

Innovative Approach in Bone and Joint Infections: Bone Substitutes, Phages

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

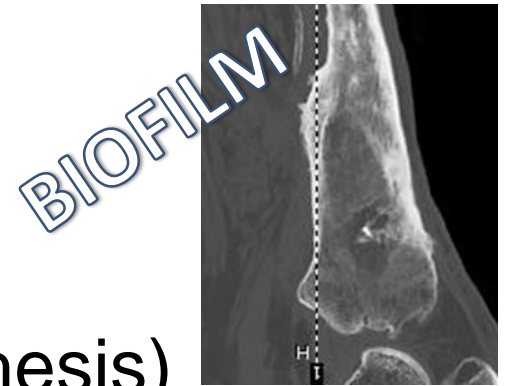
Centre International de Recherche en Infectiologie, CIRI, Inserm U1111, CNRS
UMR5308, ENS de Lyon, UCBL1, Lyon, France

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



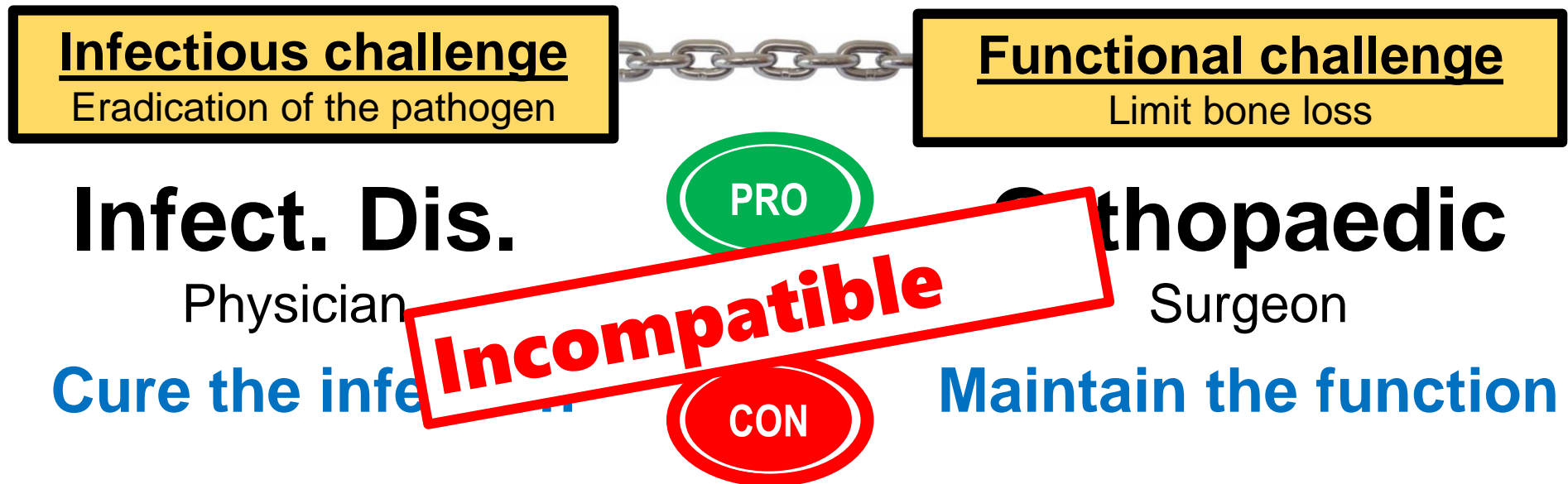
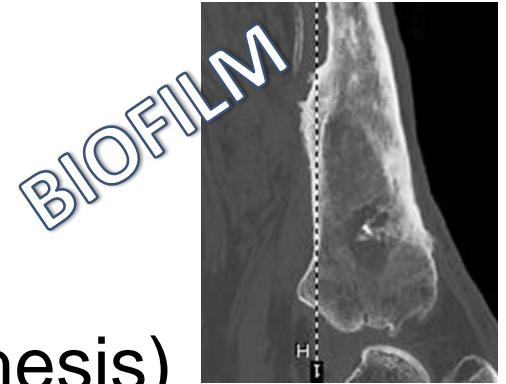
Chronic bone and joint infection

- One of the most difficult-to-treat ID
- Bacterial mechanisms of persistence
- Sequestrum in chronic osteomyelitis
- Implant surface (osteosynthesis, prosthesis)

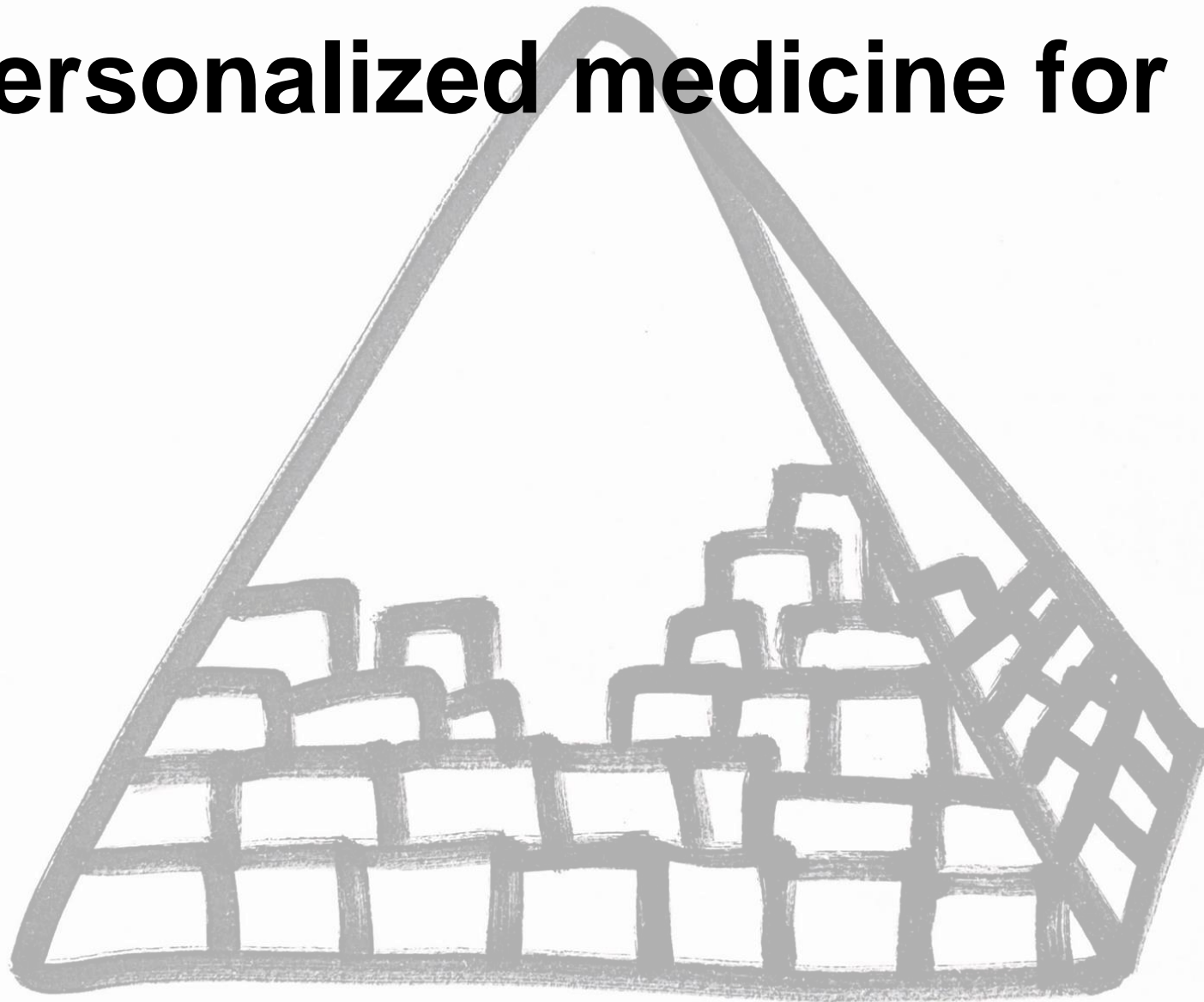


Chronic bone and joint infection

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Personalized medicine for BJI



