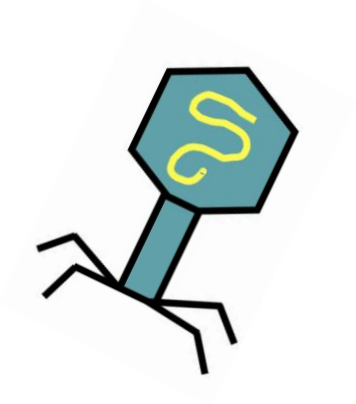
Dossiers Phagotherapie



Pr. Tristan Ferry
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)

Lyon 1

CRIOAc LYON

@FerryLyon

ciri Centre International de Recherche en Infectiologie

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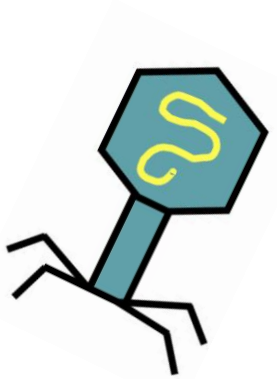
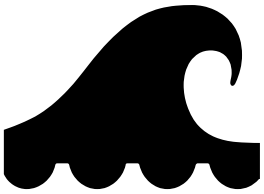
What is a « bacteriophage » ?



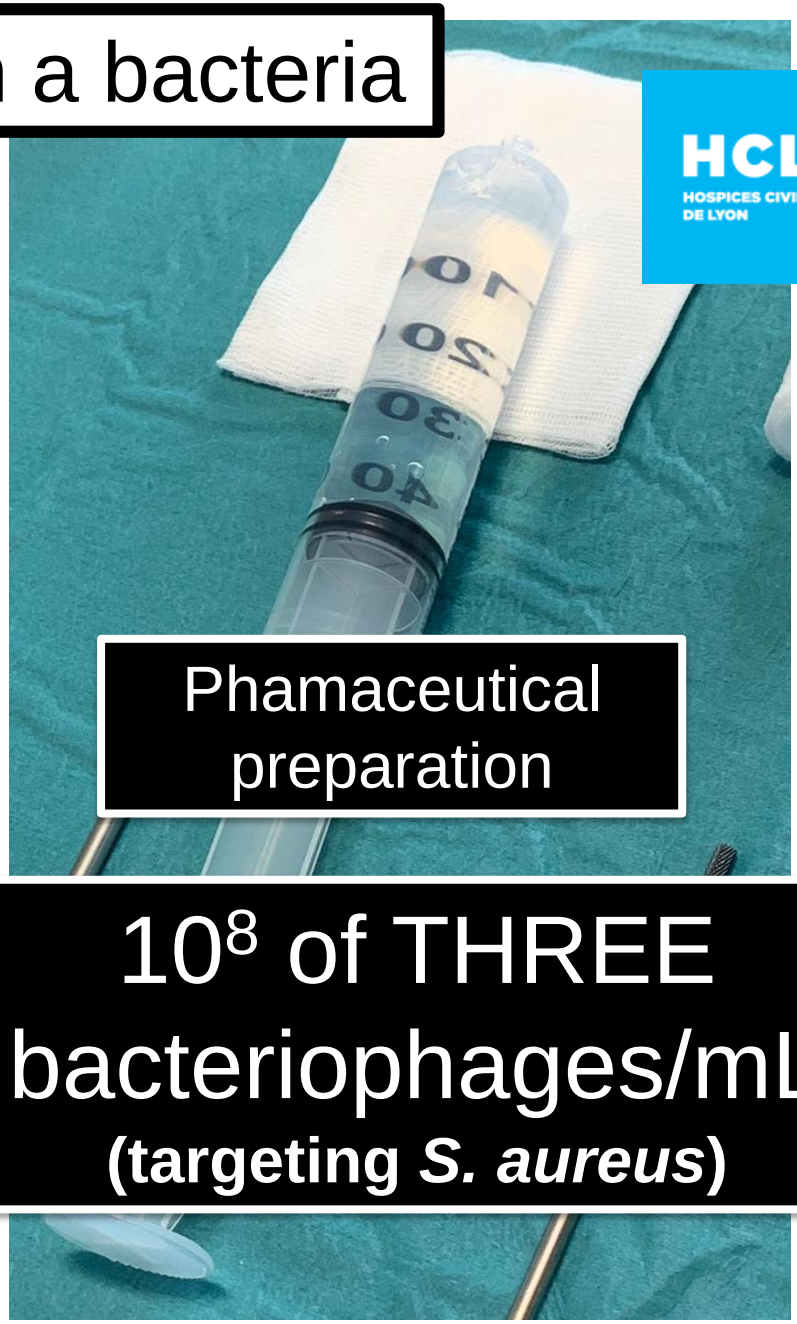
- Suffix –phage, *phagos* φαγεῖν (*phagein*), "to eat", “to devour"
- **Viruses that infect ONLY bacteria**
- Classification (*myoviridae, podoviridae, etc…)*
- **A phage is specific to A type of bacteria**
- **Largely abundant in the biosphere: 10^{31} bacteriophages on the planet, more than every other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



10 to 100 fold smaller than a bacteria

Translucent tap water

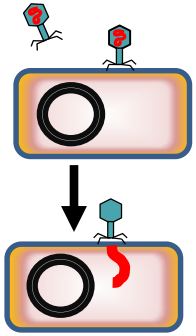
X million of ≠ Bactériophage**S** !!!
(targeting environmental bacteria)



Phamaceutical preparation

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

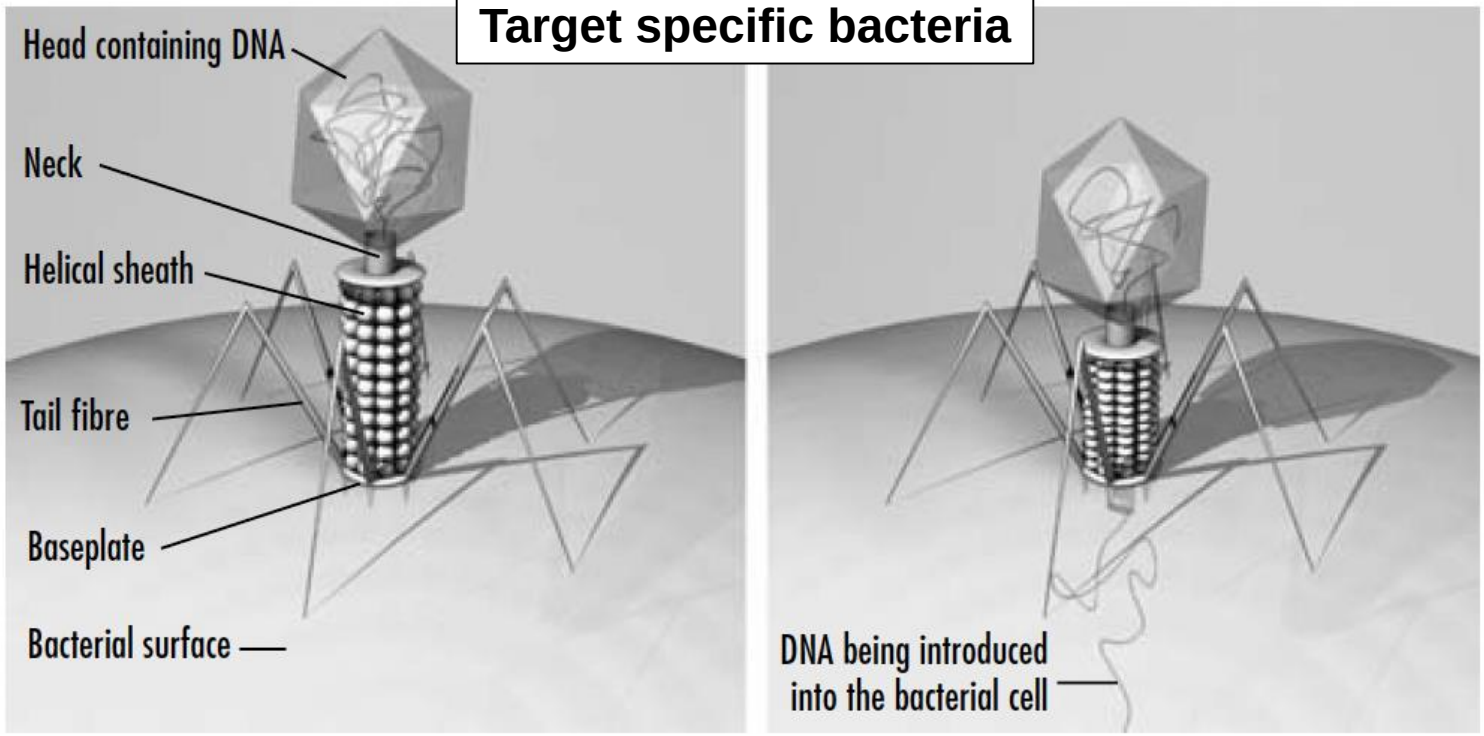
Ferry T.



Cell recognition

DNA injection

Environmental viruses
Target specific bacteria



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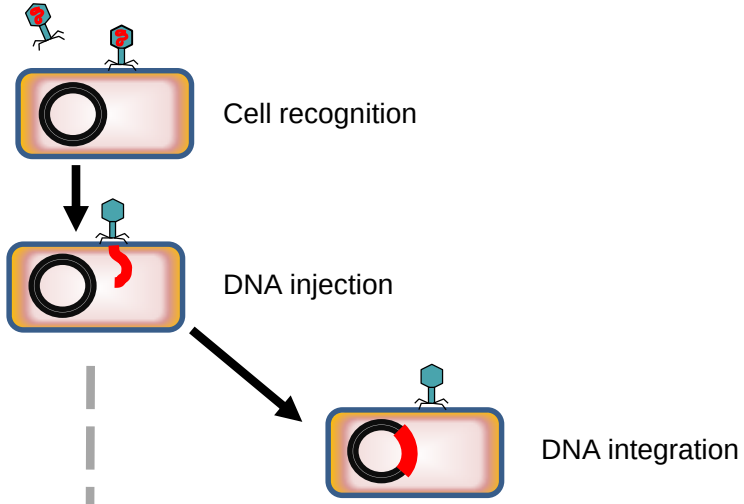
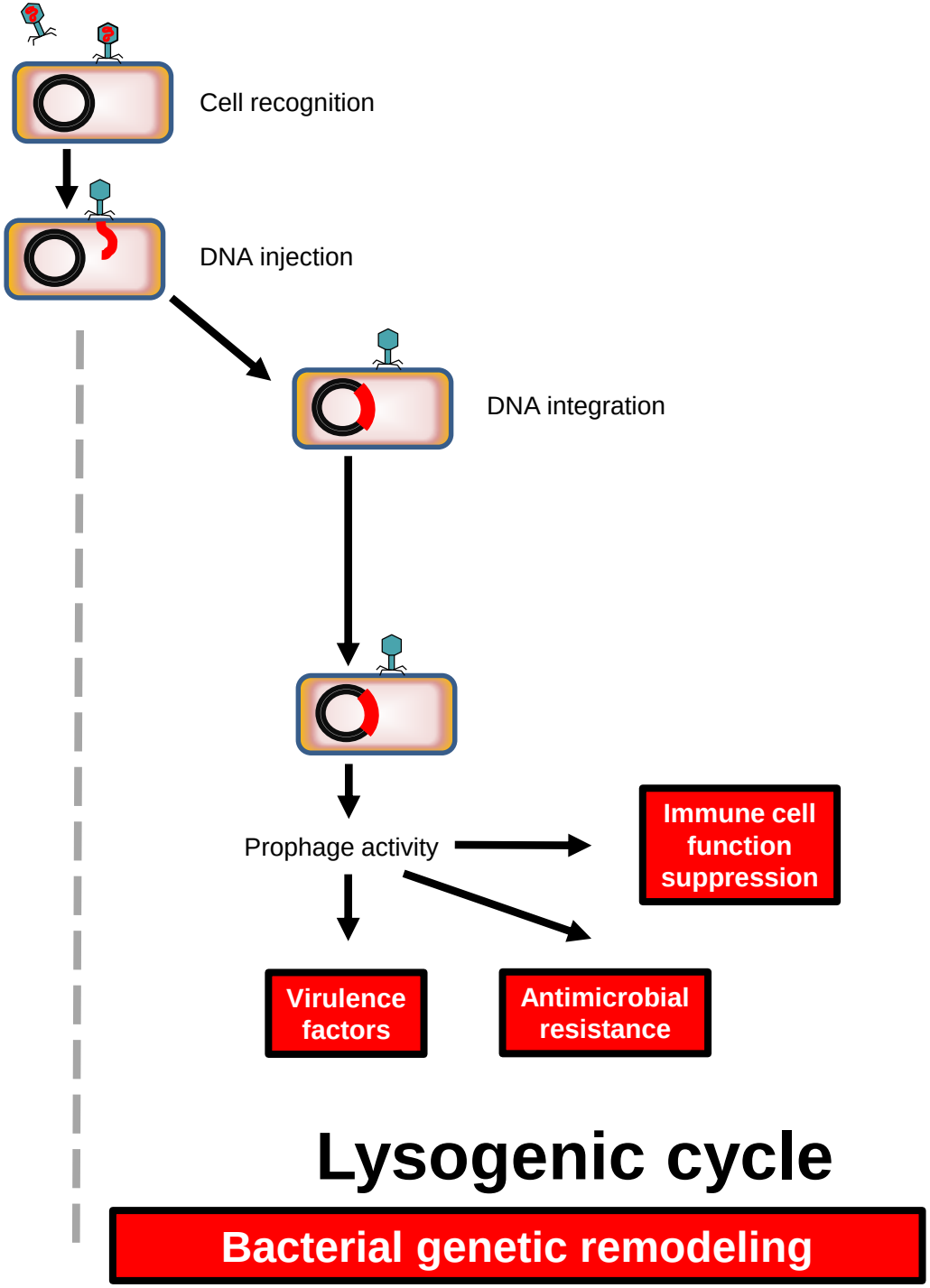


