2,3,4,5} on behalf of the Lyon BJI Study group

VIEWS

3,770

5,711
TOTAL VIEWS



78

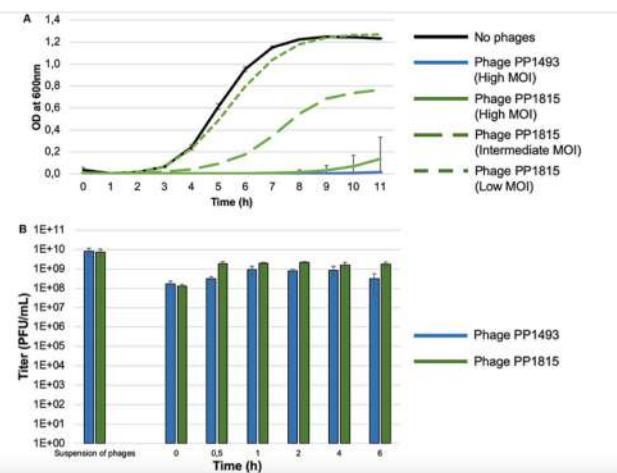
The Potential Innovative Use of Bacteriophages Within the DAC® Hydrogel to Treat Patients With Knee Megaprostheses Infection Requiring “Debridement Antibiotics and Implant Retention” and Soft Tissue Coverage as Salvage Therapy

Tristan Ferry^{1,2,3,4*}, Cécile Batailler^{2,3,5}, Charlotte Petitjean⁶, Joseph Chateau⁷, Cindy Fevre⁶, Emmanuel Forestier⁸, Sophie Brosset⁷, Gilles Leboucher⁹, Camille Kolenda^{2,3,4,10}, Frédéric Laurent^{2,3,4,10} and Sébastien Lustig^{2,3,5} on behalf of the Lyon BJI Study Group

4,970
TOTAL VIEWS



10



J Antimicrob Chemother 2018; **73**: 2901–2903
doi:10.1093/jac/dky263
Advance Access publication 27 July 2018

Innovations for the treatment of a complex bone and joint infection due to XDR *Pseudomonas aeruginosa* including local application of a selected cocktail of bacteriophages

Tristan Ferry^{1–4*}, Fabien Boucher^{1,4,5}, Cindy Fevre⁶, Thomas Perpoint^{1,4}, Joseph Chateau^{1,2,4,5}, Charlotte Petitjean⁶, Jérôme Josse^{2–4,7}, Christian Chidiac^{1,2–4}, Guillaume L'hostis⁶, Gilles Leboucher⁸ and Frédéric Laurent^{2–4,7} on behalf of the Lyon Bone and Joint Infection Study Group[†]

CITATIONS



2,316



16



More metrics information

Case series  procedure called « PhagoDAIR »

Phage Therapy as Adjuvant to Conservative Surgery and Antibiotics to Salvage Patients With Relapsing *S. aureus* Prosthetic Knee Infection

5,711

TOTAL VIEWS



Tristan Ferry^{1,2,3,4*}, Camille Kolenda^{2,3,4,5}, Cécile Batailler^{2,3,6},
Claude-Alexandre Gustave^{2,3,4,5}, Sébastien Lustig^{2,3,6}, Matthieu Malatray^{3,6}, Cindy Fevre⁷,
Jérôme Josse^{2,3,4,5}, Charlotte Petitjean⁷, Christian Chidiac^{1,2,3,4}, Gilles Leboucher⁸ and
Frédéric Laurent^{2,3,4,5} on behalf of the Lyon BJI Study group



HCL
HOSPISES CIVILS
DE LYON



#PhagoDAIR

Debridement Antibiotics and Implant Retention

CASE REPORT

published: 16 November 2020
doi: 10.3389/fmed.2020.570572

Clinical cases (2nd treated patient)

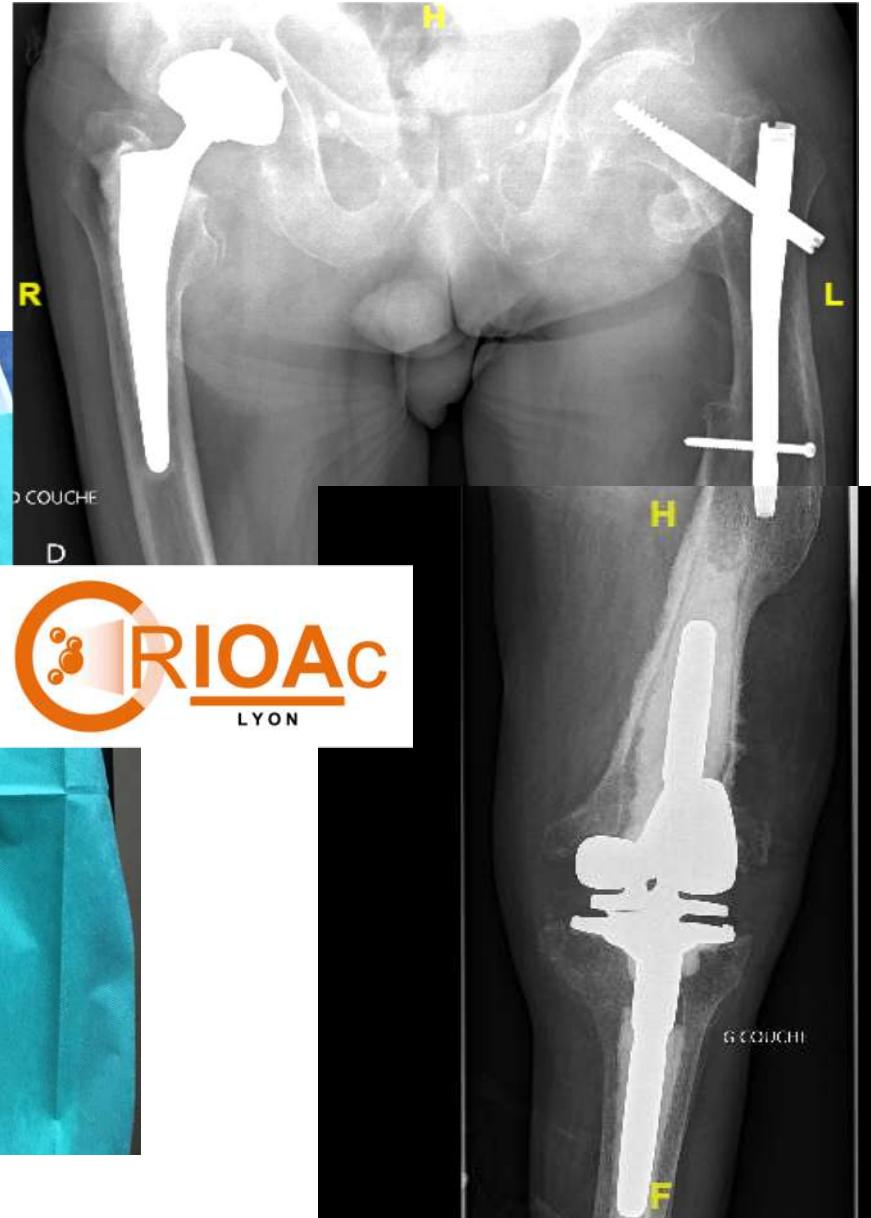
80-year-old man

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

Failure

Complex orthopaedic situation with past femoral fracture

Impossible to walk (painful knee)