Personalized medicine for BJI



**OPTIMAL
SEPTIC
SURGERY**

Personalized medicine for BJI

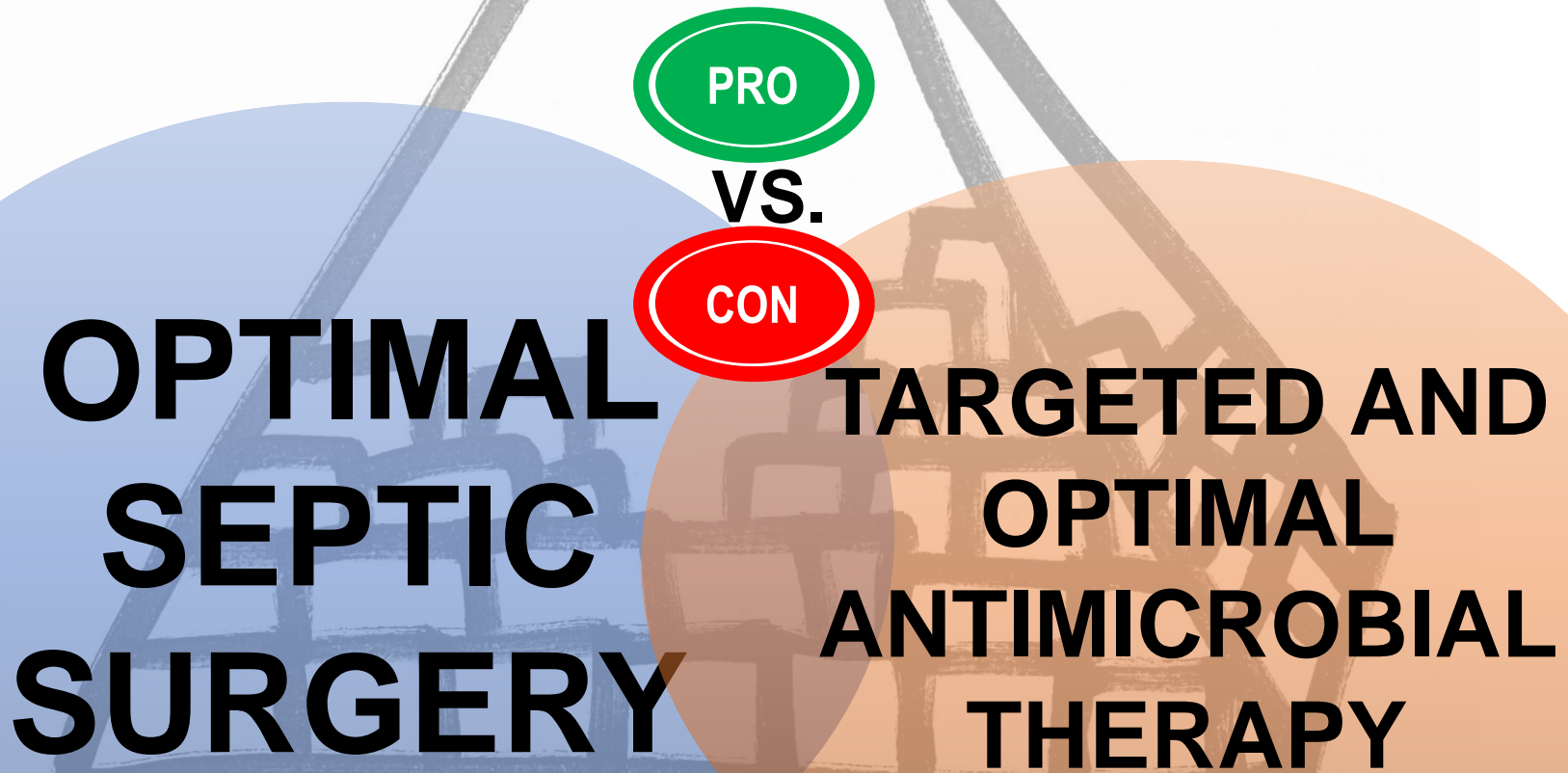


A Venn diagram with two overlapping circles. The left circle is blue and contains the text 'OPTIMAL SEPTIC SURGERY'. The right circle is orange and contains the text 'TARGETED AND OPTIMAL ANTIMICROBIAL THERAPY'. The intersection of the two circles is shaded in a darker brownish-orange. In the background, there is a faint, large triangle and a faint image of a medical building.