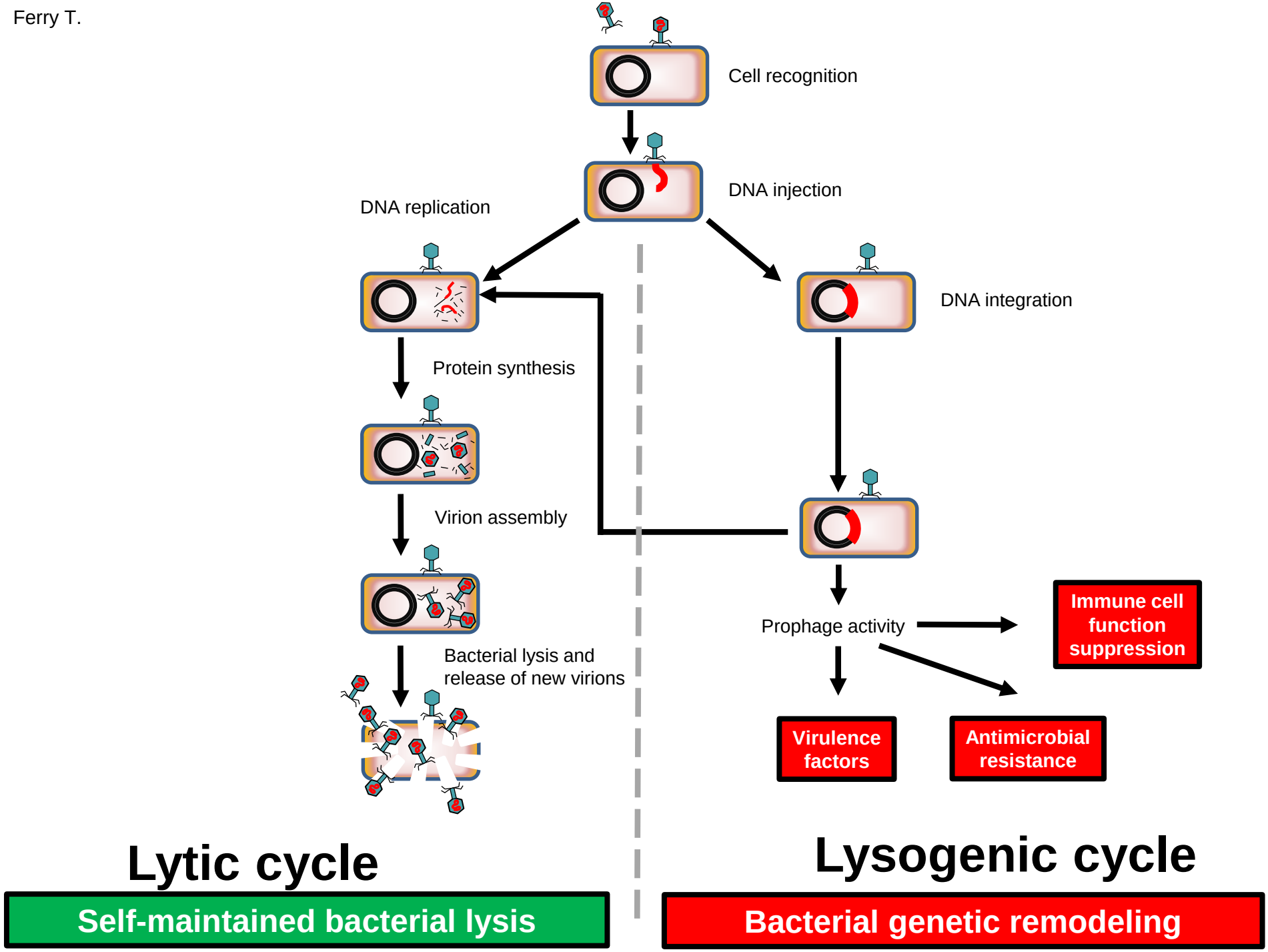
Lysogenic cycle

Bacterial genetic remodeling

Ferry T.


Cell recognition
DNA injection
DNA integration
Prophage activity
Immune cell function suppression
Virulence factors
Antimicrobial resistance
Lysogenic cycle
Bacterial genetic remodeling

Ferry T.


Cell recognition
DNA injection
DNA replication
DNA integration
Protein synthesis
Virion assembly
Bacterial lysis and
release of new virions
Prophage activity
Immune cell
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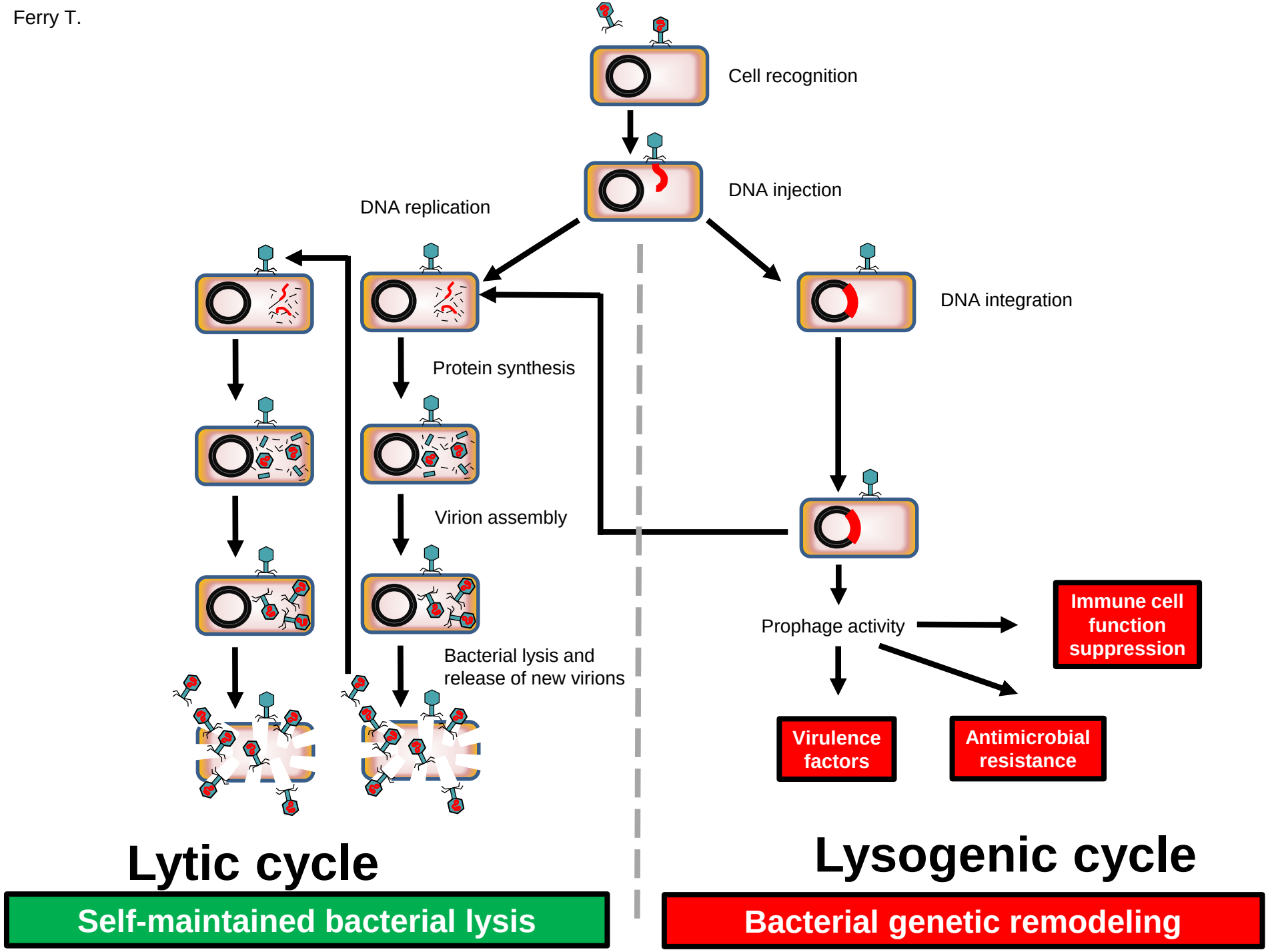
Antimicrobial
resistance
Lytic cycle
Self-maintained bacterial lysis
Lysogenic cycle
Bacterial genetic remodeling

Ferry T.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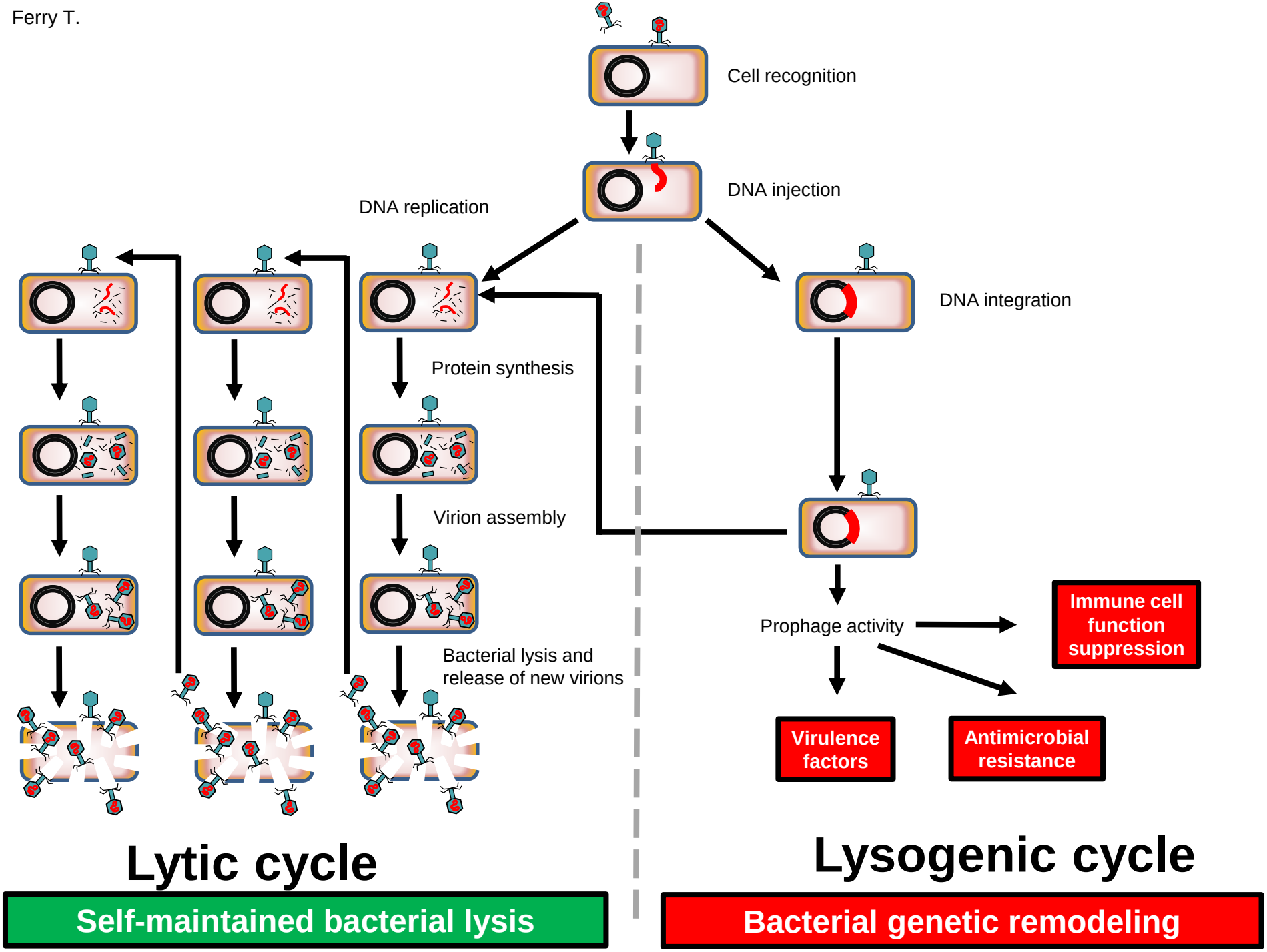
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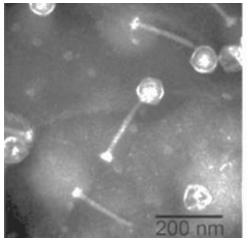
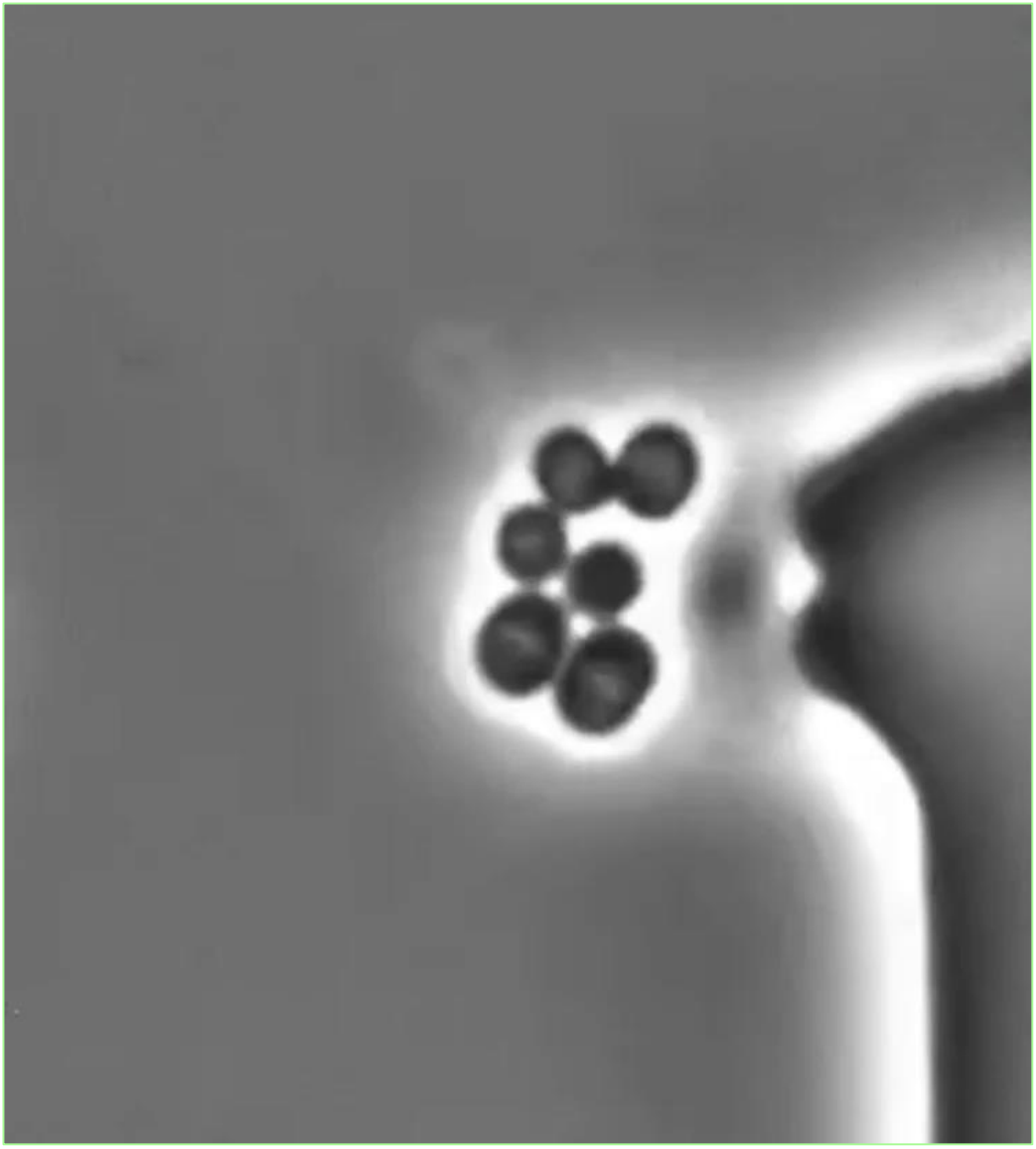
Bacterial genetic remodeling

A clear antibacterial activity!