PhagoDAIR I

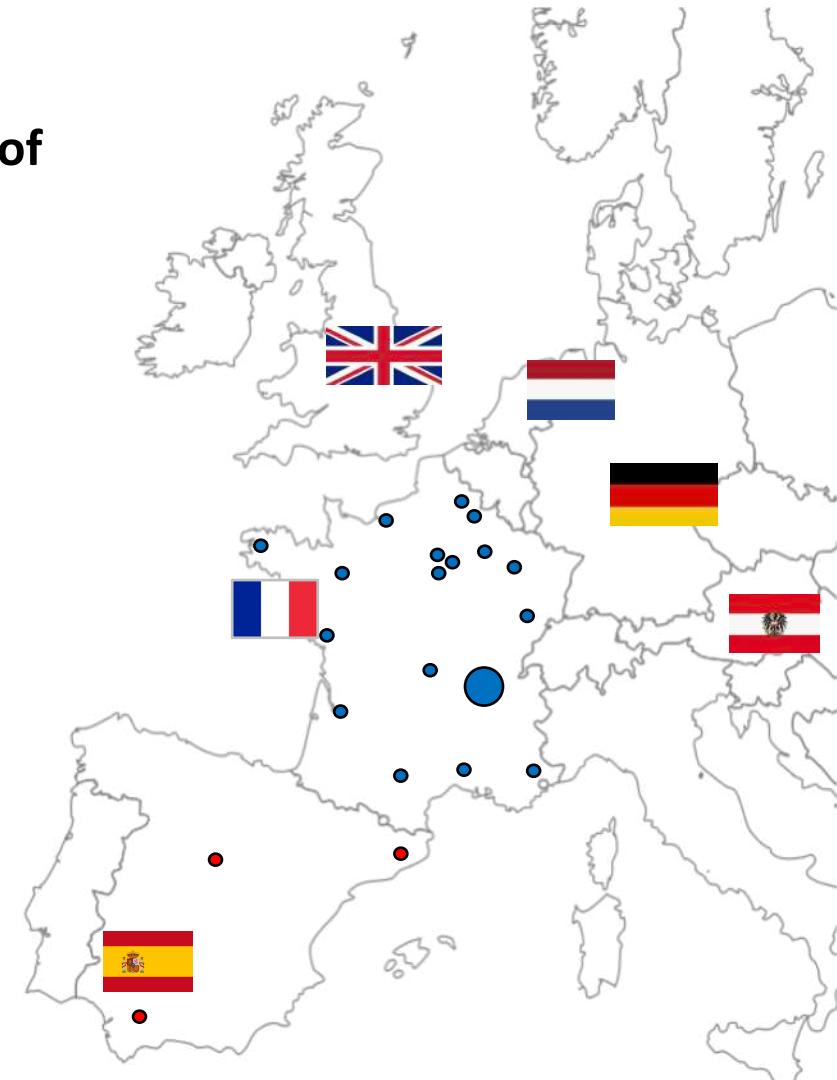
A Pilot, Multicenter, Randomized, Non-Comparative, Double-Blind Study of
Phage Therapy in Patients with Hip or Knee PJI due to *S. aureus*
Treated with DAIR and Antibiotic Therapy

Inclusion Criteria

1. *S. aureus* monomicrobial knee or hip PJI with clinical signs of infection with indication of DAIR and **Suppressive Antibiotics Therapy (SAT)**.
2. Phagogram displaying the susceptibility of the strain to at least one of the anti-*Staphylococcus aureus* bacteriophages

Primary Objective

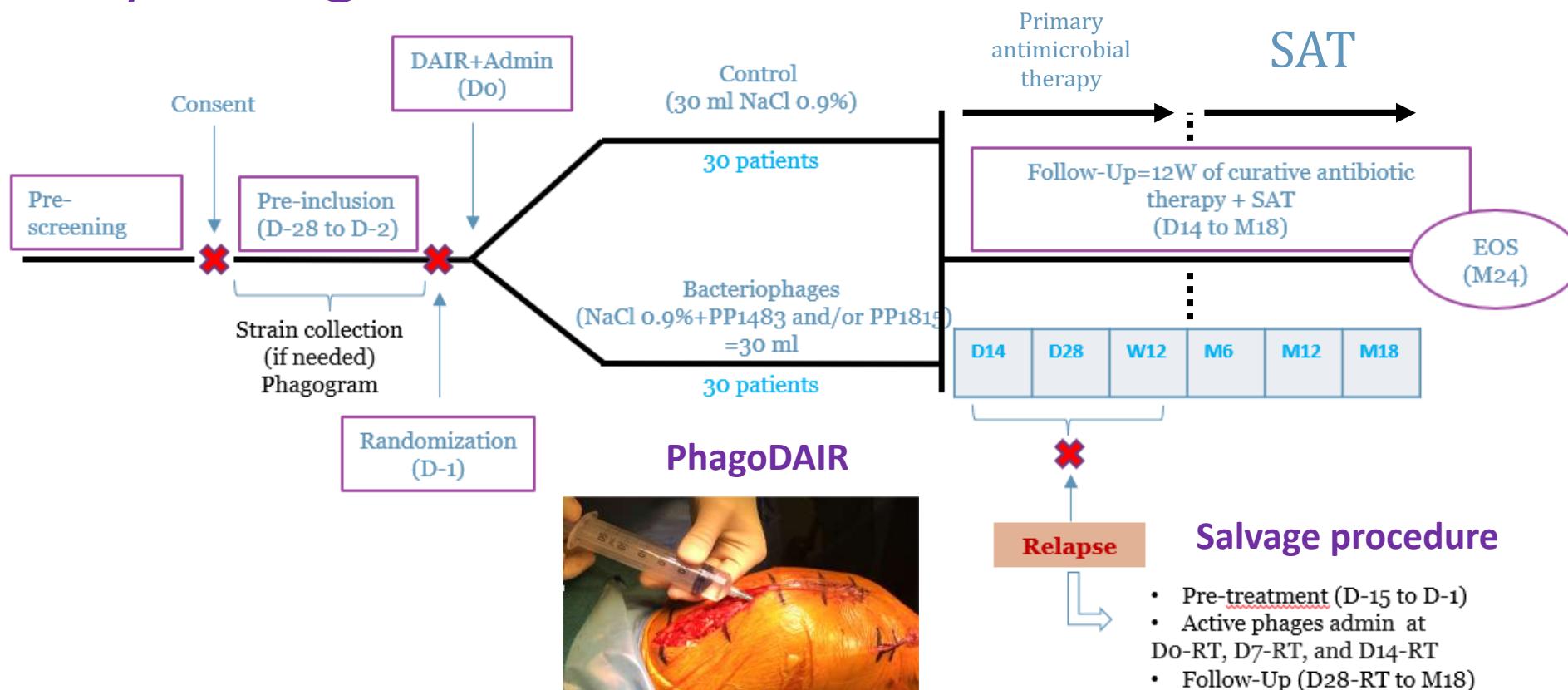
To estimate the **rate of clinical control of infection at Week 12±2** which will allow to calculate the sample size for future comparative studies.



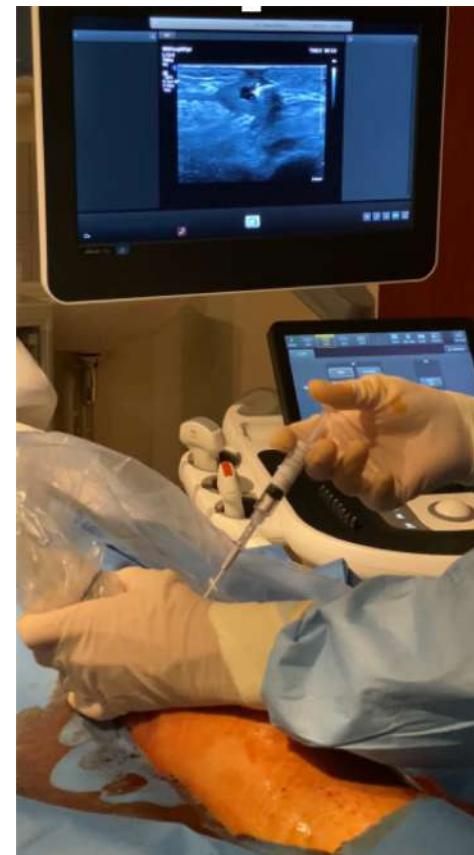
PhagoDAIR I

A Pilot, Multicenter, Randomized, Non-Comparative, Double-Blind Study of Phage Therapy in Patients with Hip or Knee PJI due to *S. aureus* Treated with DAIR and Antibiotic Therapy

Study design



Salvage procedure



Phage Therapy for Limb-threatening Prosthetic Knee *Klebsiella pneumoniae* Infection: Case Report and In Vitro Characterization of Anti-biofilm Activity

Edison J. Cano,^{1,2} Katherine M. Calisch,^{2,3} Paul L. Bollyky,⁴ Jonas D. Van Belleghem,⁴ Robin Patel,^{1,2,5} Joseph Fackler,⁶ Michael J. Brownstein,⁶ Bri'Anna Horne,⁶ Biswajit Biswas,⁷ Matthew Henry,^{7,8} Francisco Malagon,⁷ David G. Lewallen,⁹ and Gina A. Suh¹

¹Division of Infectious Diseases, Mayo Clinic, Rochester, Minnesota, USA, ²Infectious Diseases Research Laboratory, Mayo Clinic, Rochester, Minnesota, USA, ³Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, Minnesota, USA, ⁴Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA, ⁵Division of Clinical Microbiology, Mayo Clinic, Rochester, Minnesota, USA, ⁶Adaptive Phage Therapeutics, Gaithersburg, Maryland, USA, ⁷Genomics and Bioinformatics Department, Biological Defense Research Directorate, Naval Medical Research Center-Frederick, Fort Detrick, Maryland, USA, ⁸Geneva Foundation, Tacoma, Washington, USA, and ⁹Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota, USA

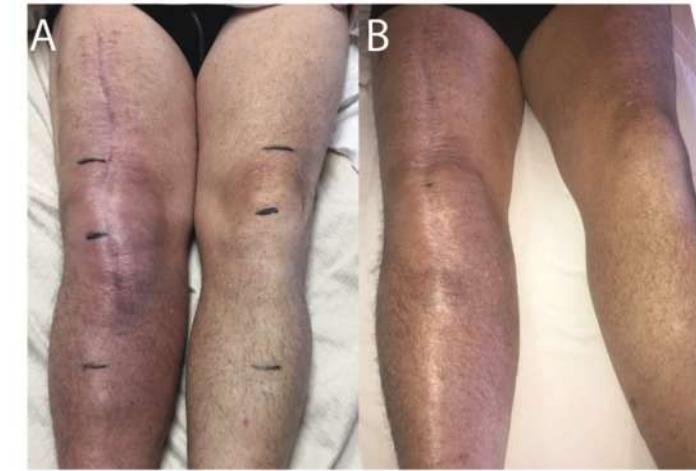


Figure 3. Phage therapy resulted in reduced erythema and swelling. Images are shown of the patient's lower extremities (A) before and (B) after completion of phage therapy.