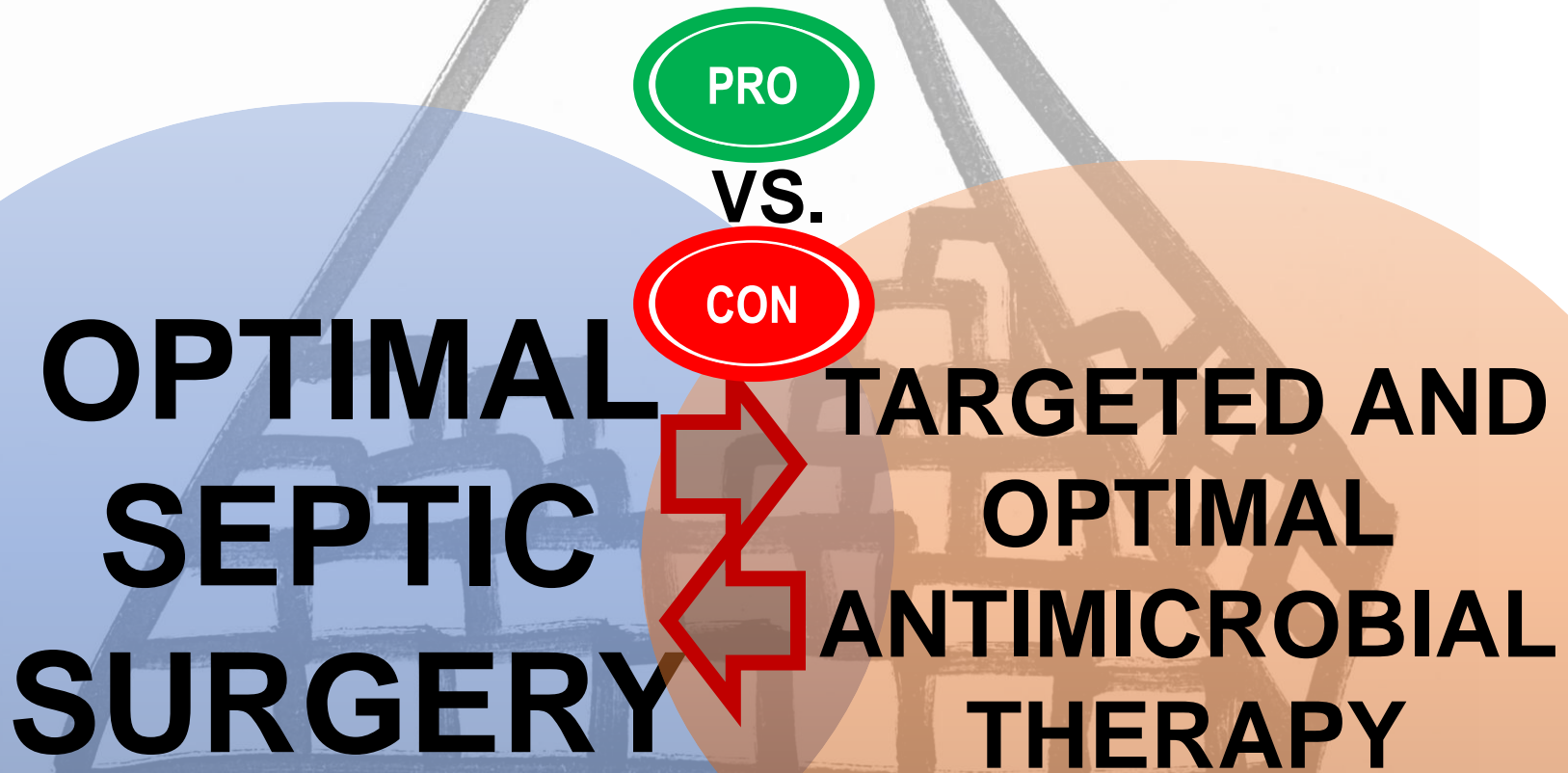
**OPTIMAL
SEPTIC
SURGERY**

**TARGETED AND
OPTIMAL
ANTIMICROBIAL
THERAPY**

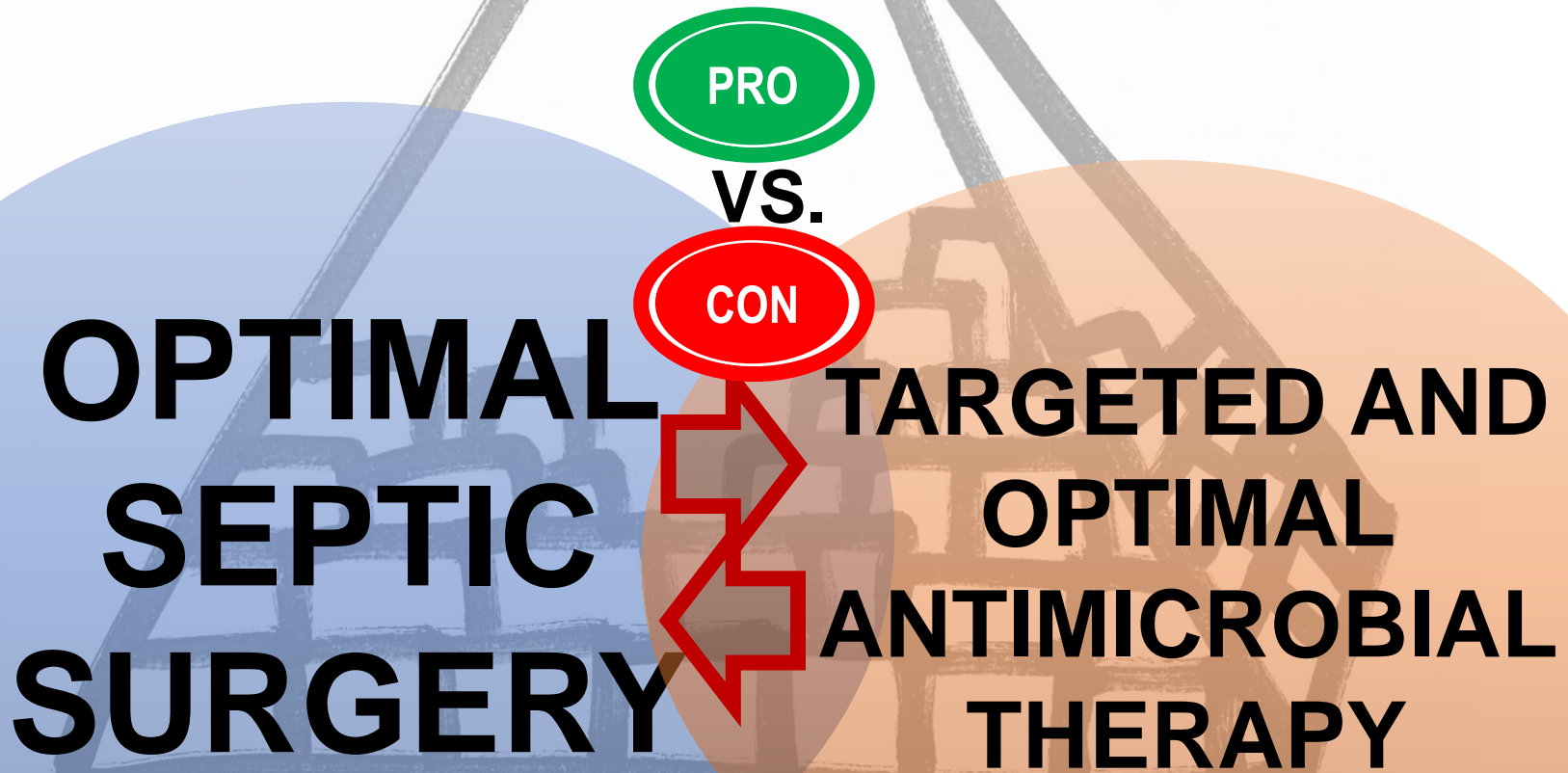
Personalized medicine for BJI



Personalized medicine for BJI



Personalized medicine for BJI



Personalized medicine for BJI

MULTIDISCIPLINARY MEETING

THE BEST INDIVIDUALIZED MEDICOSURGICAL STRATEGY

PRO

VS.