S. aureus being lysed by the Sa2 phage



Bacterial DNA appeared in green



Courtesy Pascal Maguin
Luciano Marraffini Lab
THE ROCKEFELLER UNIVERSITY

History of phage therapy

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

History of phage therapy

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- He treated **<u>shigellosis</u>** (diarrhea) in children with **<u>oral intake</u>** of specific "filtered" **<u>bacteriophages</u>** that he found in stools of patients who spontaneously healed from… shigellosis

History of phage therapy

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- He founded **Eliava institute in Georgia** and the **"Laboratoire Français des Bactériophages"** in Paris

History of phage therapy

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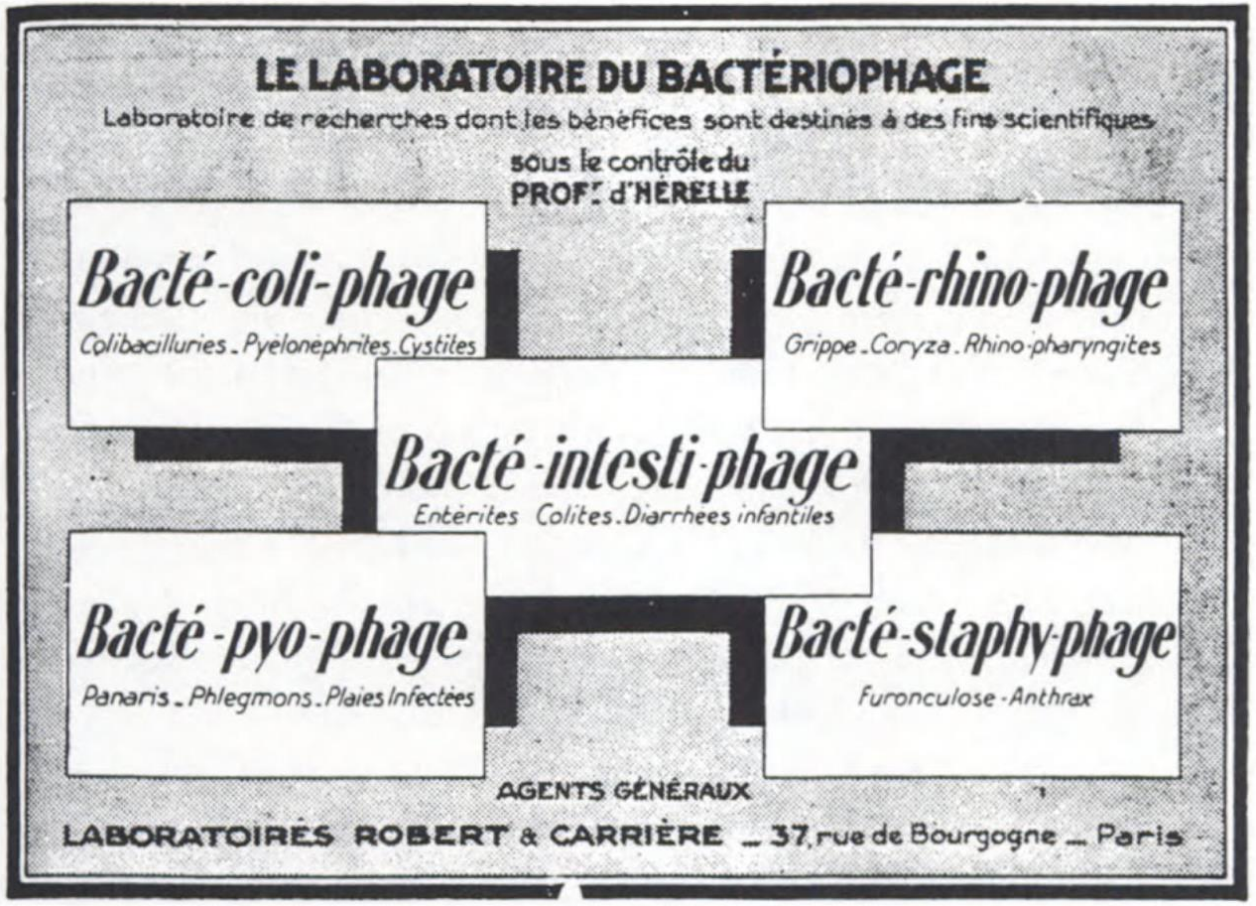

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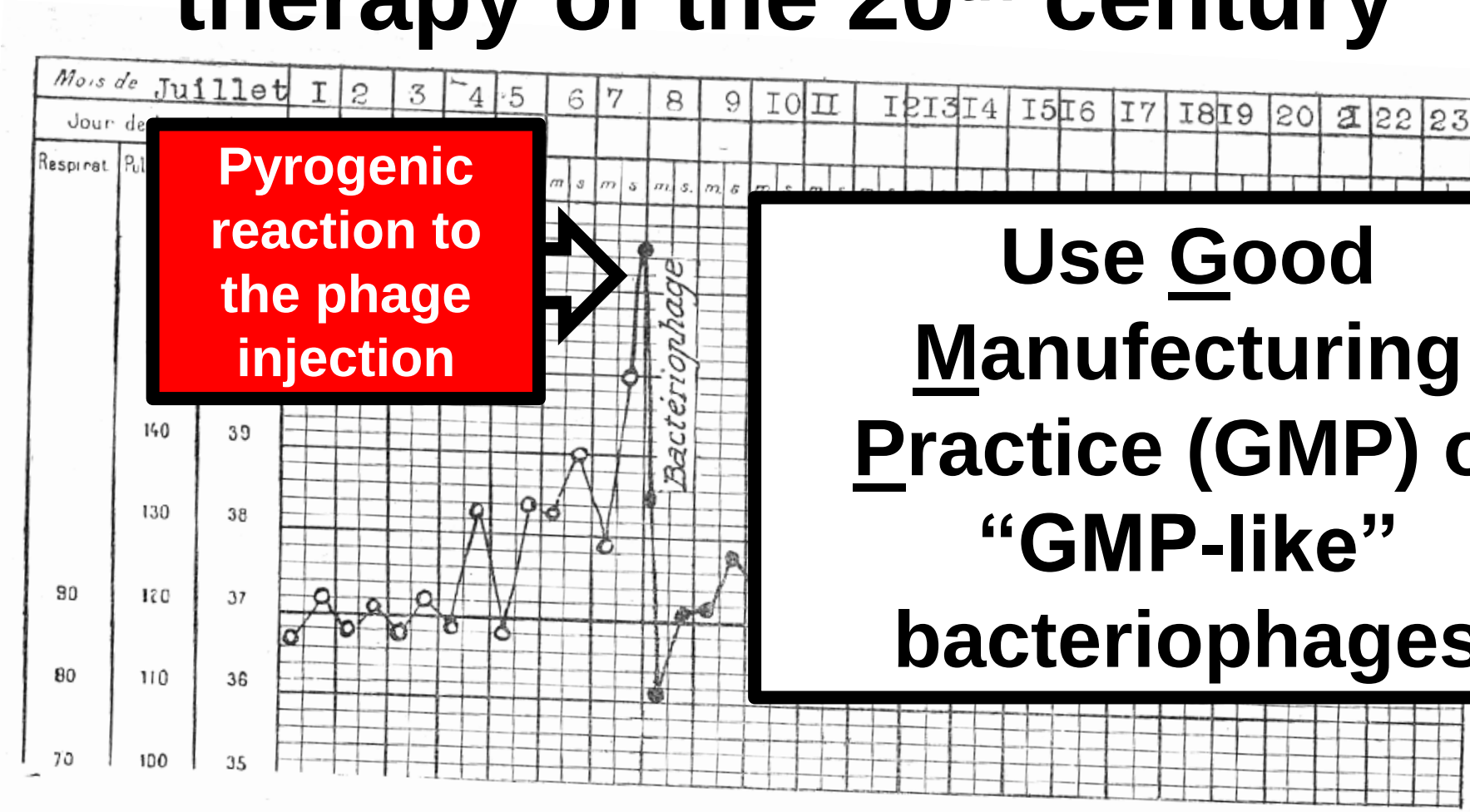
- H orgia and the **“Laboratoire Français des Bactériophages”** in Paris

Lessons to be learned of phage therapy of the 20th century



Pyrogenic reaction to the phage injection

Use Good Manufecturing Practice (GMP) or "GMP-like" bacteriophages

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.

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 cnrayer 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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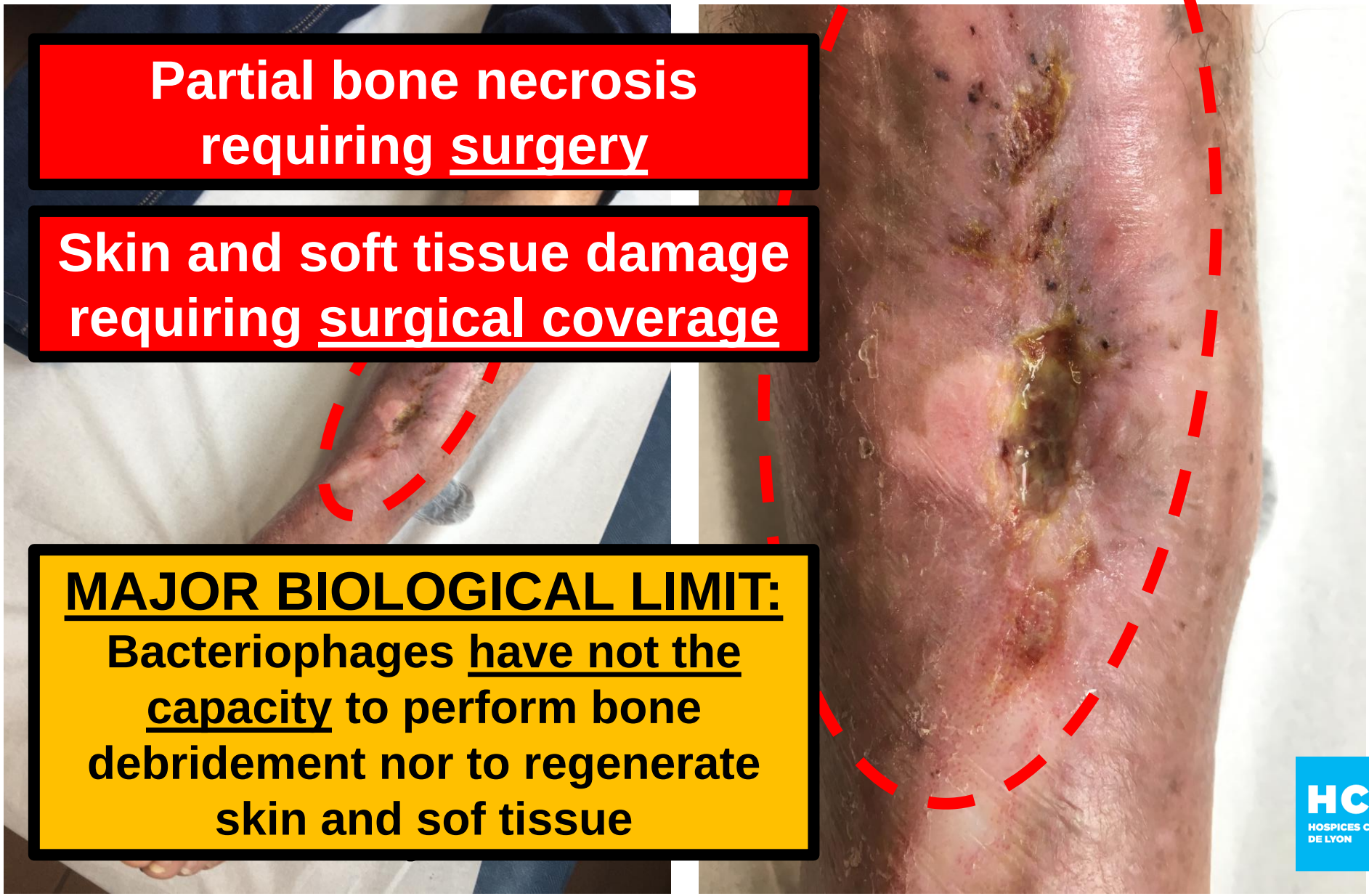


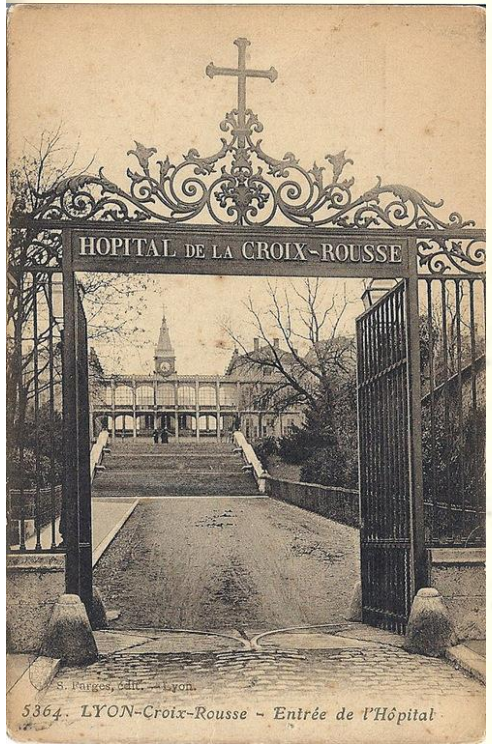
Patient with a relapsing infection after Phage therapy in Tbilissi

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.