NO SURGERY! 40 doses of exclusive INTRAVENOUS phages (1 injection each weekday)



Case Report

Successful Treatment of a Recalcitrant *Staphylococcus epidermidis* Prosthetic Knee Infection with Intraoperative Bacteriophage Therapy

James B. Doub^{1,*}, Vincent Y. Ng², Eleanor Wilson¹, Lorenzo Corsini³  and Benjamin K. Chan⁴

Single LOCAL injection during DAIR





U.S. National Library of Medicine

ClinicalTrials.gov

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Phage Therapy Versus Placebo in Conjunction With DAIR in Patients With Chronic Prosthetic Joint Infection Who Previously Failed Surgery for PJI

An Open-Label Multicenter Study to Evaluate the Safety and Efficacy of PhageBank™ Phage Therapy in Conjunction With Debridement, Antibiotics, and Implant Retention (DAIR) for Patients With First Time Culture Proven Chronic Prosthetic Joint Infection

A Pilot, Multicenter, Randomized, Non-Comparative, Double-Blind Study of Phage Therapy in Patients with Hip or Knee PJI due to *S. aureus* Treated with DAIR and Antibiotic Therapy



Etc.

Clinical case (3rd treated patient)

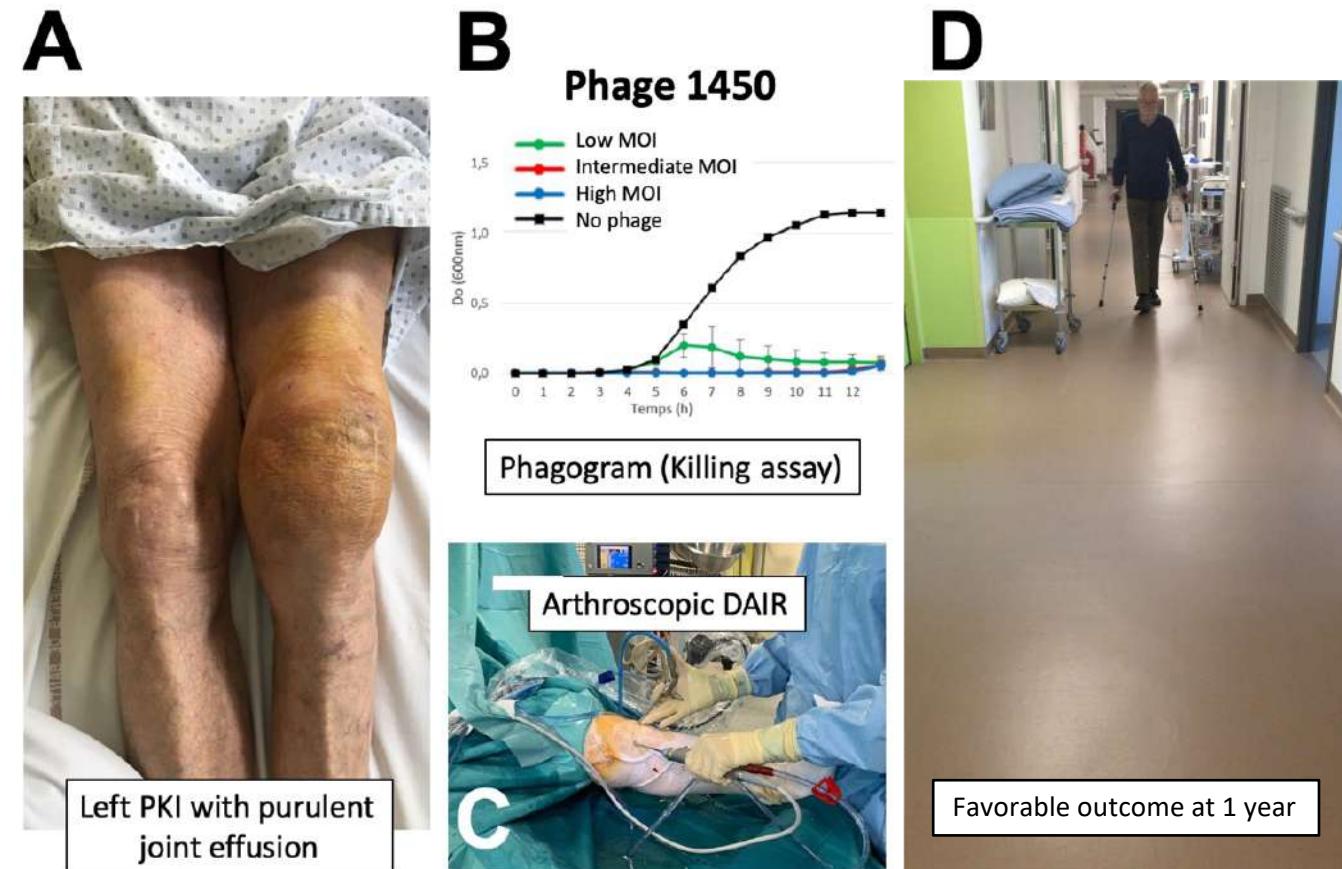
Arthroscopic DAIR with phages to salvage
P. aeruginosa prosthetic knee infection

88-year-old man

Relapsing *P. aeruginosa* prosthetic left knee infection

End-stage cardiac failure

Contraindicated to open DAIR



PHAGE *in* LYON



Clinical case (not published; 21th treated patients)



72-year-old man

Relapsing *P. aeruginosa* prosthetic right hip PJI with femoral osteomyelitis and large abscess

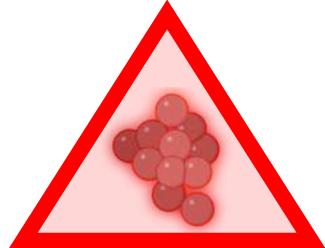
Disarticulation was proposed

Local?
IV?

Local + IV?



A large panel of severe bacterial infections



Central nervous system infections

Implant-associated meningitis

Lung infections

Ventilator-associated pneumonia
Exacerbation in cystic fibrosis
Exacerbations in bronchiectasis

Urinary tract infections

Pyelonephritis
Ureteral stent-associated infection



Cardiovascular infections

Endocarditis
Cardiac electronic device infection
Prosthetic-valve endocarditis
Vascular graft infection

Muskuloskeletal infections

Wound infection
Osteomyelitis, fracture-related infection
Implant-associated bone and joint infection
Prosthetic joint infection

Digestive-tract infection

Typhoid fever, shigellosis
Cholera

Clinical case (12th treated patient)

74-year-old man

Melanoma treated with anti-PD1

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

Spinal pain summer 2018

Spondylodiscitis with **spinal abscess**

Pandrug-resistant *P. aeruginosa* in culture!



PHAGE*in*LYON



Clinical case (12th treated patient)