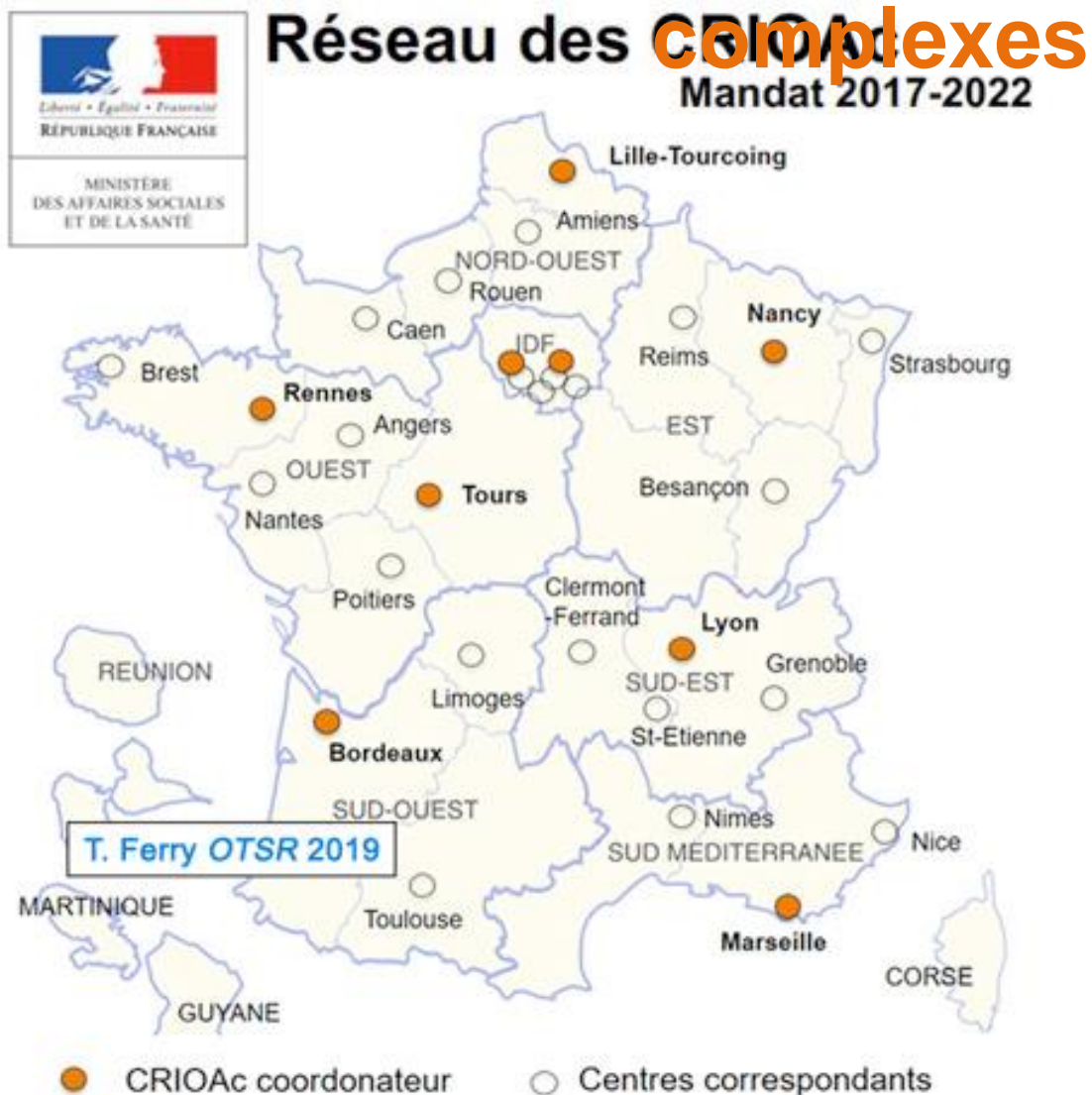
CON

**OPTIMAL
SEPTIC
SURGERY**

**TARGETED AND
OPTIMAL
ANTIMICROBIAL
THERAPY**



Centre de Référence des Infections Ostéo-Articulaires



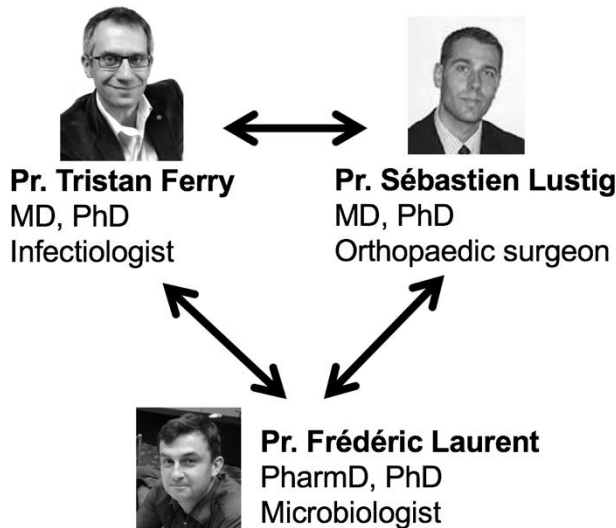


Réseau des **CRIOAc**
Mandat 2017-2022

le-Tourcoing

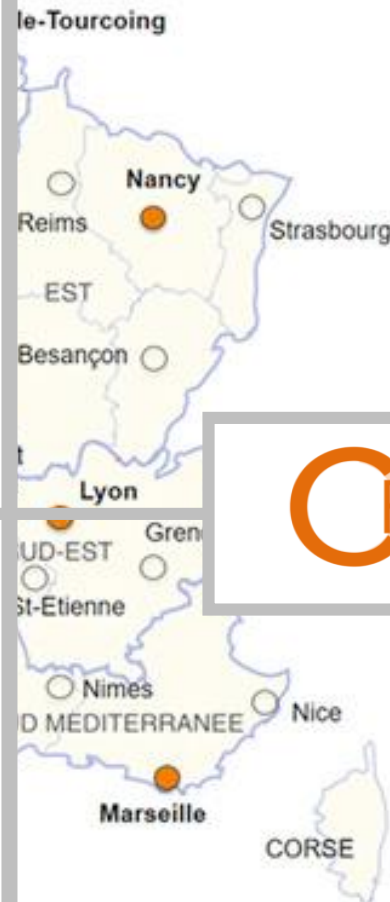
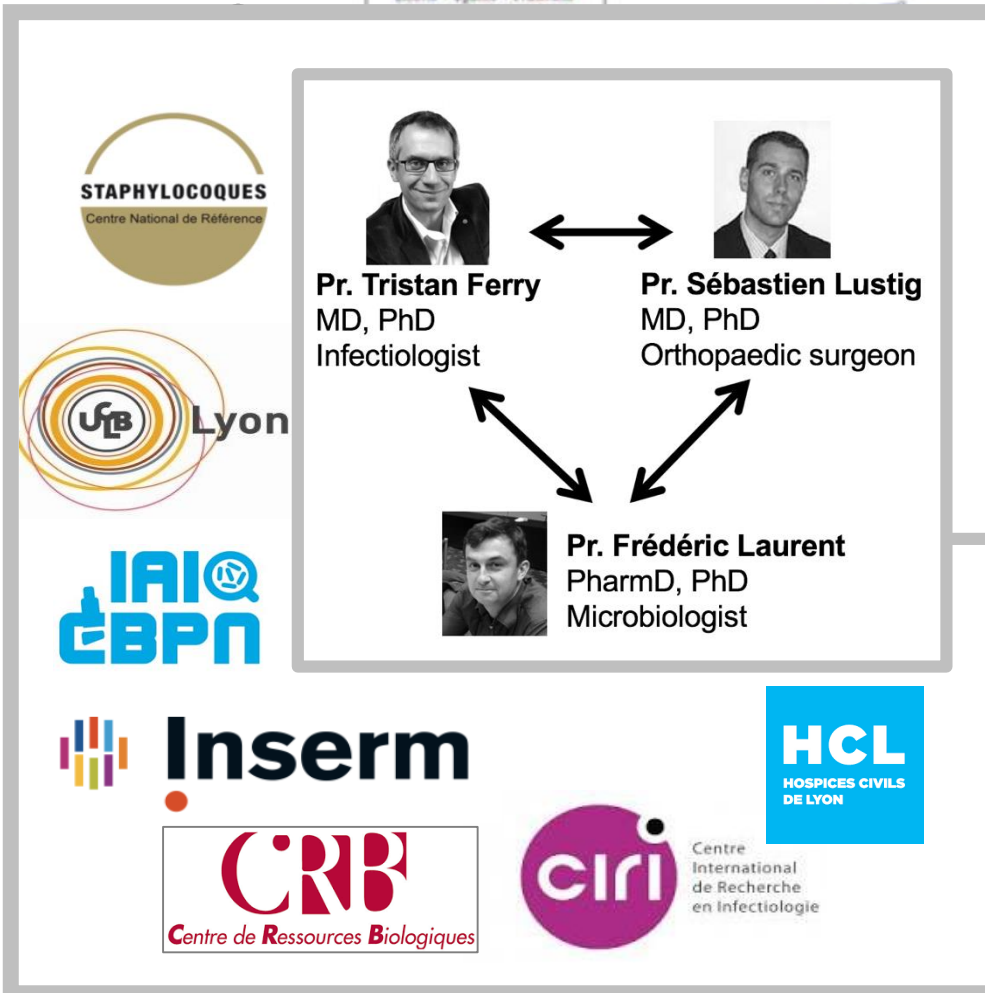