Les bacilles pyocyaniques sont fréquemment résistants aux antibiotiques usuels. Cepend… cutanées, otitiques, bron… leur être attribuées semble être en augmentation. Leur caractère rebelle est une de leurs caractéristiques. I… thérapeutique différente de celles… n connaissait l'existence de bact… Mais l'emploi de stock-bactériop… ntre, l'adaptation par sélection d'une variété de bactériophage à la souche isolée du malade permet une actio… sur bouillon nutritif ordinaire… est par contre indispensable de l… in dilué pour pouvoir l'introdu… arachidienne intraveineuse, int…

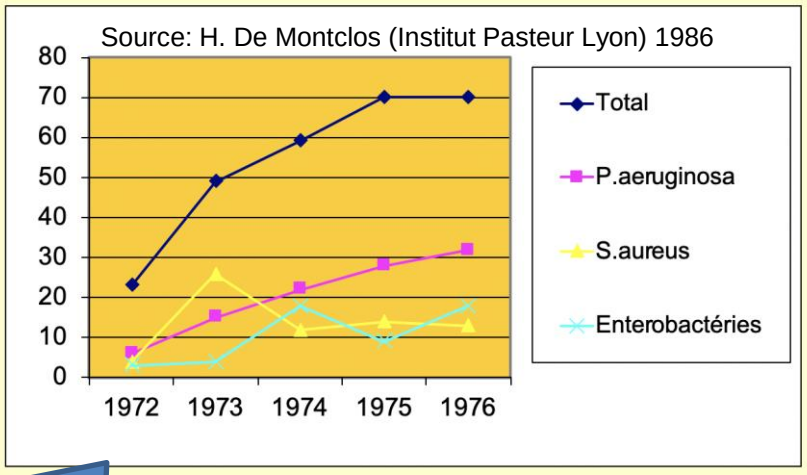
Un certain n… pportés dans cette publication.

Antimicrobial resistance

Phage banking
Phage training

Meningitis
Skin and soft tissue
Bone and joint

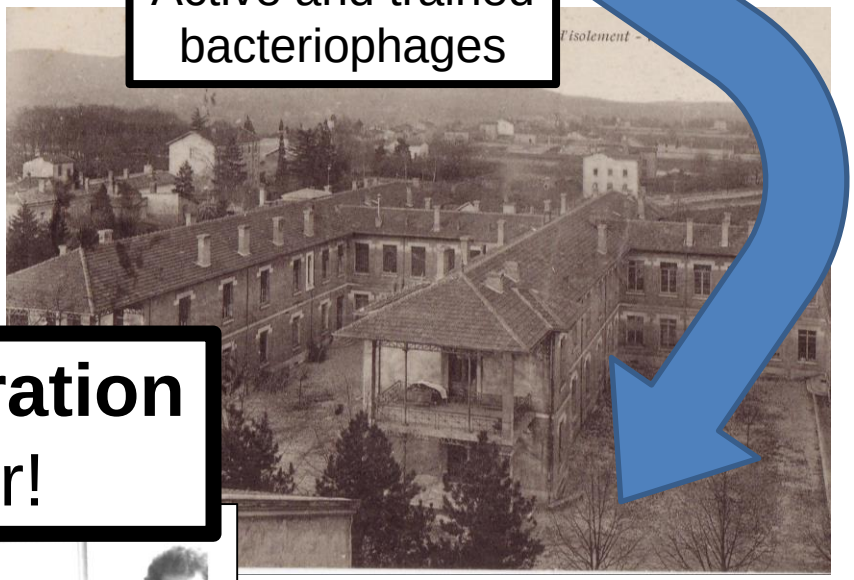
Clinique des Maladies Infectieuses, Hôpital de la Croix-Rousse
Hospices Civils de Lyon
1958-1960



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

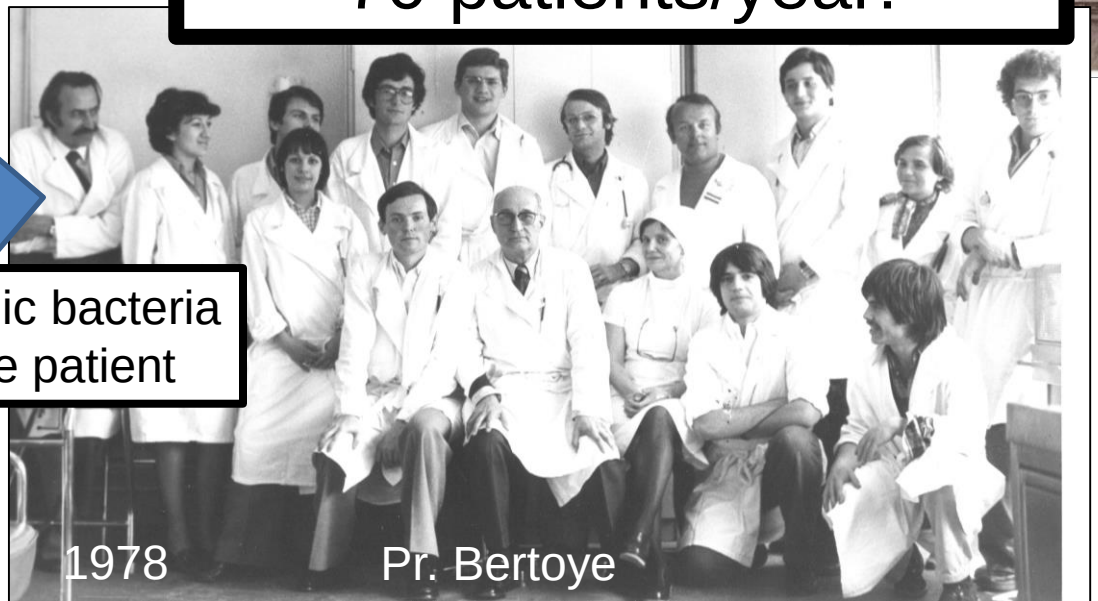
Institut Pasteur Lyon

Active and trained bacteriophages



Academic collaboration
70 patients/year!

Pathogenic bacteria from the patient

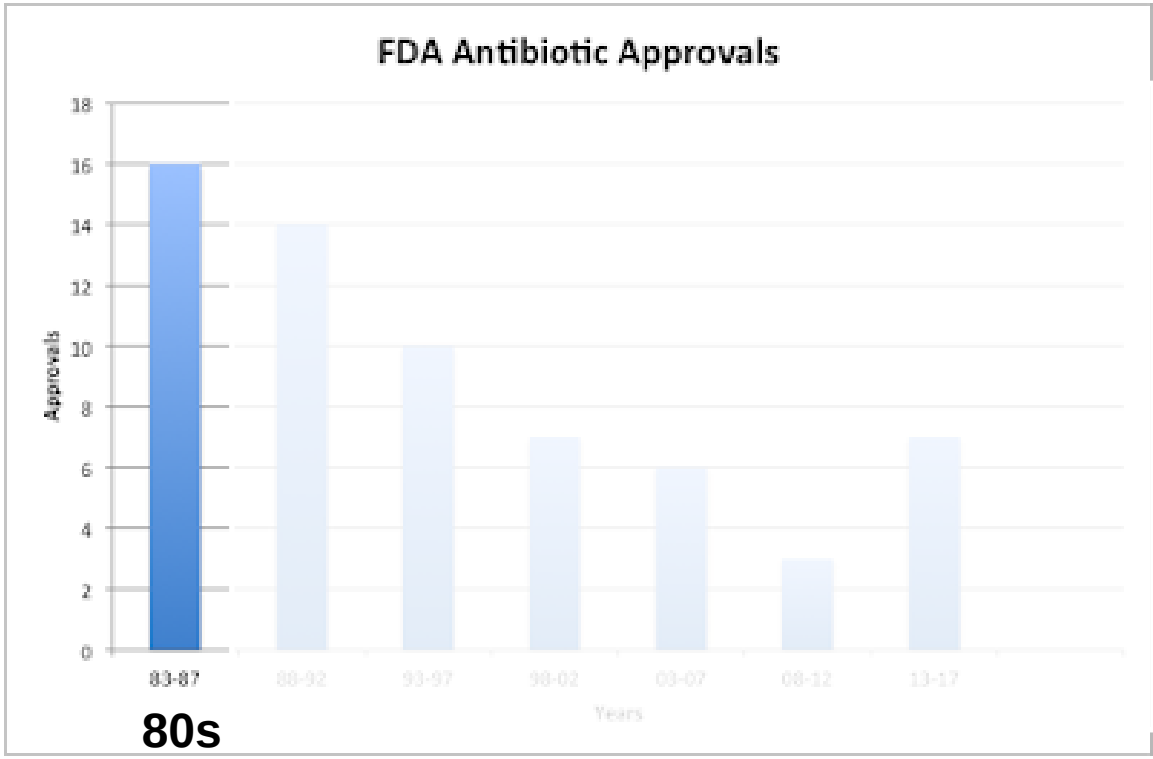


Infectious Disease clinic

HCL
HOSPICES CIVILS DE LYON

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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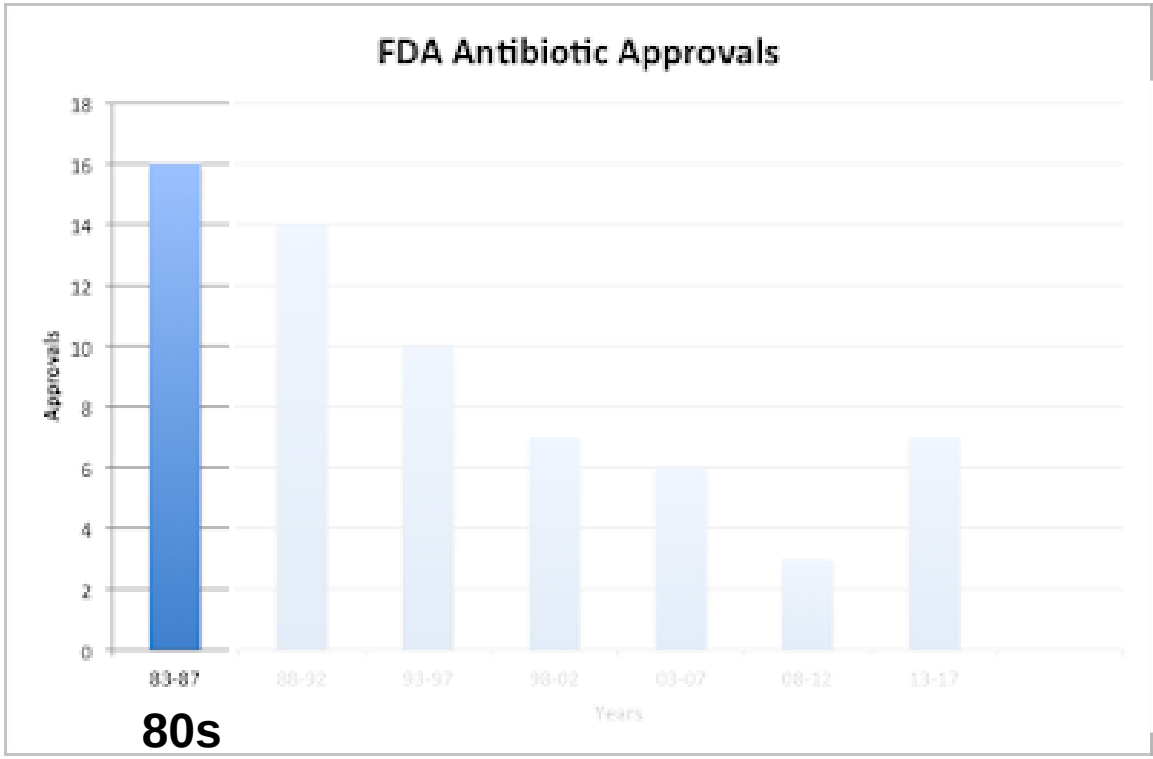

80s

VS.