74-year-old man

Melanoma treated with anti-PD1

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

Spinal pain summer 2018

Spondylodiscitis with spinal

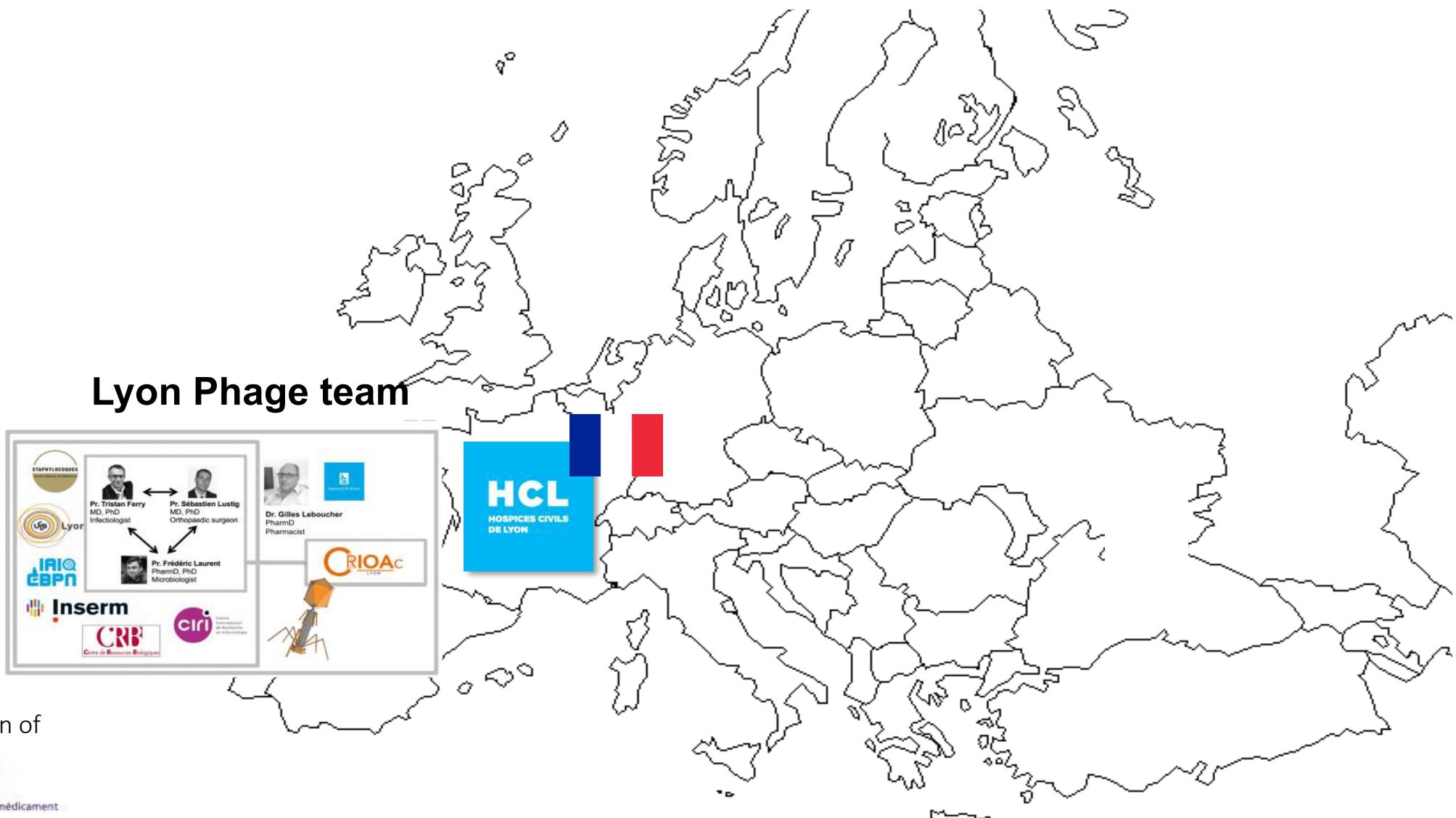
Pandrug-resist



The strain was also spontaneously
resistant to bacteriophages !!!

<i>Pseudomonas aeruginosa</i>	CMI (mg/l)
Ticarcilline + Ac. Clav	R (> 64)
Pipéracilline	R (> 64)
Pipéracilline + Tazobactam	R (> 64)
Ceftazidime	R (> 32)
Céfèpime	R (> 32)
Aztréonam	R (> 32)
Imipénème	R (> 8)
Meropenème	R (> 8)
Gentamicine	R (> 8)
Tobramycine	R (> 8)
Amikacine	R (> 32)
Ciprofloxacine	R (> 2)
	R (> 4)
	R
S (8) → R	
S E-test : 1 → R	
R	
E-test : > 256	
R	
E-test : 64	

Unique European academic collaboration



Under the supervision of



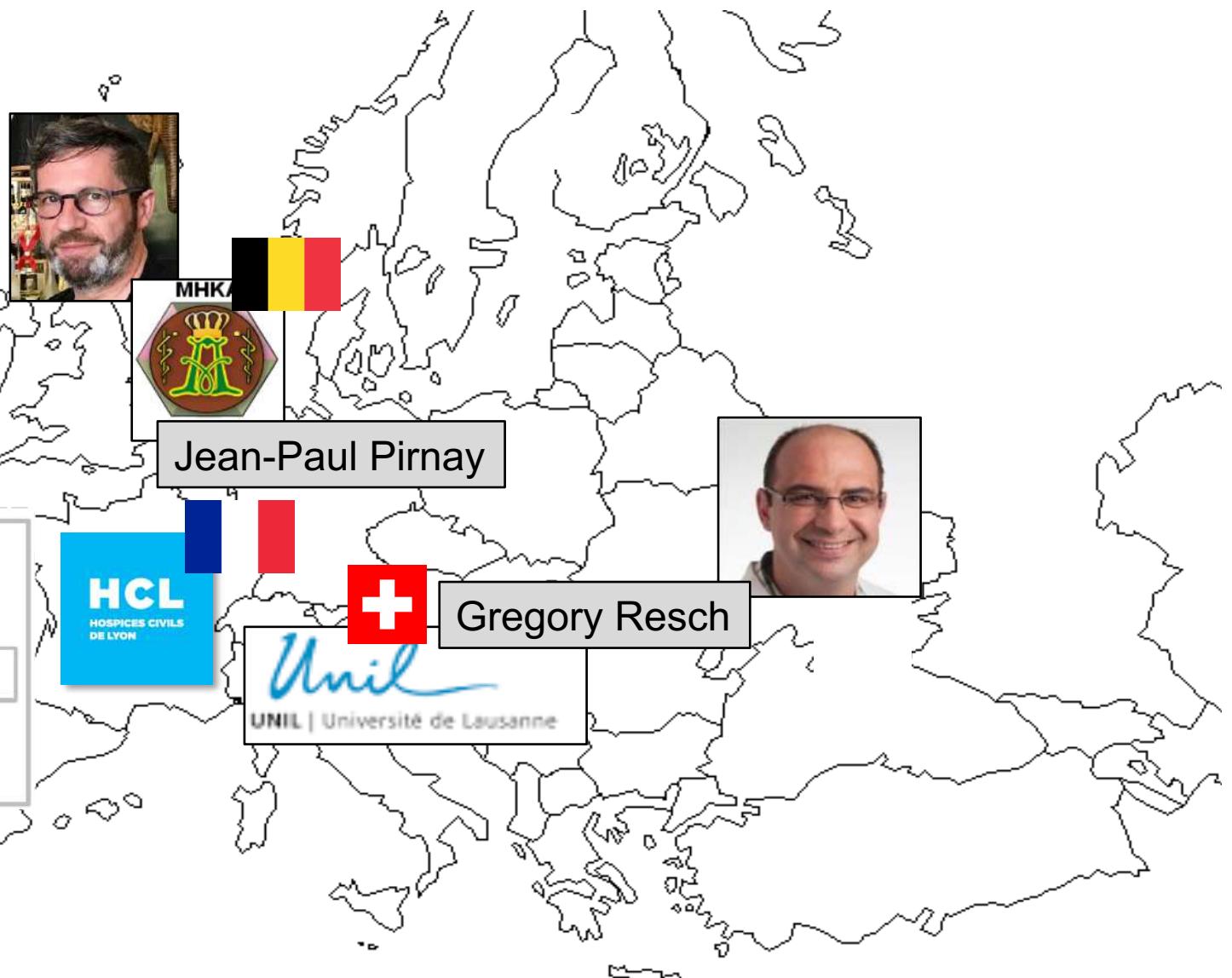
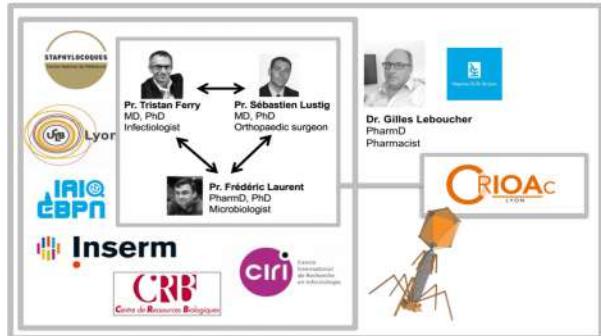
Agence nationale de sécurité du médicament
et des produits de santé