tres correspondants

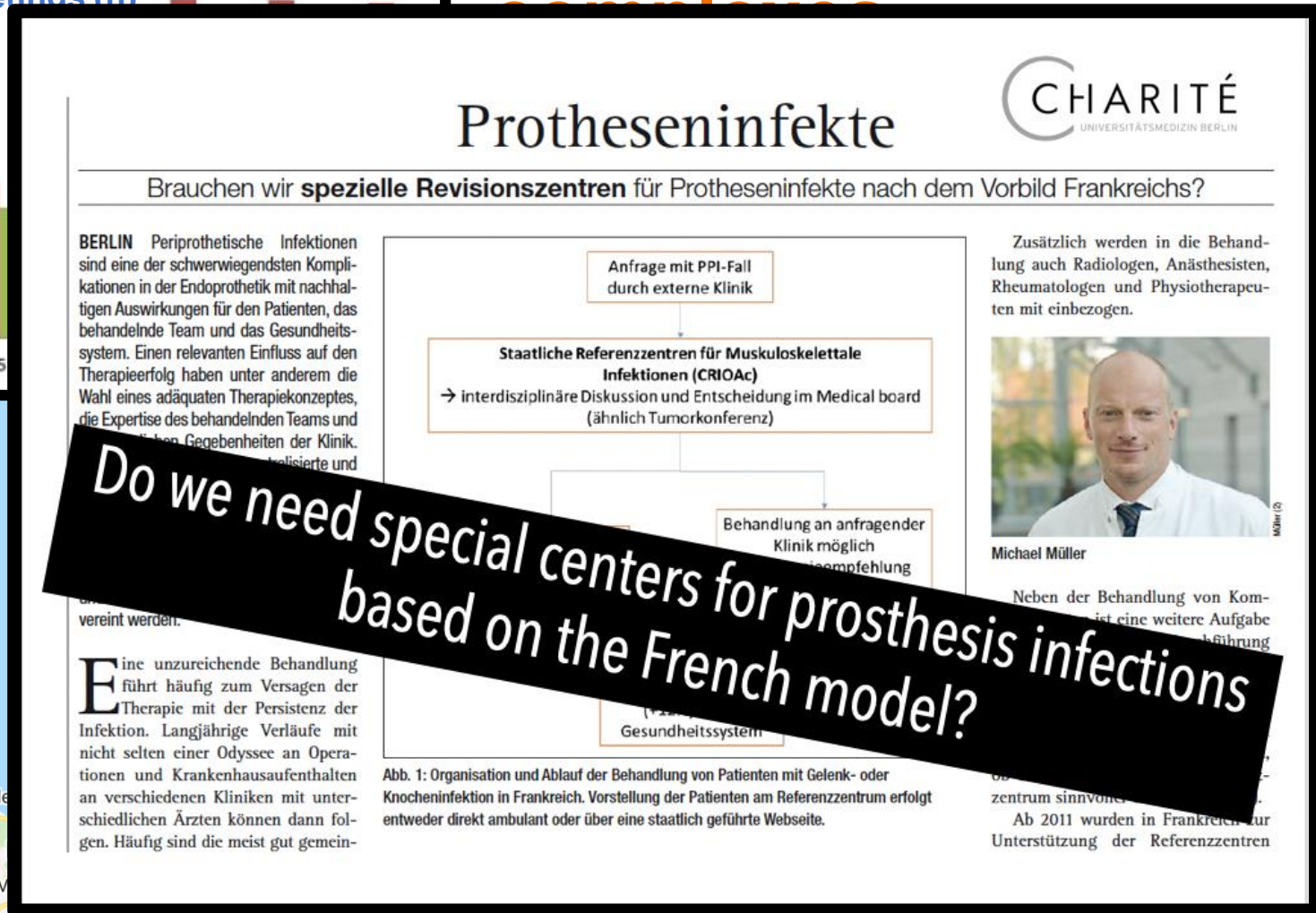
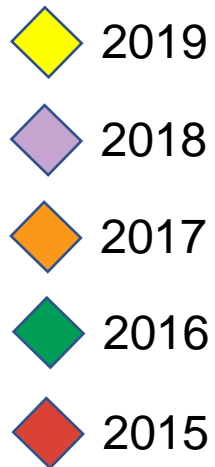




Réseau des **CRIOAc**
Mandat 2017-2022



autres correspondants



Personalized medicine for BJI



**OPTIMAL
SEPTIC
SURGERY**

**TARGETED AND
OPTIMAL
ANTIMICROBIAL
THERAPY**

MULTIDISCILINAR MEETING

Personalized medicine for BJI

Antibiotic-loaded
PMMA cements

**Antibiotic-
loaded bone
substitutes**

ADJUVANT

**INNOVATIVE ANTI-
INFECTIVE AGENTS**

Bacteriophages

Bacteriophage-
derived lysins

New antibiotics
targeting the biofilm

**OPTIMAL
SEPTIC
SURGERY**

**TARGETED AND
OPTIMAL
ANTIMICROBIAL
THERAPY**

MULTIDISCIPLINAR MEETING

The following case brings up to date the concept of local antibiotherapy

BJI = local infection

Legitimate to want to act locally

von Eiff C. et al.
Clin Infect Dis. 1997



- Gentamicin beads
- Non-optimal surgery
- Low local release
- Without systemic antibiotics



Failure



**Acquisition
of resistance and/or
small colony variants**



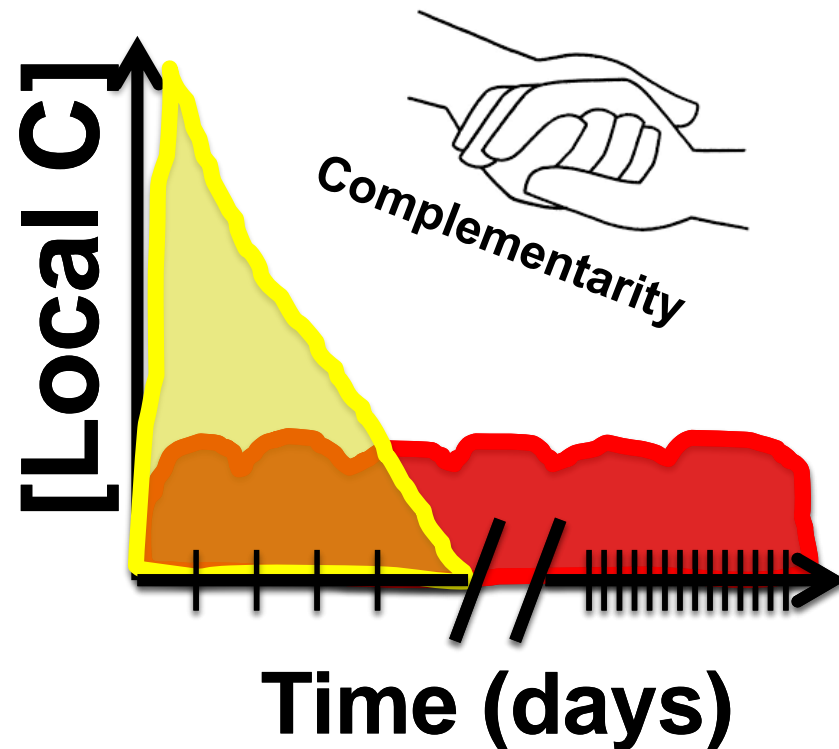
Innovation = local therapy



Antibiotics administered systemically



Antibiotics administered locally with particular carriers (ex. bone substitute)



**DISRUPTIVE
Strategy**

**Antibiofilm
agents**

Local administration
with carriers

Clinical case #1

39-year-old man

Relapsing *P. aeruginosa* implant-associated infection despite 'DAIR', and despite implant removal

Septic nonunion with persistent fully susceptible *P. aeruginosa* infection

Amputation



VS.



Bone resection +
innovative way to
treat and rebuild
the bone



Clinical case #1

39-year-old man

Relapsing *P. aeruginosa* implant-associated infection despite 'DAIR', and despite implant removal

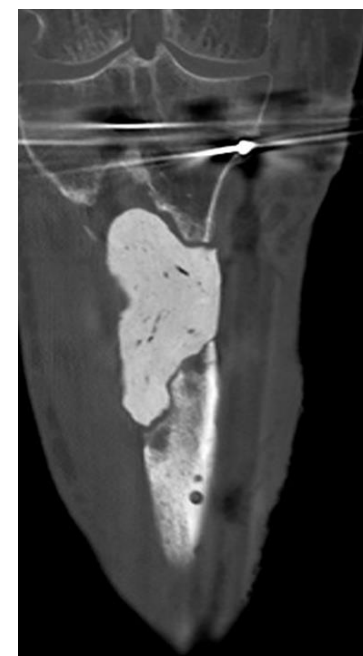
Septic nonunion with persistent fully susceptible *P. aeruginosa* infection

Multidisciplinary decision:

1st step: Bone resection + spacer

2nd step: Gastrocnemius flap

3rd step: Osteosynthesis + Bone reconstruction with CERAMENT™ G and CERAMENT™ V + autograft + allograft