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

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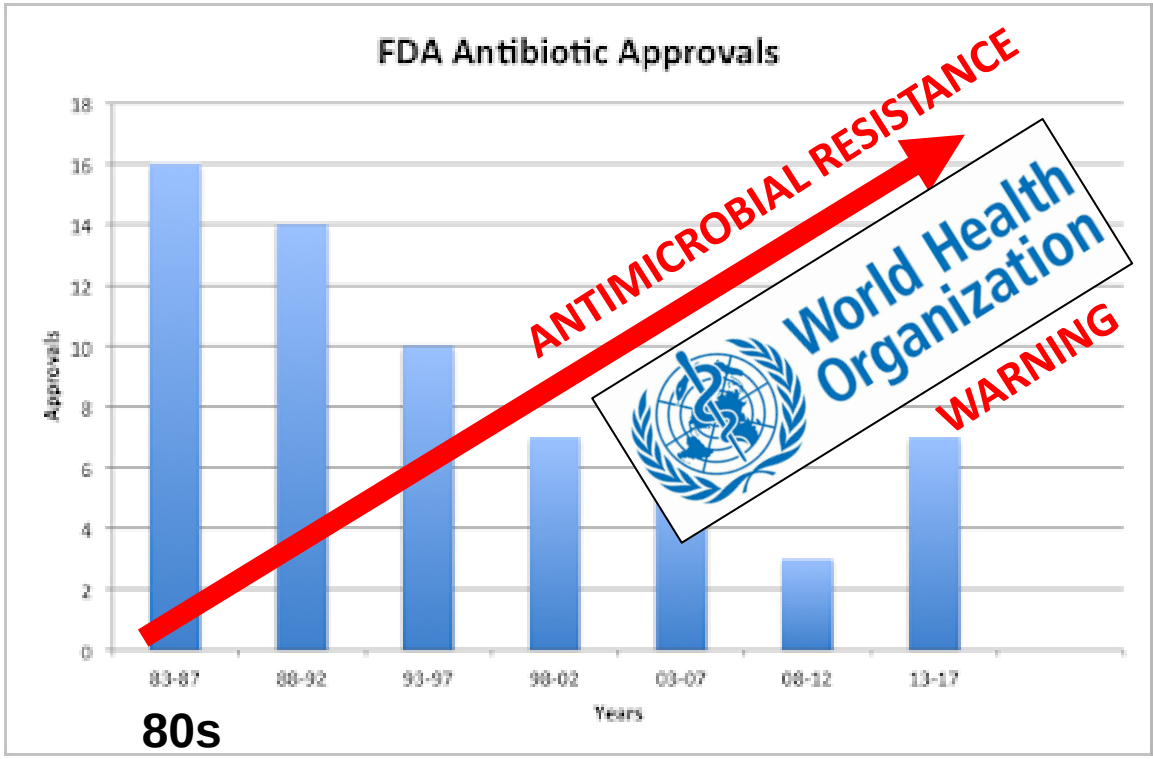

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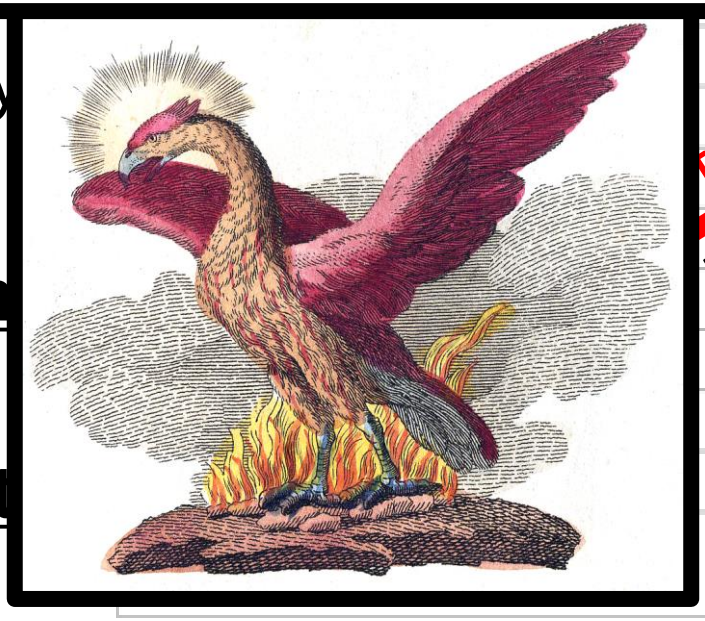
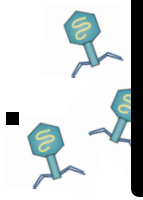
Phages as the Phoenix?



VS.

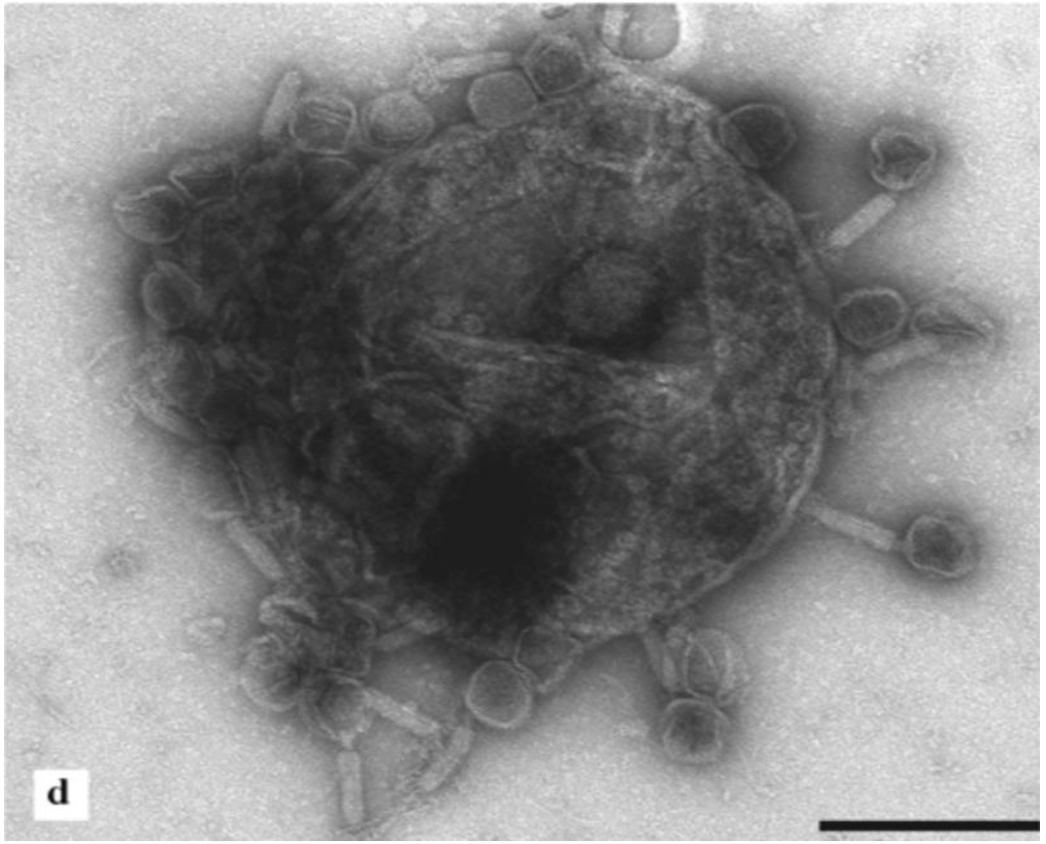


Complex virus-based personalized treatment without clear industrial process, not considered as a drug

Cocktails produced in 2020 by the Eliava Institute

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

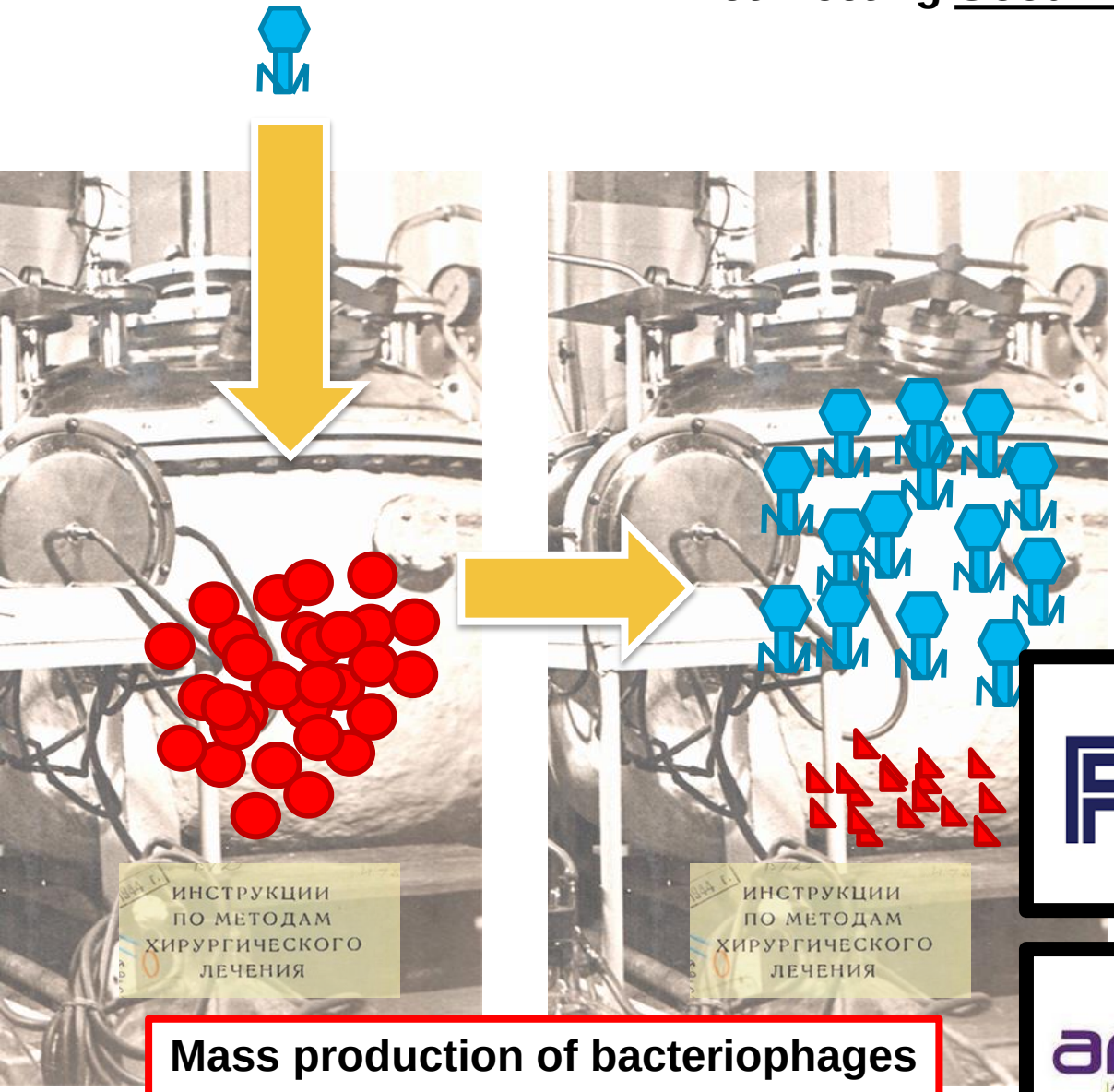
Bacteriophage ISP (*Myoviridae*)



Merabishvili et al. PloS ONE 2009

T. Ferry. *The story of Phage therapy*

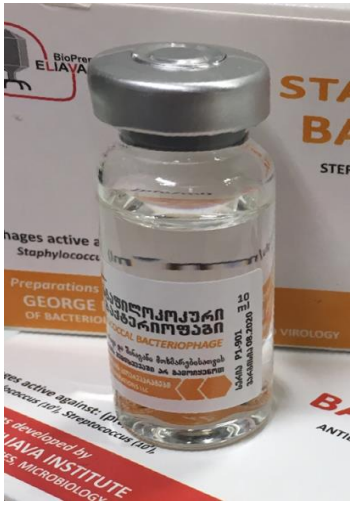
Not meeting Good Manufacturing Practices (GMP)



Mass production of bacteriophages in Soviet Union during WWII

T. Ferry. *The story of Phage therapy*

Pyrogenic Bacterial remnant?



10^6 phages/mL

FDA

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

AMPLIPHI BIOSCIENCES CORPORATION
ARMATA PHARMACEUTICALS
PHERECYDES PHARMA

GMP

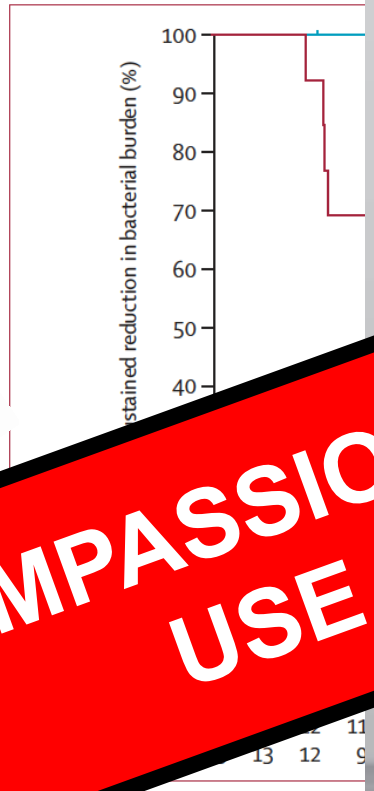
APPROVED

FOR

CLINICAL TRIALS

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



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

COMPASSIONATE USE

osa

RECYDES
RMA

Lancet Infect Dis 2018

PHOSA

PHERECYDES PHARMA

PHOSA & Phagothérapie | Consortium PHOSA | Communication | Contact

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ARF ASSOCIATION DES RÉGIONS DE FRANCE