French Health Authority

Unique European academic collaboration



Lyon Phage team



Under the supervision of



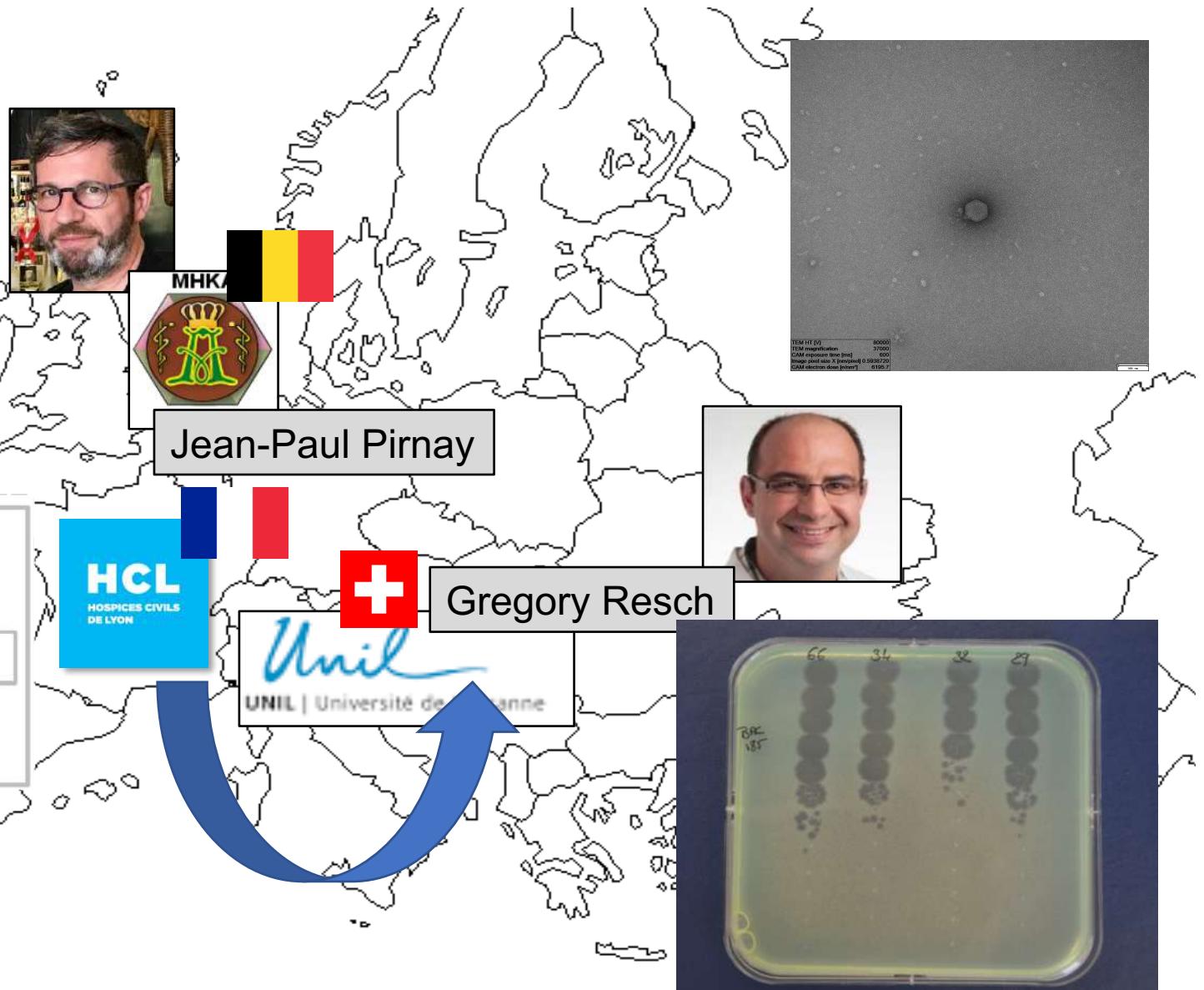
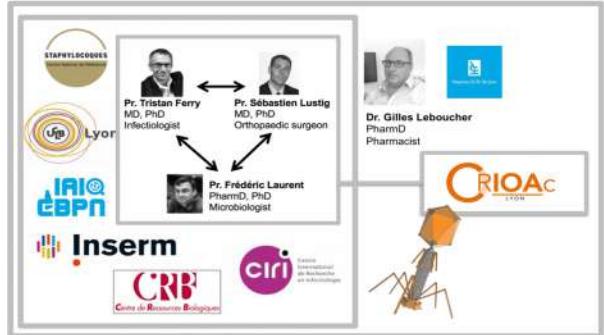
Agence nationale de sécurité du médicament
et des produits de santé

French Health Authority

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Lyon Phage team



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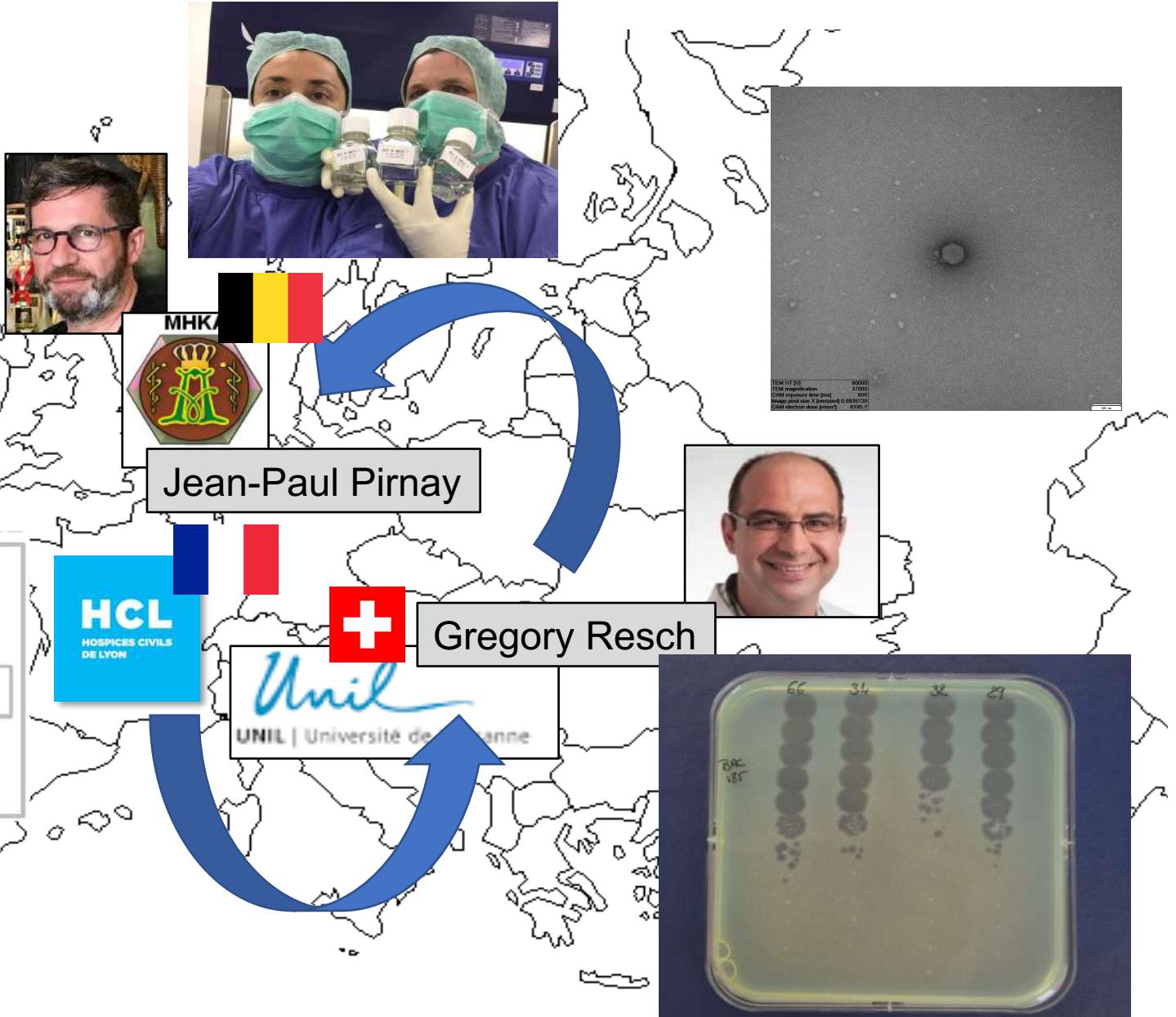
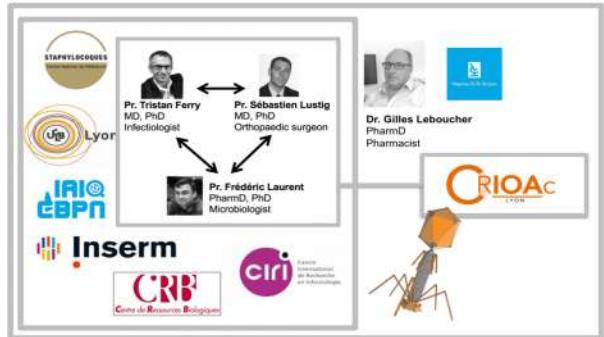
Agence nationale de sécurité du médicament
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et des produits de santé