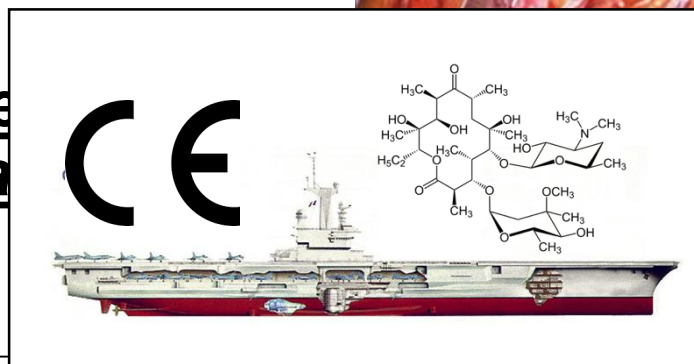
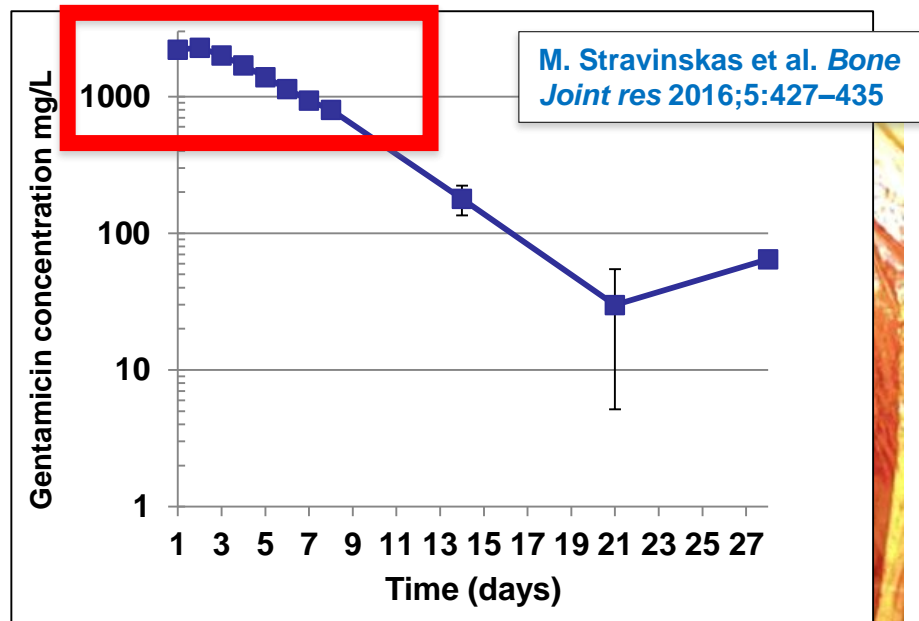


Clinical case #1

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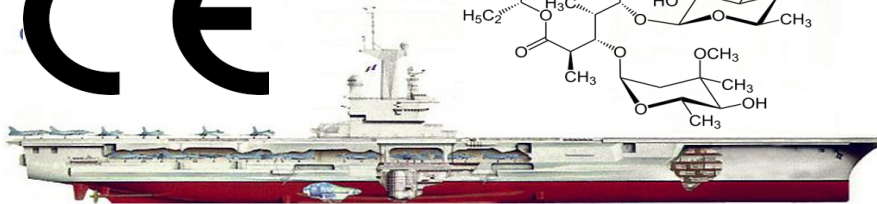
2nd step: Gastrocnemius flap

3rd step: Osteosynthesis + Bone reconstruction with CERAMENT™ G and CERAMENT™ V + autograft + allograft



Clinical case #1

CE



Available in the market as a device
(not as an antibiotic)
But no clinical data
So no reimbursement

**Favorable outcome
at 3 years**

Multidisciplinary decision

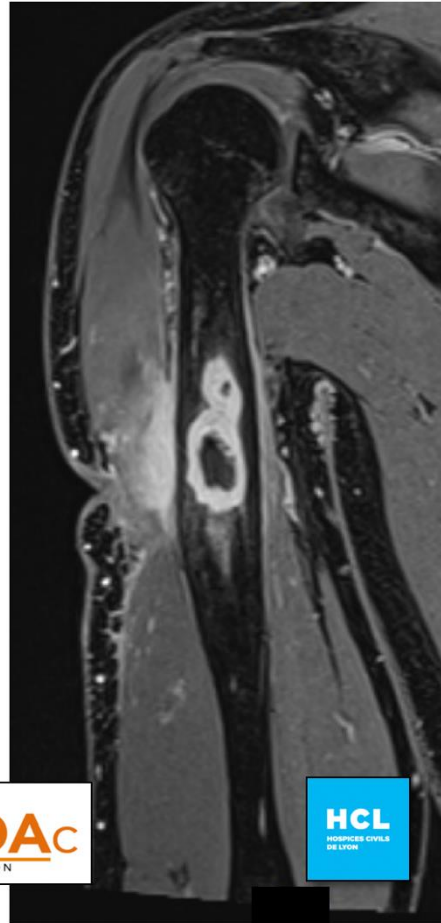
1st step: Bone resection + spacer

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reconstruction with CERAMENT™ G and
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CONVICTION clinical trial

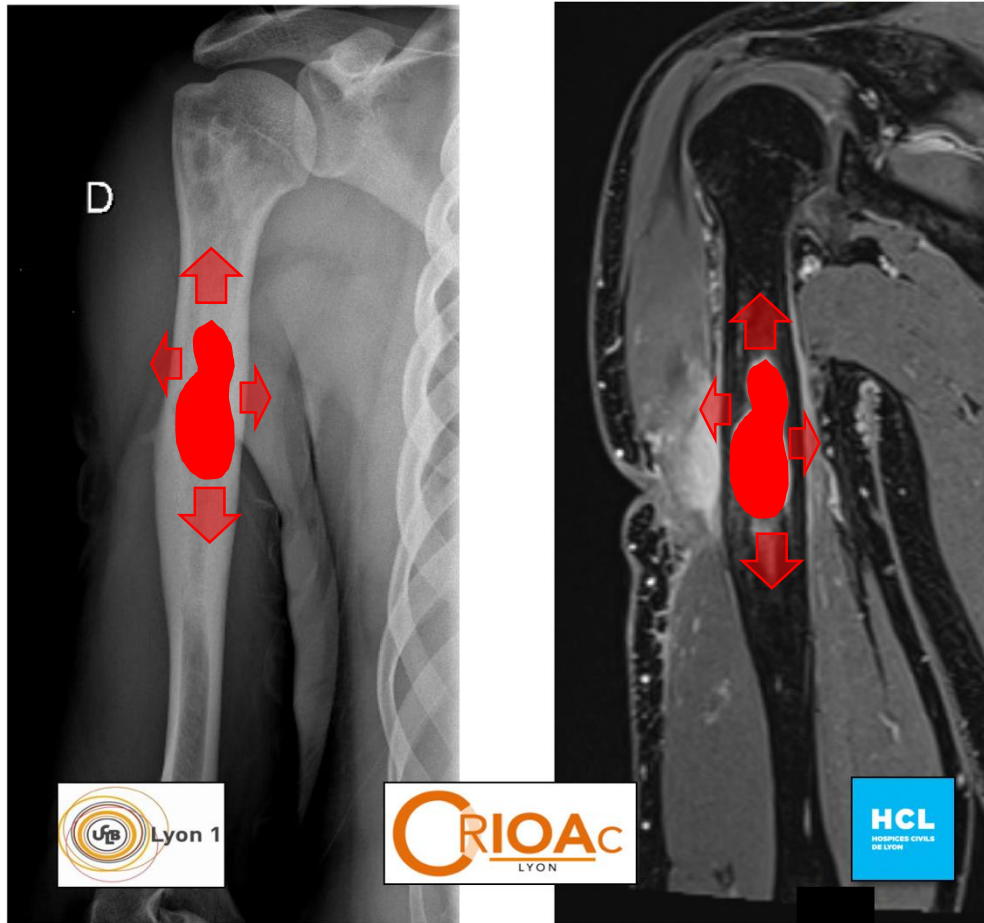


Evaluation of the efficiency of the bone substitute **Cerament-G®** locally delivering gentamicin in the treatment of **chronic osteomyelitis of long bones: randomized multicentre study in the CRIOAc network**