bpifrance

CRIOAC LYON

BioFilm Control

UCBL Lyon 1

PHERECYDES PHARMA

Phage discovery to find active bacteriophages against Staphylococci

Vivexia laboratory

HCL HOSPICES CIVILS DE LYON

ciri Centre International de Recherche en Infectiologie

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

Phages anti-S. aureus

REFERENCE CENTERS FOR THE MANAGEMENT OF BONE AND JOINT INFECTION

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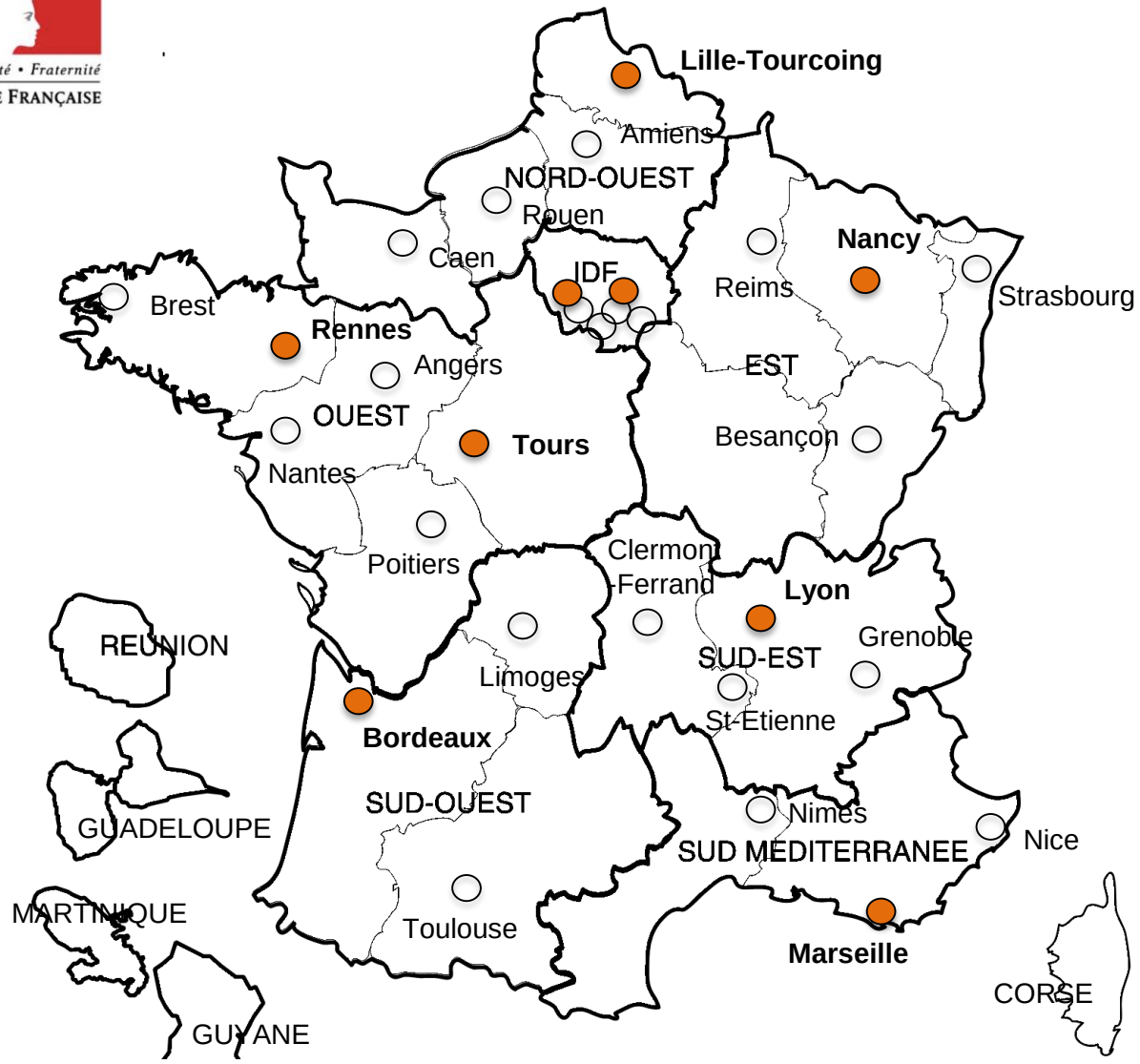

“CRIOAc” Network

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

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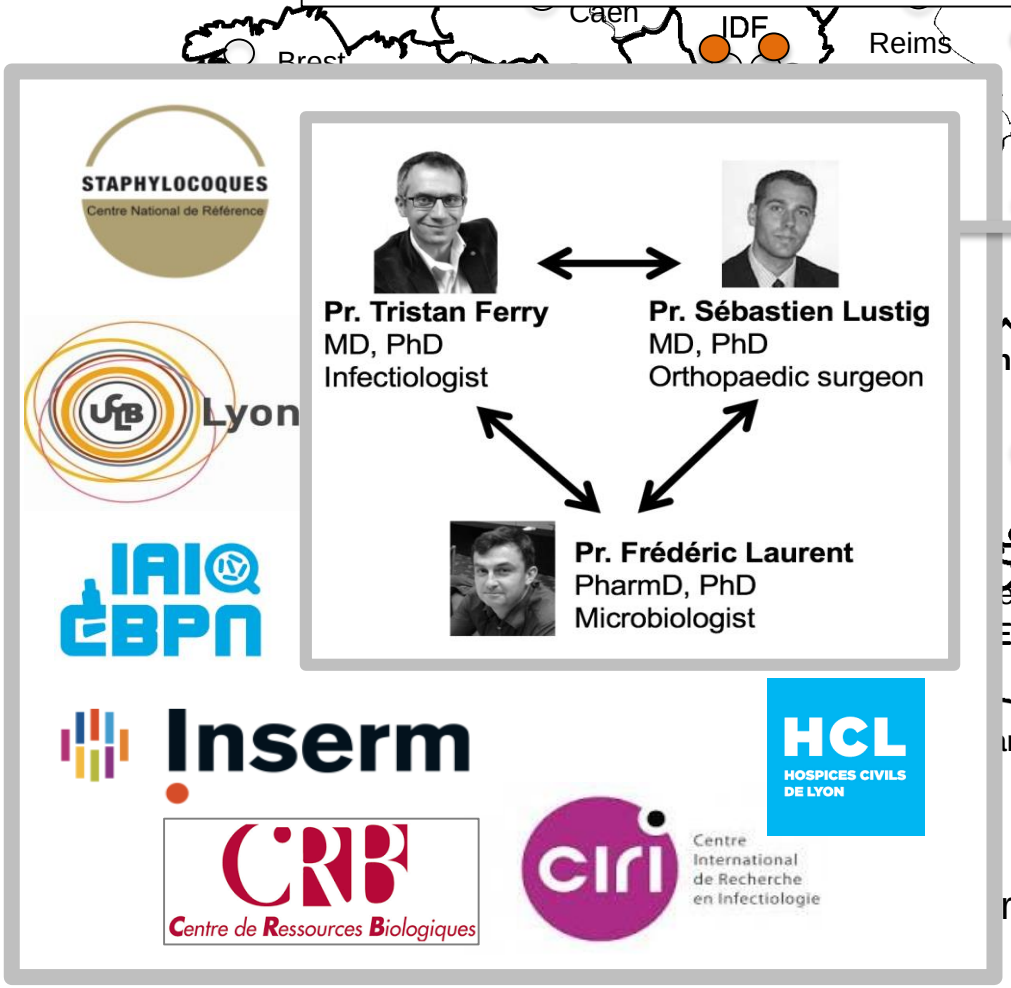
http://www.crioac-lyon.fr

@CrioacLyon

CRIOAc Lyon



STAPHYLOCOQUES
Centre National de Référence

Pr. Tristan Ferry
MD, PhD
Infectiologist

Pr. Sébastien Lustig
MD, PhD
Orthopaedic surgeon

Pr. Frédéric Laurent
PharmD, PhD
Microbiologist

CRIOAc LYON

- Multidisciplinar management of the patient
- Better understanding of the pathophysiology of BJI
- Promotion of innovative treatments

Lyon

IAI
EBPN

Inserm

HCL
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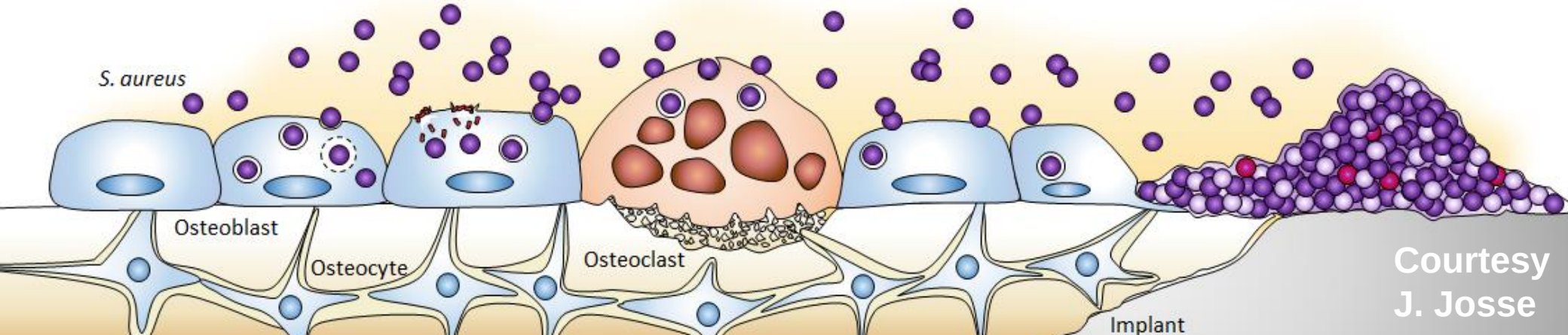
CRB
Centre de Ressources Biologiques

ciri
Centre International de Recherche en Infectiologie

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

Persisters in chronic BJI

"Bacterial cells that escape the effects of antibiotics without undergoing genetic change"



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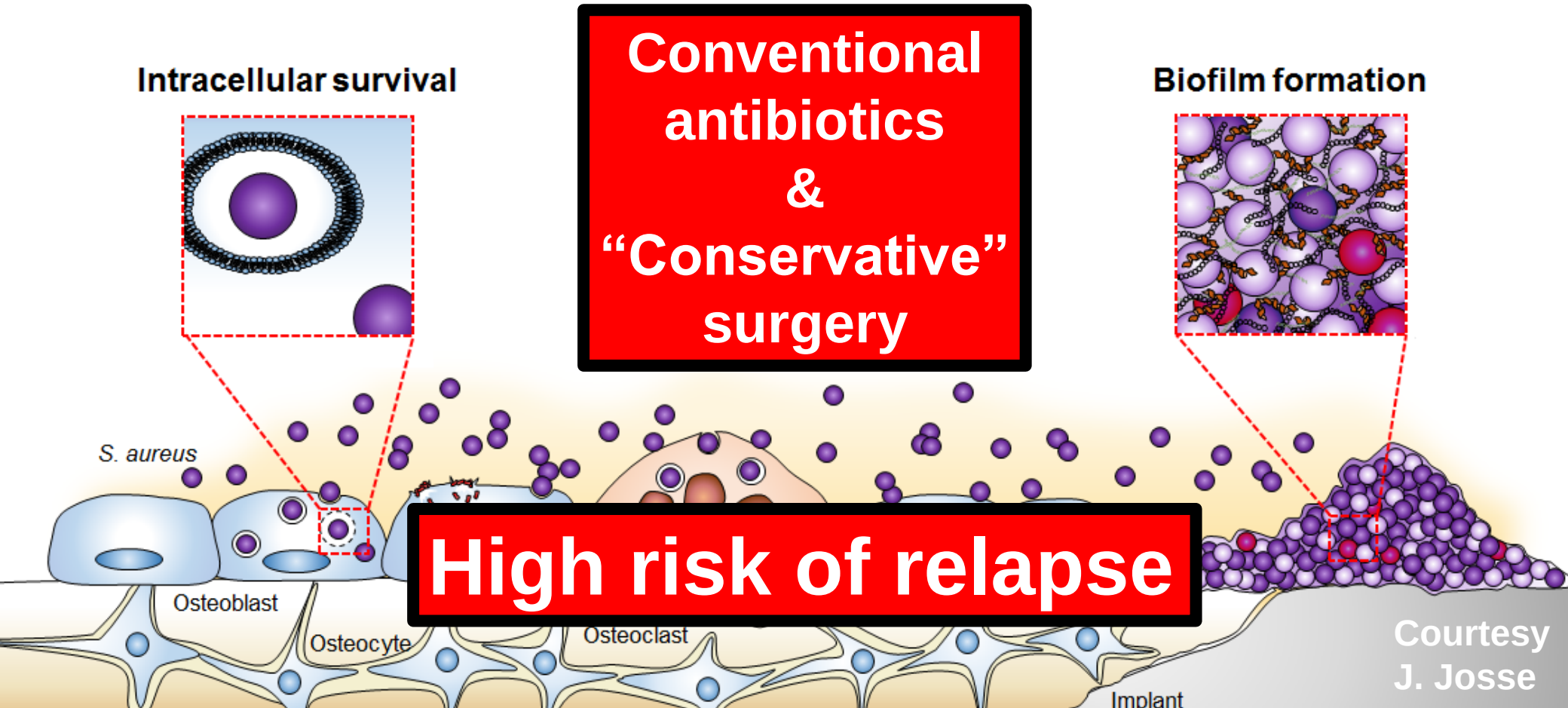