French Health Authority

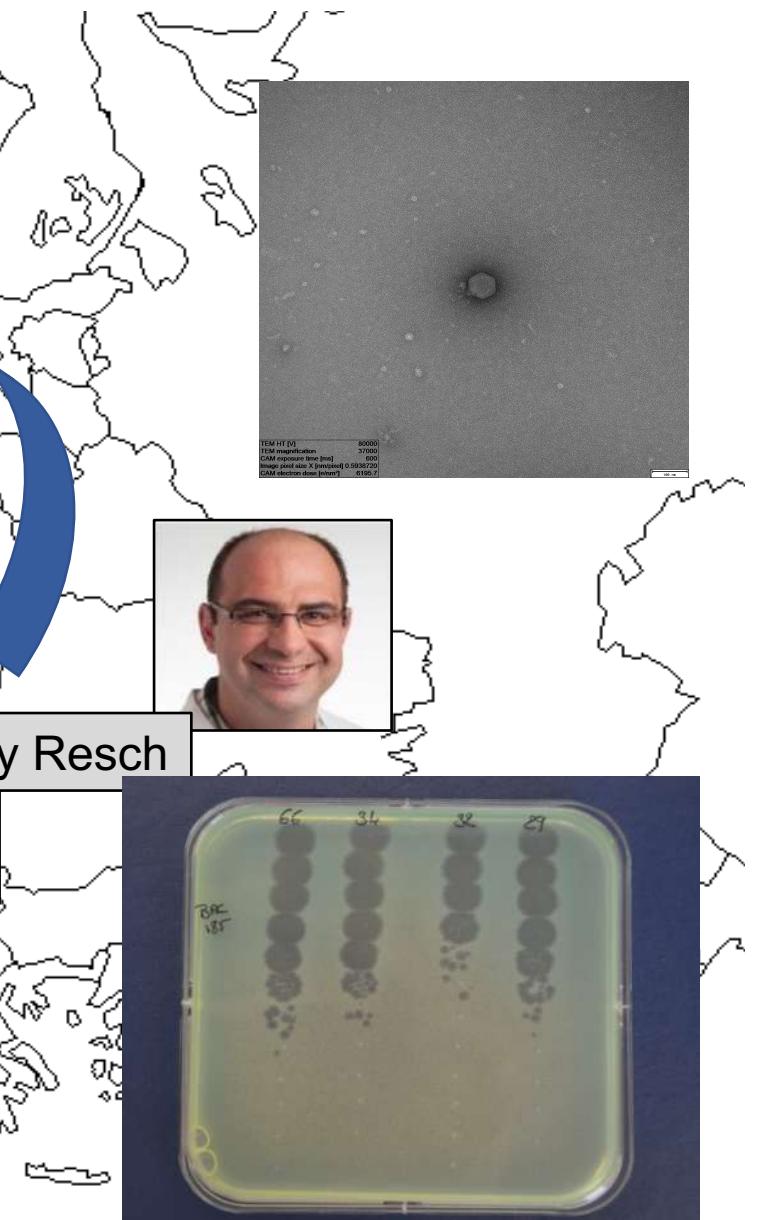
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Lyon Phage team



Jean-Paul Pirnay



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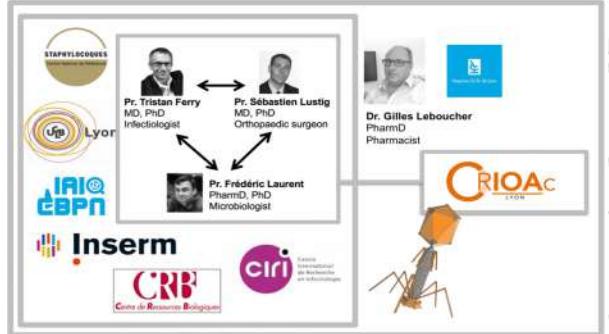
Agence nationale de sécurité du médicament
et des produits de santé

French Health Authority

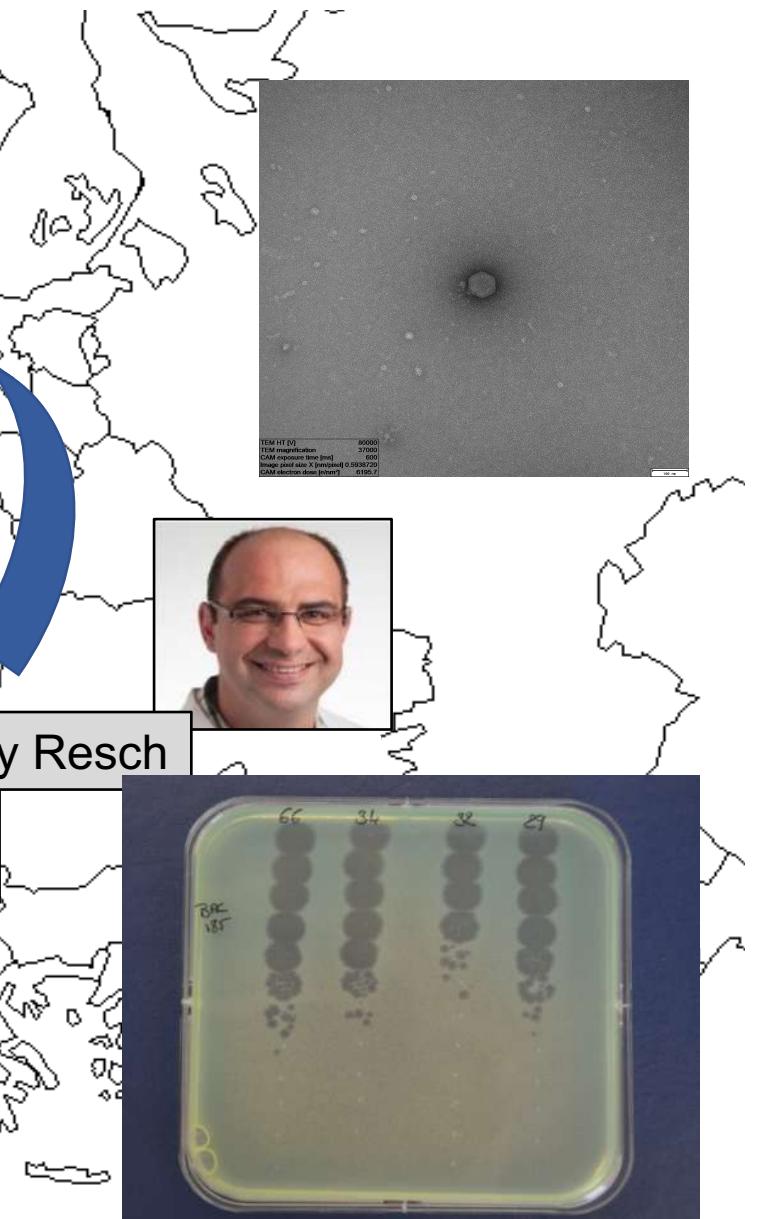
Unique European academic collaboration



Lyon Phage team



Jean-Paul Pirnay



Gregory Resch

Under the supervision of



Agence nationale de sécurité du médicament
et des produits de santé

French Health Authority

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T. FERRY et al. 2022



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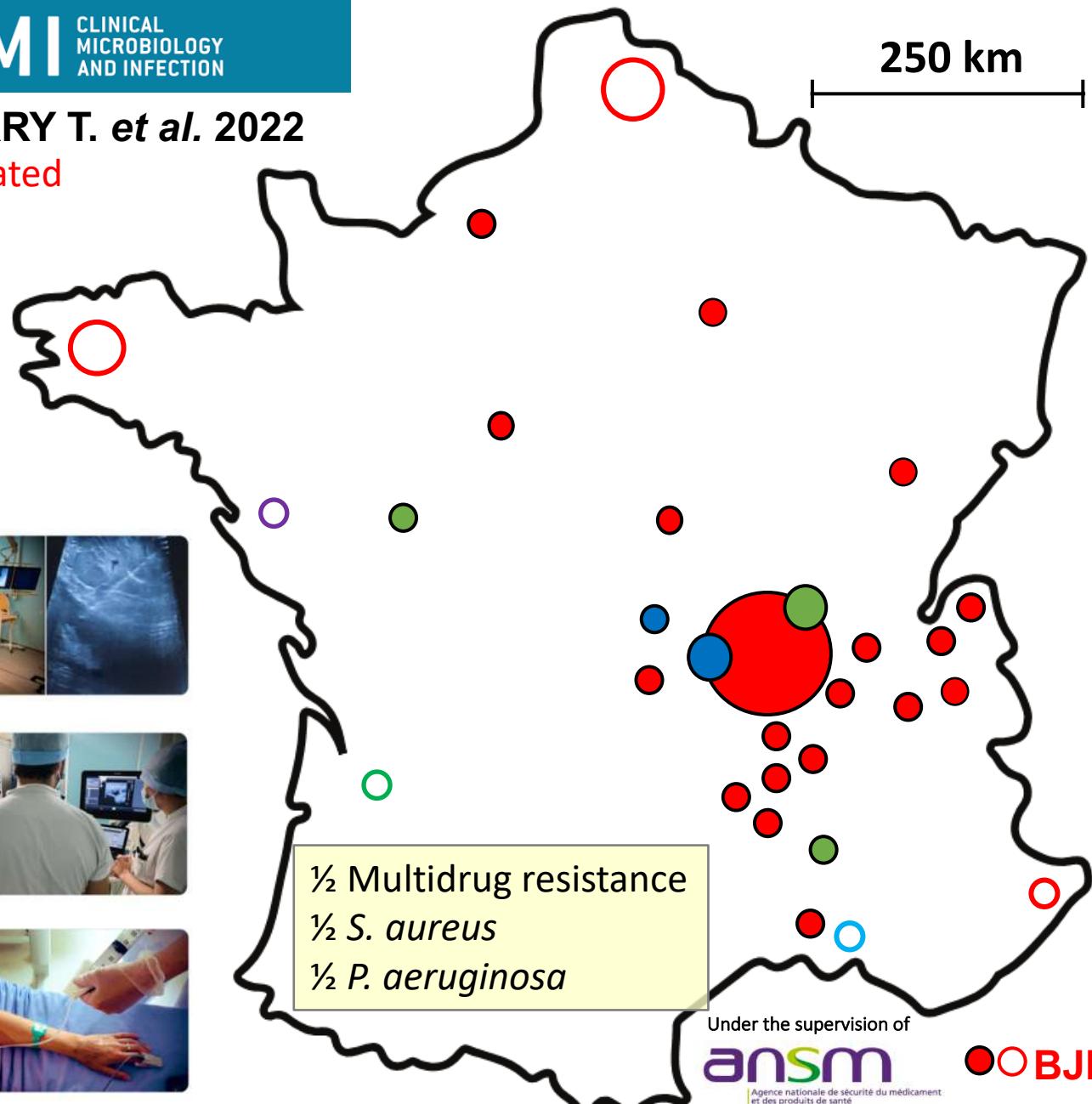
French Health Authority