**First inclusion
Q2 2021?**

T. Ferry (national grant 2019)

CONVICTION clinical trial

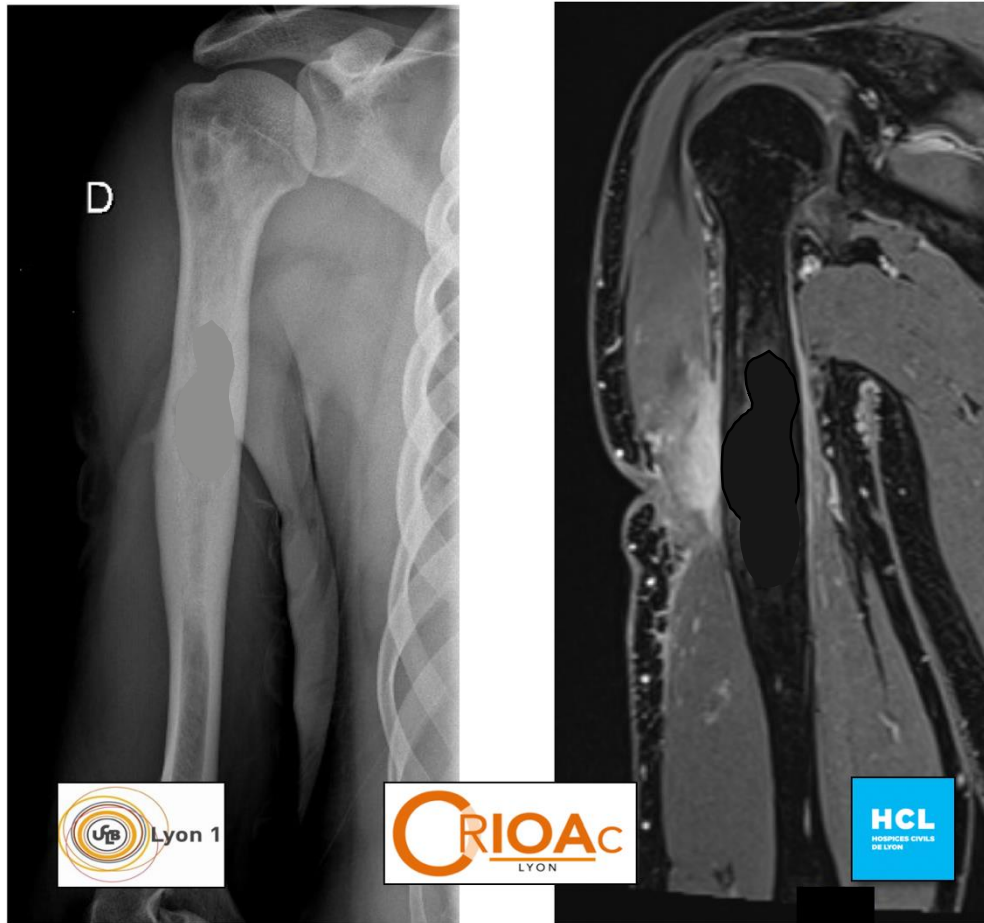


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T. Ferry PRME 2019

**First inclusion
Q2 2021?**

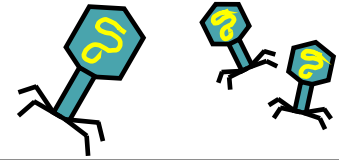
Personalized medicine

Antibiotic-loaded
PMMA cements

Antibiotic-loaded
bone substitutes

**ADJUVANT
INNOVATIVE ANTI-
INFECTIVE AGENTS**

Bacteriophages



Bacteriophage-
derived lysins

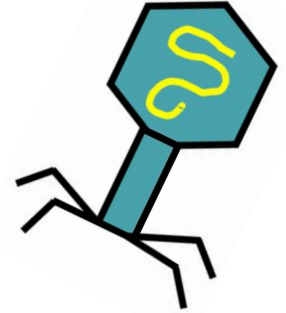
New antibiotics
targeting the biofilm

**OPTIMAL
SEPTIC
SURGERY**

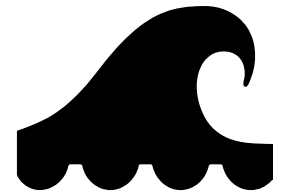
**TARGETED AND
OPTIMAL
ANTIMICROBIAL
THERAPY**

MULTIDISCIPLINAR MEETING

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:
10³¹ bacteriophages on the planet, more than every other organism**
- Especially in marine environment, sea, lake, backwater, soil, animal and human stools, etc.

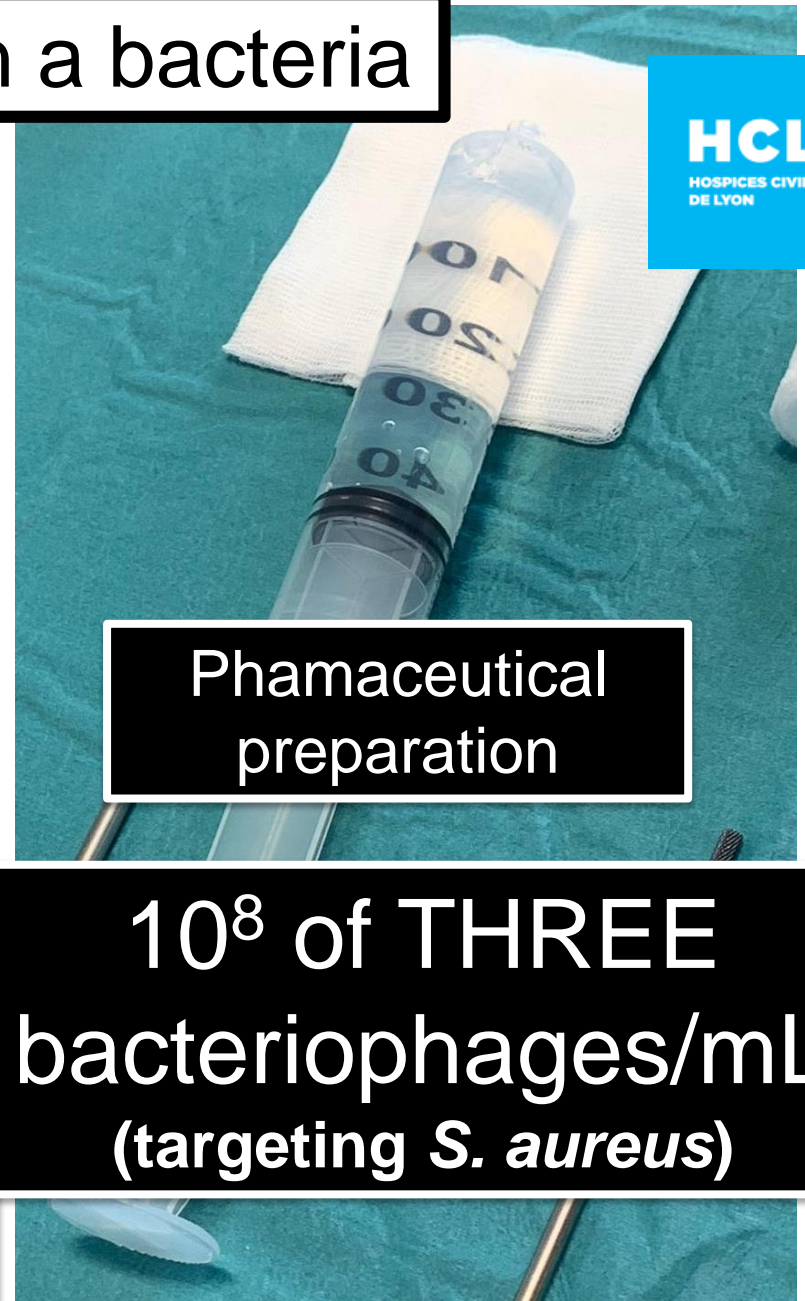


10 to 100 fold smaller than a bacteria

Translucent tap water



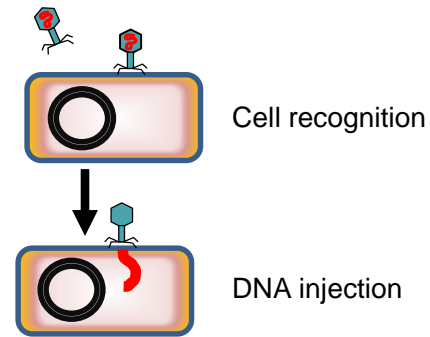
**X million of ≠
BactériophageS !!!
(targeting environmental bacteria)**