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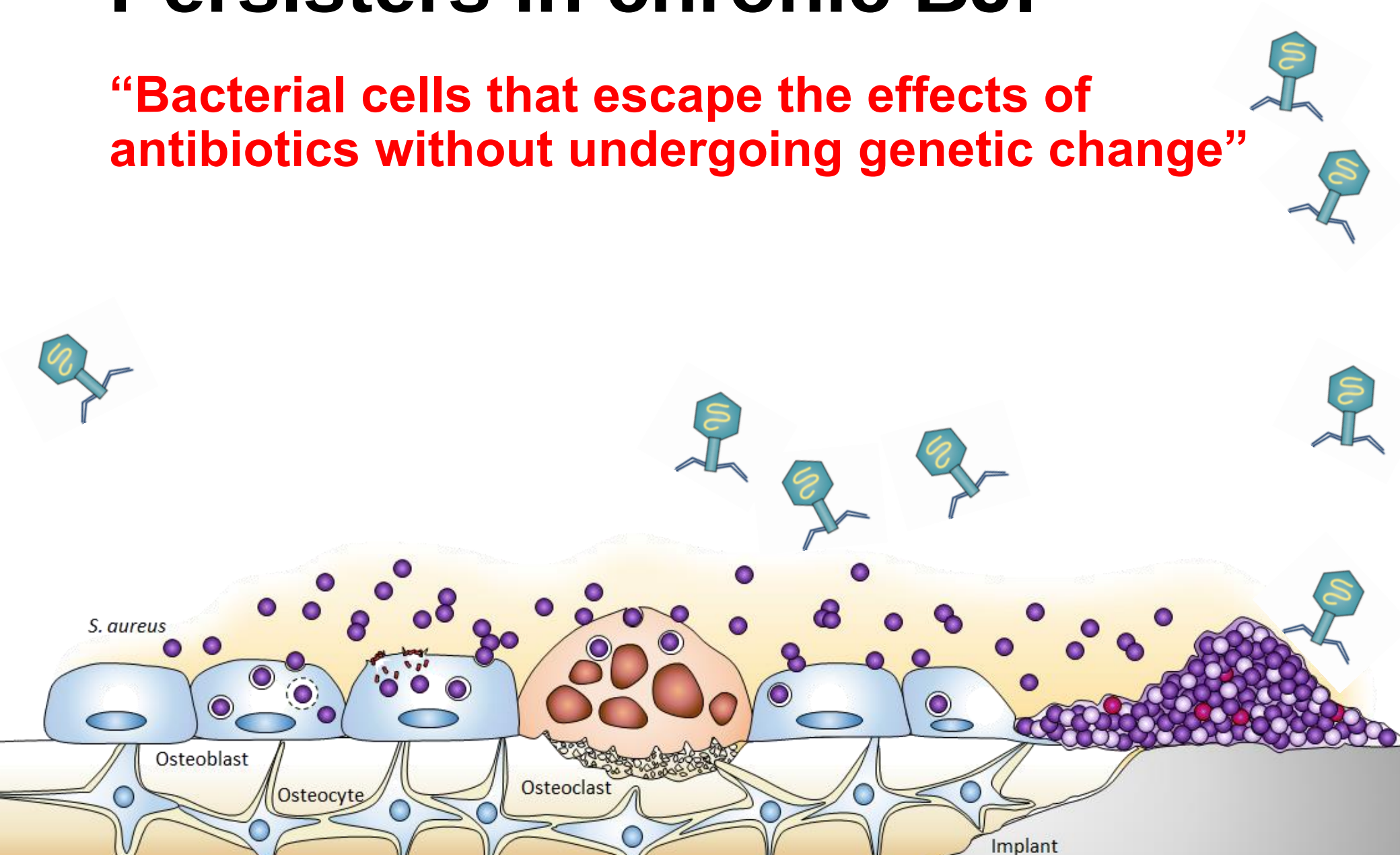
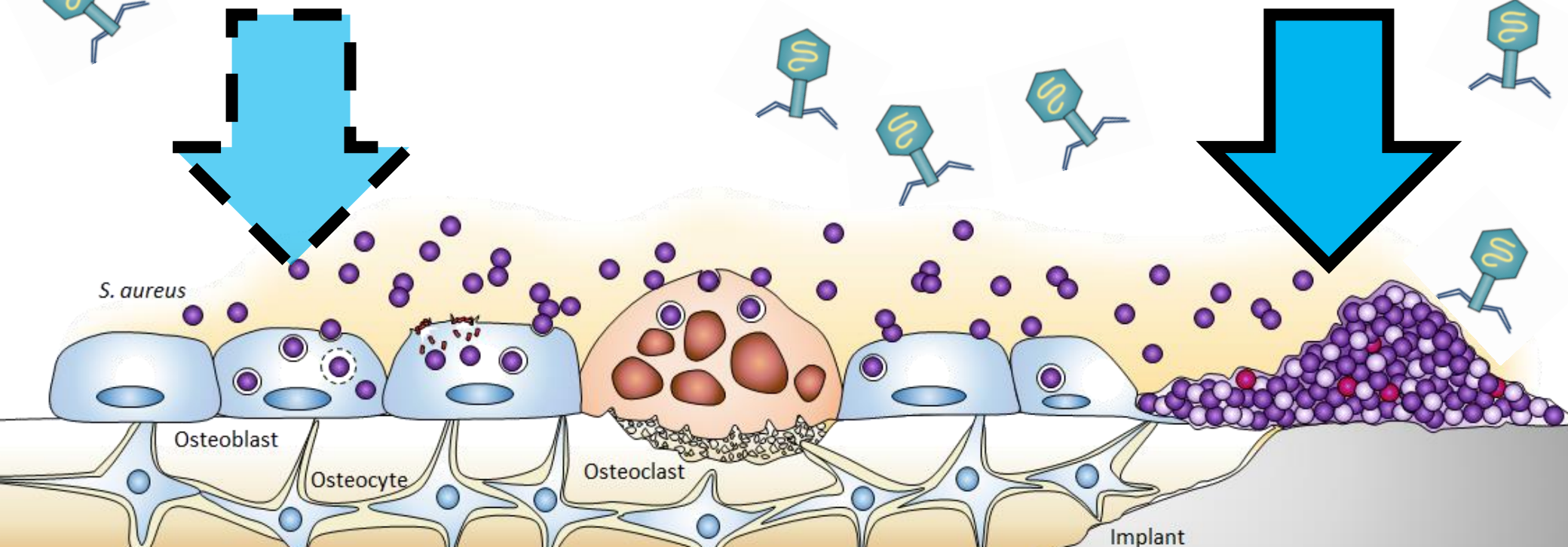


Persisters in chronic BJI

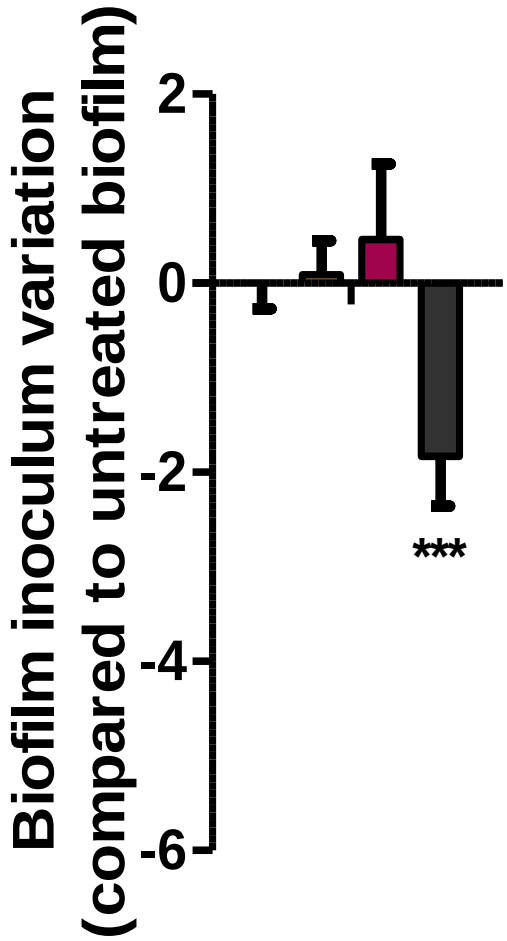
"Bacterial cells that escape the effects of antibiotics without undergoing genetic change"

Bacteriophages and lysins have anti-persister activity



C. Kolenda et al.

vancomycin



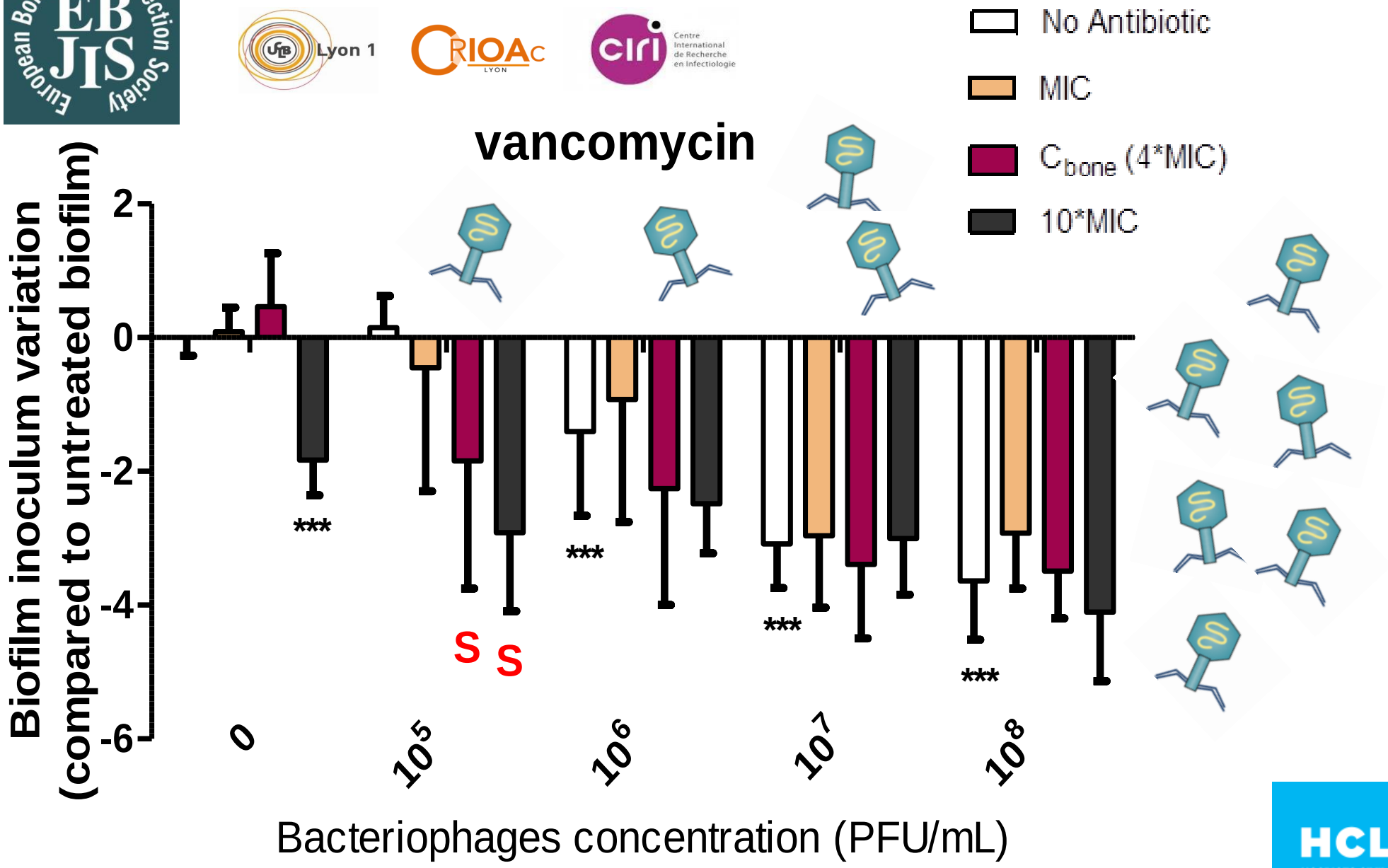
No Antibiotic

MIC

C_{bone} (4*MIC)

10*MIC

C. Kolenda et al.



Declaration of Helsinki

Medical Research Involving Human Subjects

WORLD MEDICAL ASSOCIATION

Special Communication

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

World Medical Association

JAMA 2013

The Journal of the American Medical Association

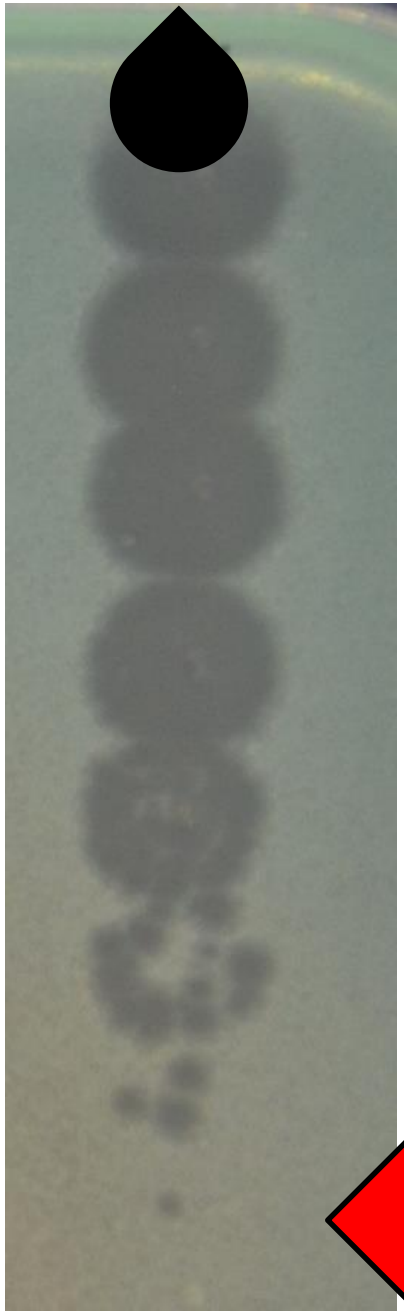
- **Unproven Interventions in Clinical Practice**

- 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

A clear antibacterial activity!