Conclusions: Personalized phage therapy is a potential adjuvant 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.**

Implementation of a Phage Therapy Center in a CRIESAC

CMI CLINICAL
MICROBIOLOGY
AND INFECTION

FERRY T. et al. 2022
Updated



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anSM
Agence nationale de sécurité du médicament
et des produits de santé



PHAGEinLYON
UFR Lyon 1 CRIESAC ciri



47 patients in Lyon since 2017
~80% of the whole patients treated in France



- 44 with phages from **PHEREZYDES PHARMA**
- 3 with phages from **MHKA HMRA**



- 40 **BJI** (including **34 PJI**)
- 4 **endocarditis/vascular graft**
- 3 **lung infections** (VAP + bacteremia, pneumonia in lung graft bronchectasia, cystic fibrosis exacerbation)

+ 11 patients managed outside Lyon
including 1 in and 1 in

Endocarditis

Pneumonia

Burn

[OVERVIEW](#)[NEWS / EVENTS](#)[PRESS RELEASES](#)[MEDIA COVERAGE](#)[EVENTS](#)[EMAIL ALERTS](#)

CONTRAFECT PARTNERS WITH LEADING ORTHOPEDIC CENTER IN EUROPE TO PROVIDE COMPASSIONATE USE OF EXEBACASE TO PATIENTS WITH CHRONIC STAPHYLOCOCCAL PROSTHETIC JOINT INFECTIONS



LYSINE
de phage

#LYSINDAIR

T. Ferry et al.



2021

Bacteriophage Lysins



Vincent A Fischetti
@microbephage



Tristan Ferry Lyon University Hospitals
@FerryLyon

Incredible talk of Pr. Vincent A. Fischetti [@microbephage](#) @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!

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

#LysinDAIR procedure



ContraFect



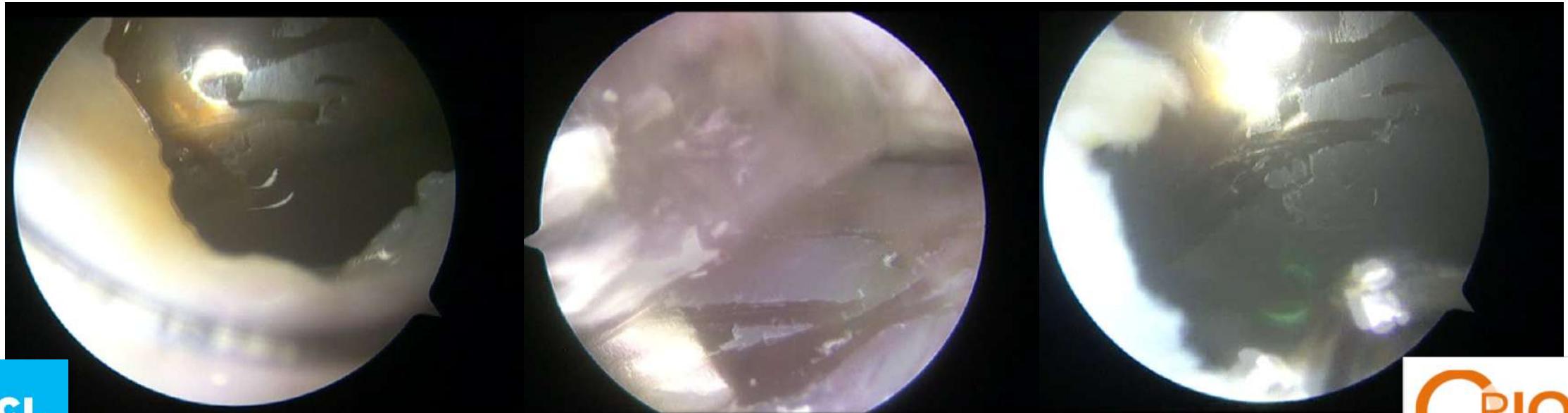
30th
ECCMID
Paris, France
18 –21 April 2020

frontiers
in Medicine

CRIOAc
LYON

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HCL
HOSPICES CIVILS
DE LYON

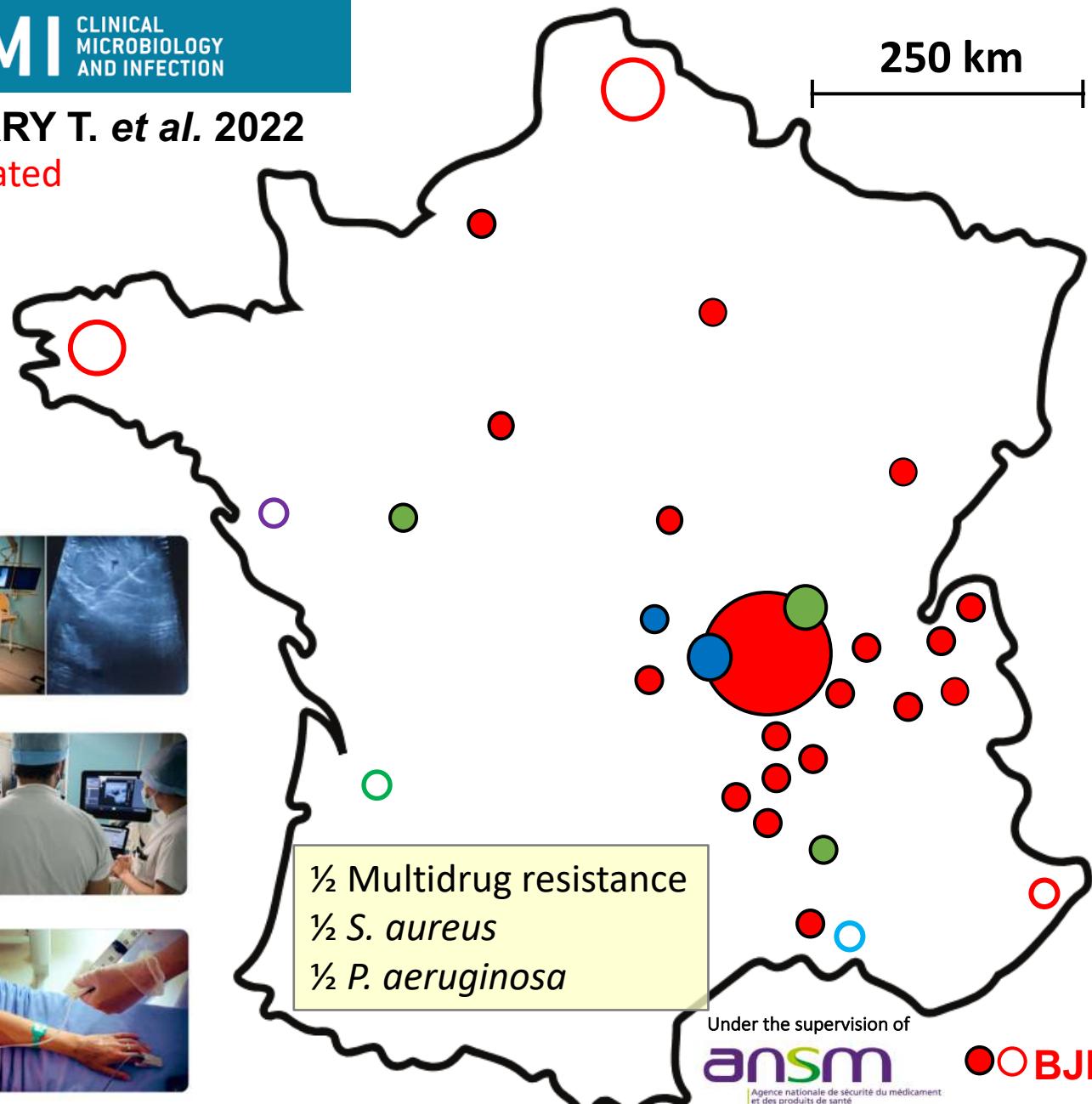
CRIOAc
LYON

The biofilm was macroscopically visible

Implementation of a Phage Therapy Center in a CRIODAC

CMI CLINICAL
MICROBIOLOGY
AND INFECTION

FERRY T. et al. 2022
Updated



Under the supervision of
anSM
Agence nationale de sécurité du médicament
et des produits de santé