Phagogram



Phage

10^{10}

10^{9}

10^{8}

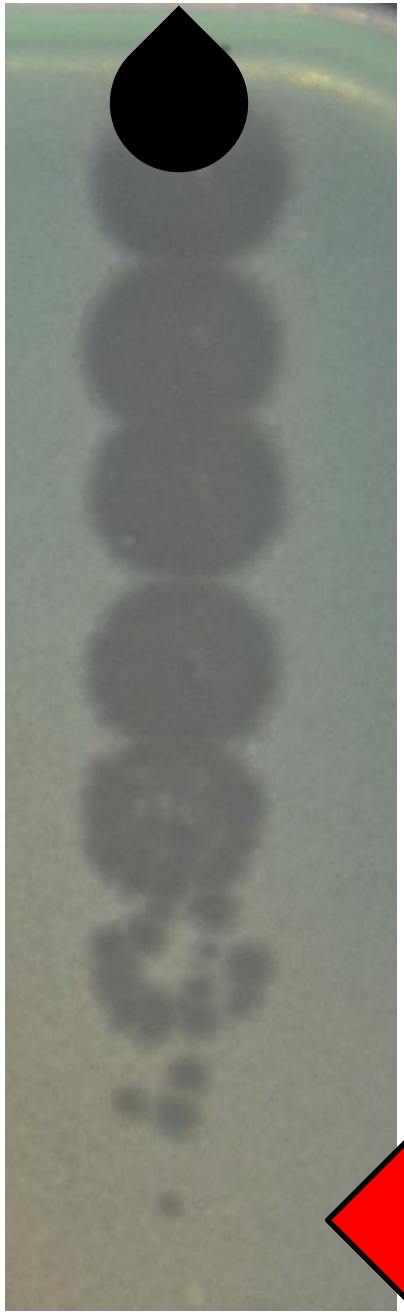
10^{7}

10^{6}

10^{5}

PFU/mL

***S. aureus* culture on a gelosis**



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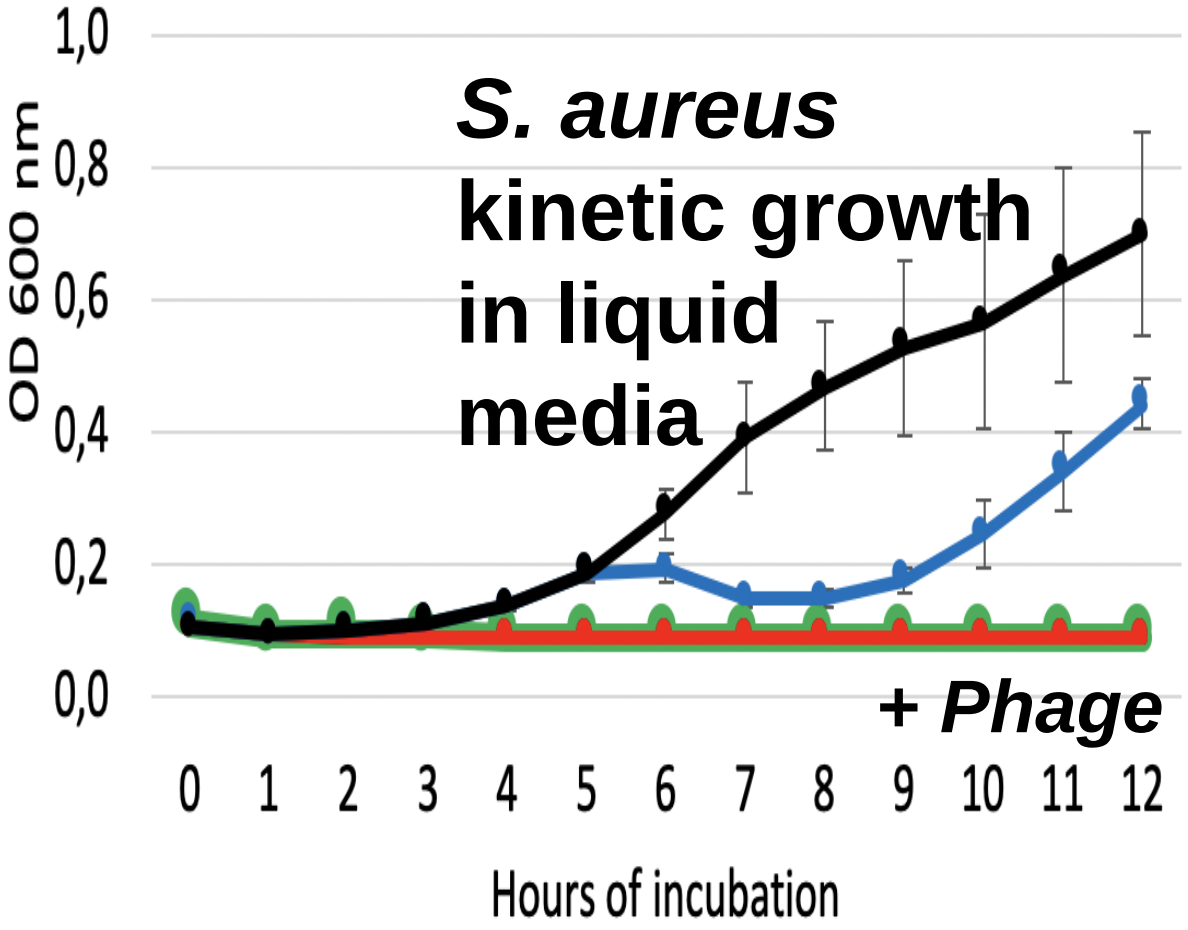
Phagogram



S. aureus **kinetic growth in liquid media**

+ Phage

S. aureus culture on a gelosis

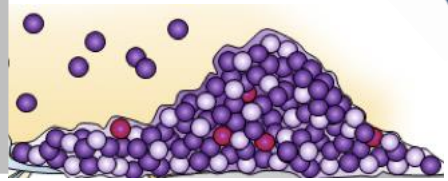
Lyon Phage team

Pr. Tristan Ferry
MD, PhD
Infectiologist

Pr. Sébastien Lustig
MD, PhD
Orthopaedic surgeon

Pr. Frédéric Laurent
PharmD, PhD
Microbiologist

Dr. Gilles Leboucher
PharmD
Pharmacist



ID Clinic

HCL HOSPICES CIVILS DE LYON

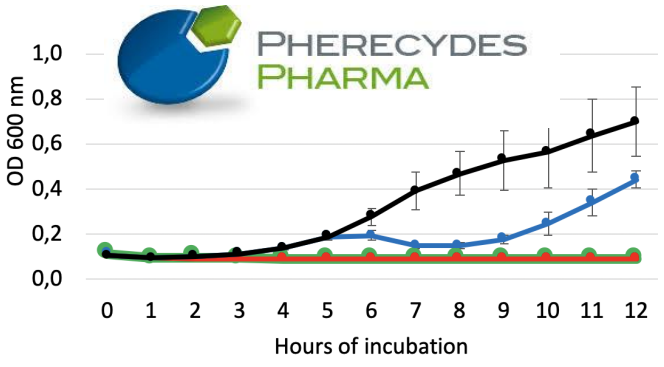
CRIOAc LYON

Surgery

HCL HOSPICES CIVILS DE LYON

Lab

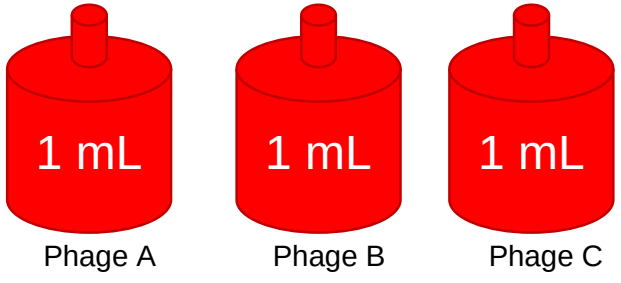
HCL HOSPICES CIVILS DE LYON



Phagogram
Selection of active bacteriophages

PHERECYDES PHARMA

Active *S. aureus* Bactériophages



Under the supervision of

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

French Health Authority

Pharmacy

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ID Clinic

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CRIOAc LYON

Surgery

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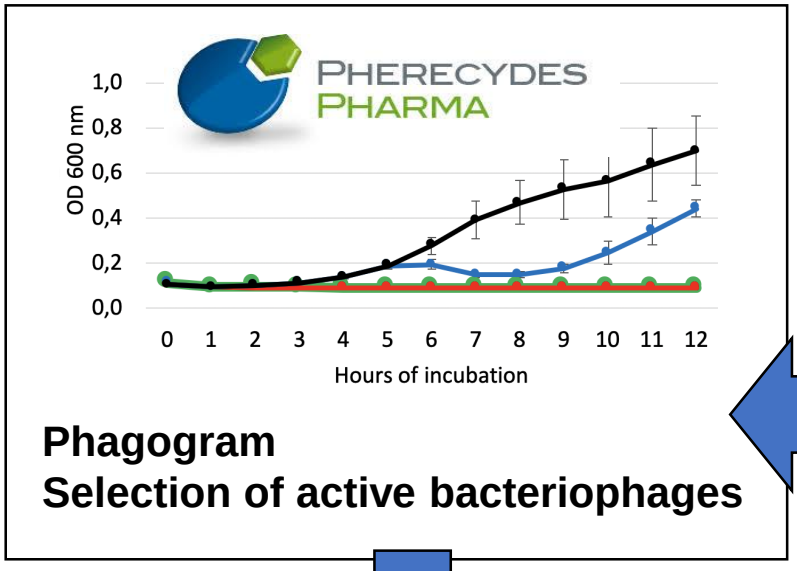


Phagogram
Selection of active bacteriophages

Lab

HCL HOSPICES CIVILS DE LYON

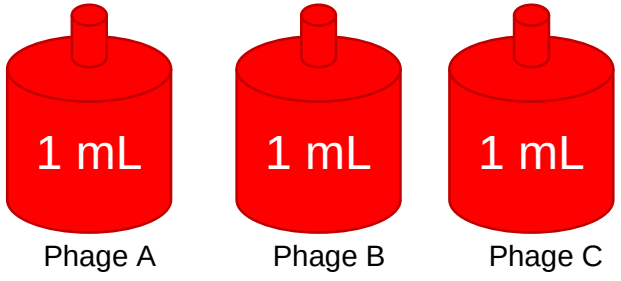
Under the supervision of

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

French Health Authority

PHERECYDES PHARMA

Active *S. aureus* Bactériophages



Pharmacy

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Extemporaneous magistral preparation of the mix of bacteriophages

‘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

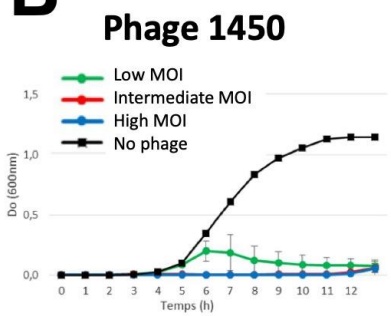
Phago DAIR

CRIOAc LYON

A

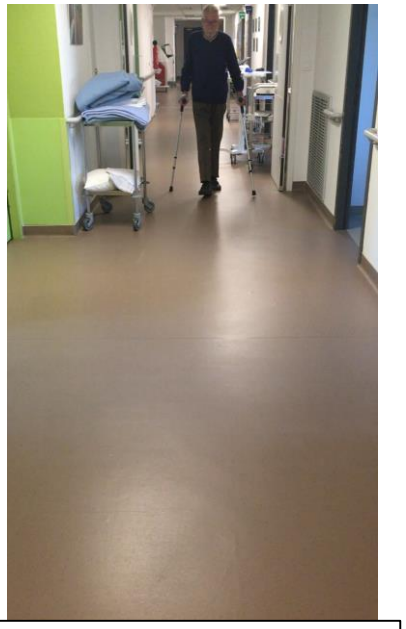
Left PKI with purulent joint effusion

B



Phagogram (Killing assay)

D



Favorable outcome at 1 year

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.**

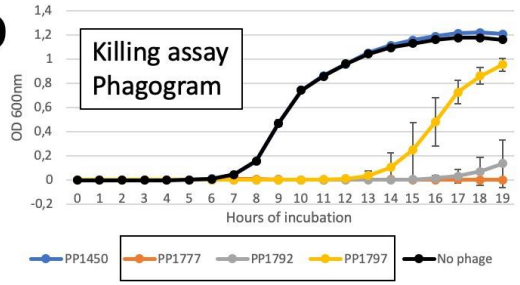
Ultrasound guided local administration of personalized cocktail of bacteriophages followed by suppressive antibiotherapy as salvage therapy in patients with relapsing total femur prosthesis infection

A

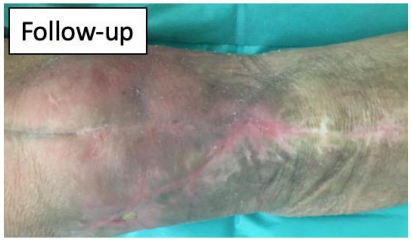
C

B

D



E



30th ECCMID
Paris, France
18 –21 April 2020

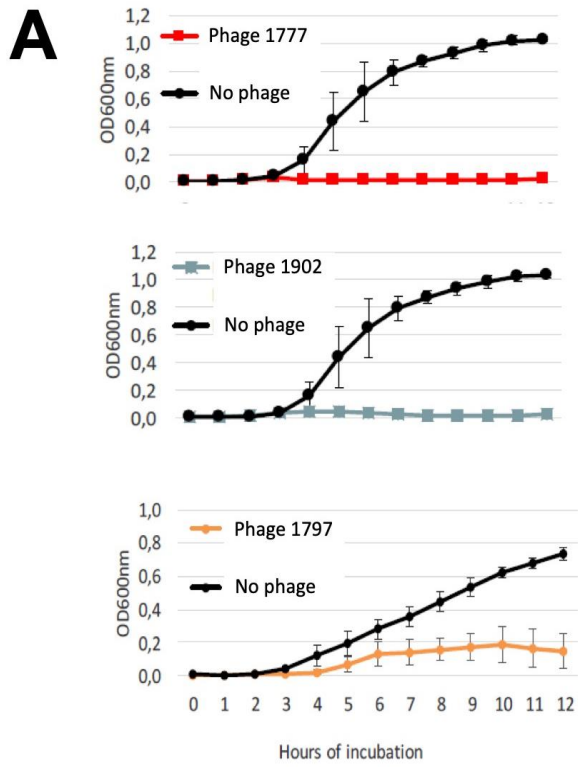
PHERECYDES PHARMA

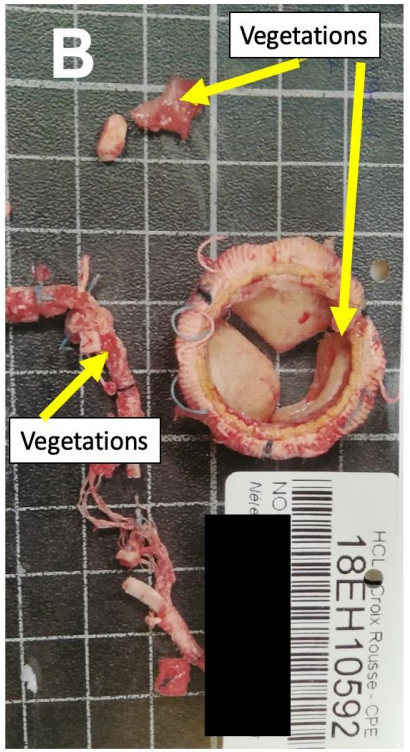
CRIOAc LYON

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.

<u>Intravenous</u> 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

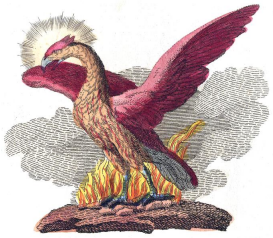


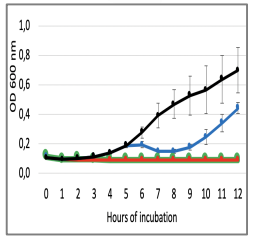


Conclusions: **The type of filter used for the magistral preparation and the duration of the perfusion influenced the phage titer, as the titer in the patient's blood.** Personalized GMP bacteriophage therapy has the potential to be used as salvage therapy of *P. aeruginosa* intravascular implant infections.

Conclusion

- Crucial need for (alternatives) **additional therapies to antibiotics** to maximize clinical success in complex bacterial infections
- Phage therapy is a **Phoenix**
- Don’t forget **Lessons from 20th century**
- Develop and use **GMP bacteriophages (phages 2.0)** ► **14 patients treated in 2 years**
- Industry / health authority / academic **collaborations**
- Reference (regional or national) clinical centers to determine **relevant indications**
- Need for **Phage discovery**, **banking**, **susceptibility**, to personalize the therapy
- **Need for national phage therapy center(s)**





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