PHAGEinLYON
UFR Lyon 1 CRIODAC ciri



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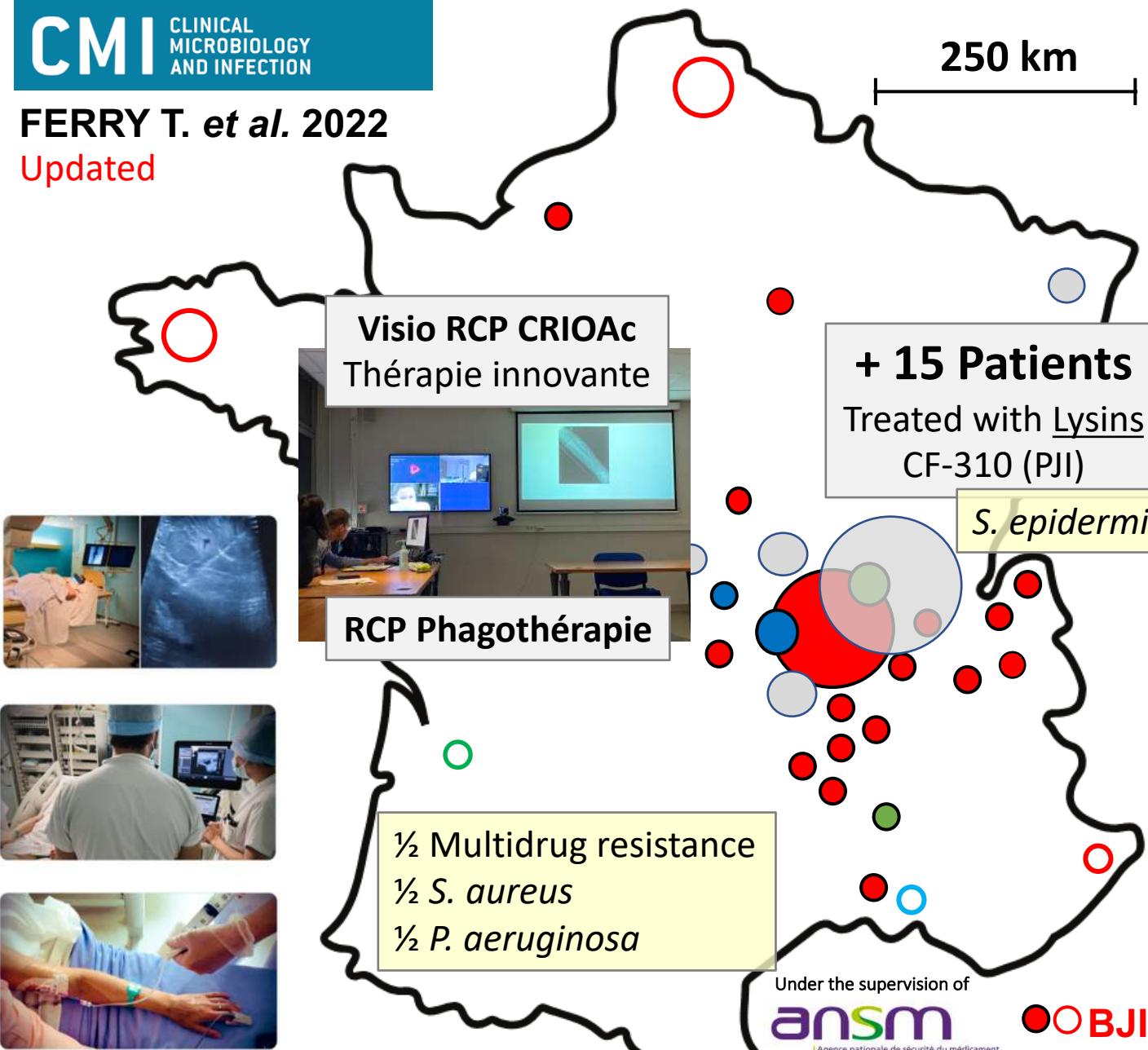
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Implementation of a Phage Therapy Center in a CRIES

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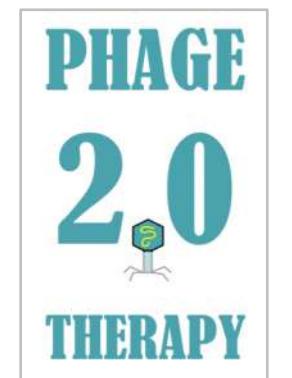
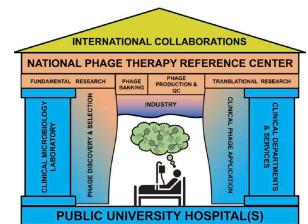
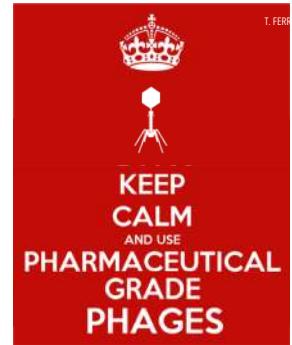
+ 11 patients managed outside Lyon O including 1 in and 1 in



O

Conclusion

- La phagothérapie est une **thérapie innovante et réémergente**
- Toutes les infections bactériennes ne sont pas de bonnes indications de phage
- En ADJUVANT à l'antibiothérapie (et potentiellement la chirurgie) dans les infections bactériennes sévères
- Nécessité d'une **mission nationale « CRIoAc thérapie innovante »**
 - Pour valider les indications pertinentes de phages dans les IOA
 - Pour orienter les prises en charge vers les essais thérapeutiques
 - Ou enfin pour orienter et accompagner le recours à des phages en « compassionnel » (nécessité d'une mission nationale **« RCP Phagothérapie »** pour préciser les modalités)
- Poser les jalons d'un centre national de phagothérapie
- Conception et réalisation d'essais thérapeutiques



**THE MYTHOLOGY
OF PHAGE THERAPY**



T. FERRY

EBM
Clinical
Trials



T. FERRY

Lyon BJI Study group



Coordinator: **Tristan Ferry**

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

Imaging – Fabien Craighero, Loïc Boussel, 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*

Coordinator: **Tristan Ferry (clinic); and Frederic Laurent (lab)**

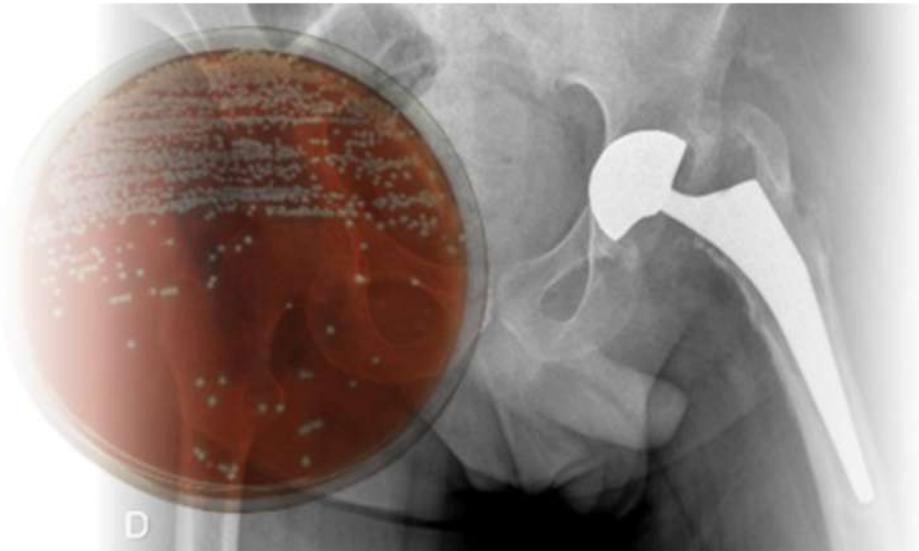
Myrtille Le Bouar, Gilles Leboucher, Thomas Briot; Mathieu Medina, Camille Kolenda, Floriane Laumay, Melanie Bonhomme, Leslie Blazere, Tiphaine Legendre, Eline Terrazzoni, Fabrice Pirot, Camille Merienne, Samira Filali, Benjamin Lapras



Croix-Rousse Hospital



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



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