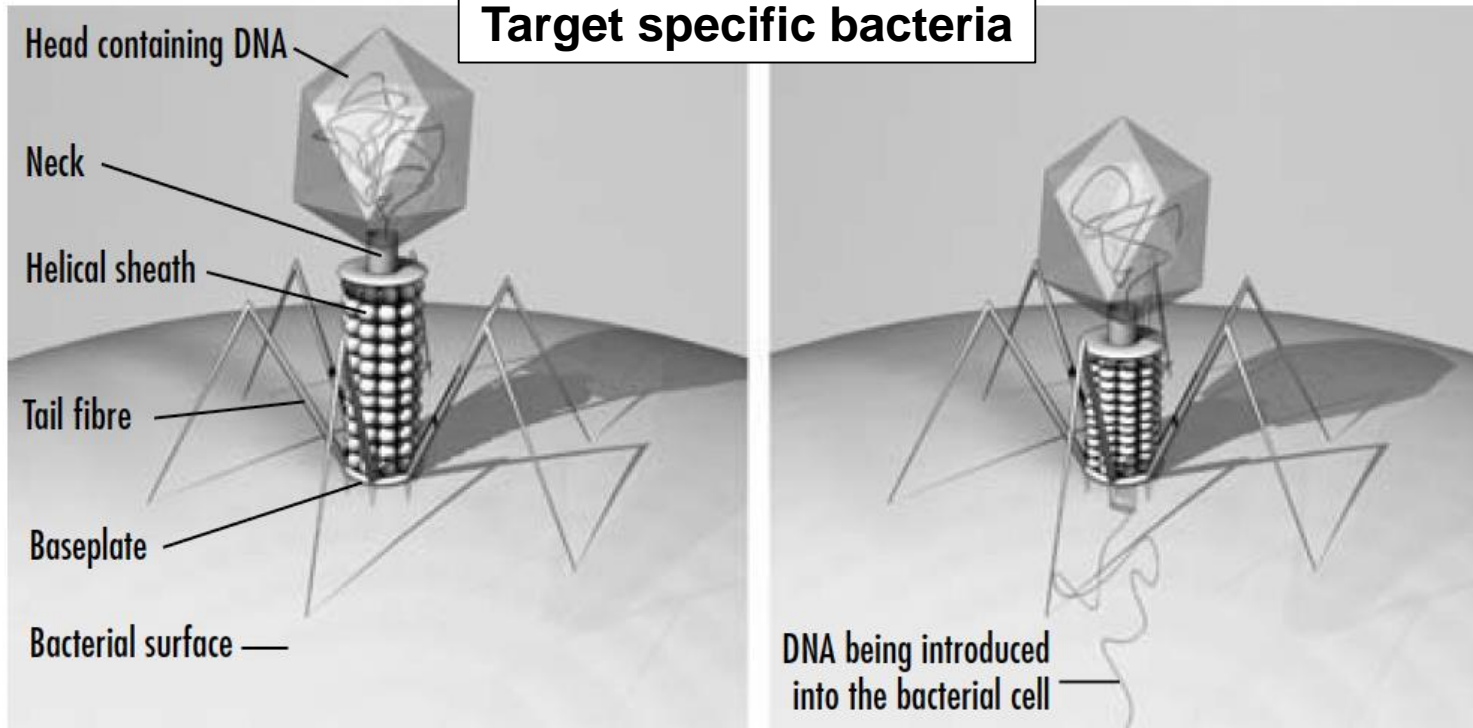
Pharmaceutical
preparation

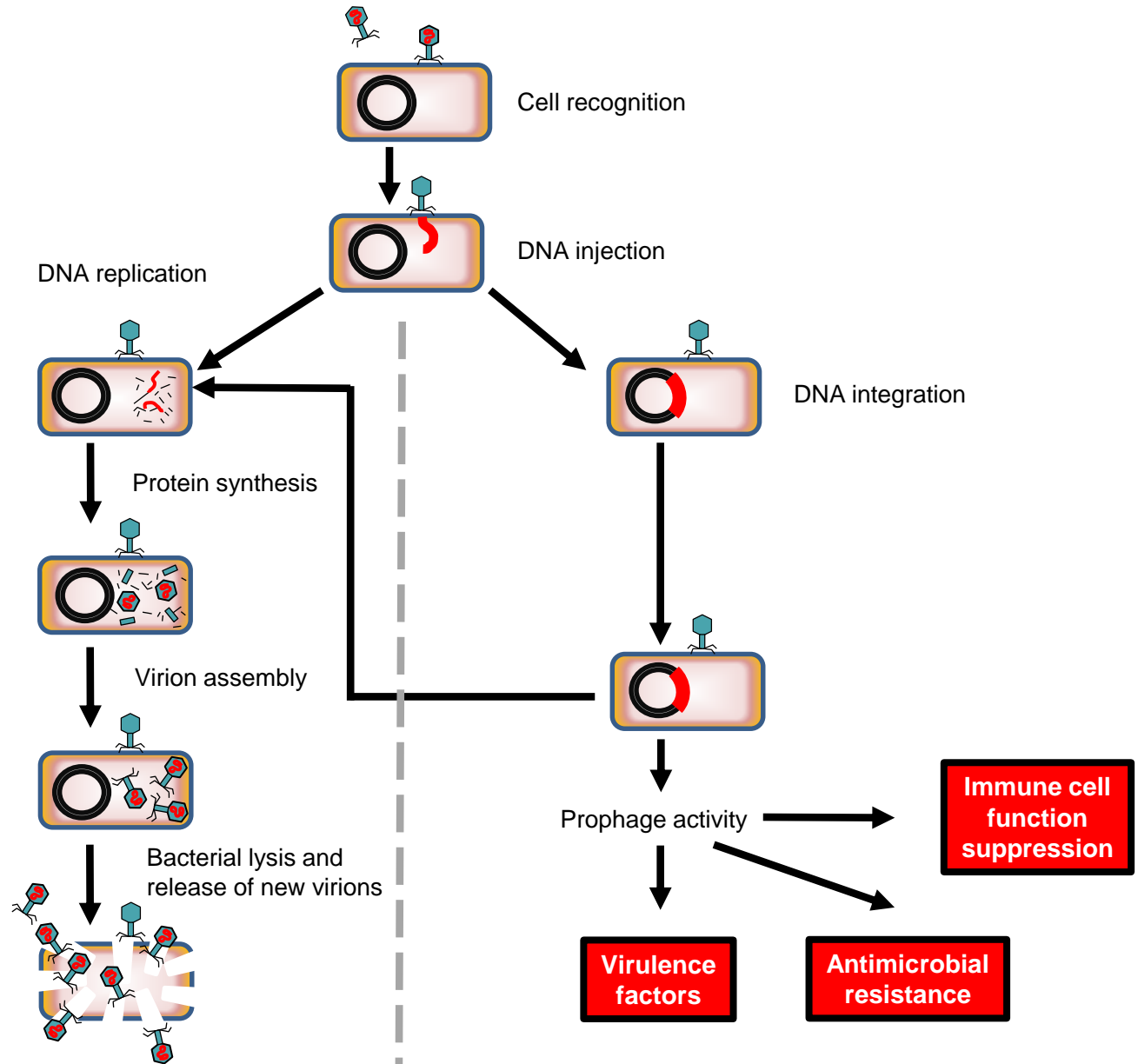
**10^8 of THREE
bacteriophages/mL
(targeting *S. aureus*)**

HCL
HOSPICES CIVILS
DE LYON



**Environmental viruses
Target specific bacteria**



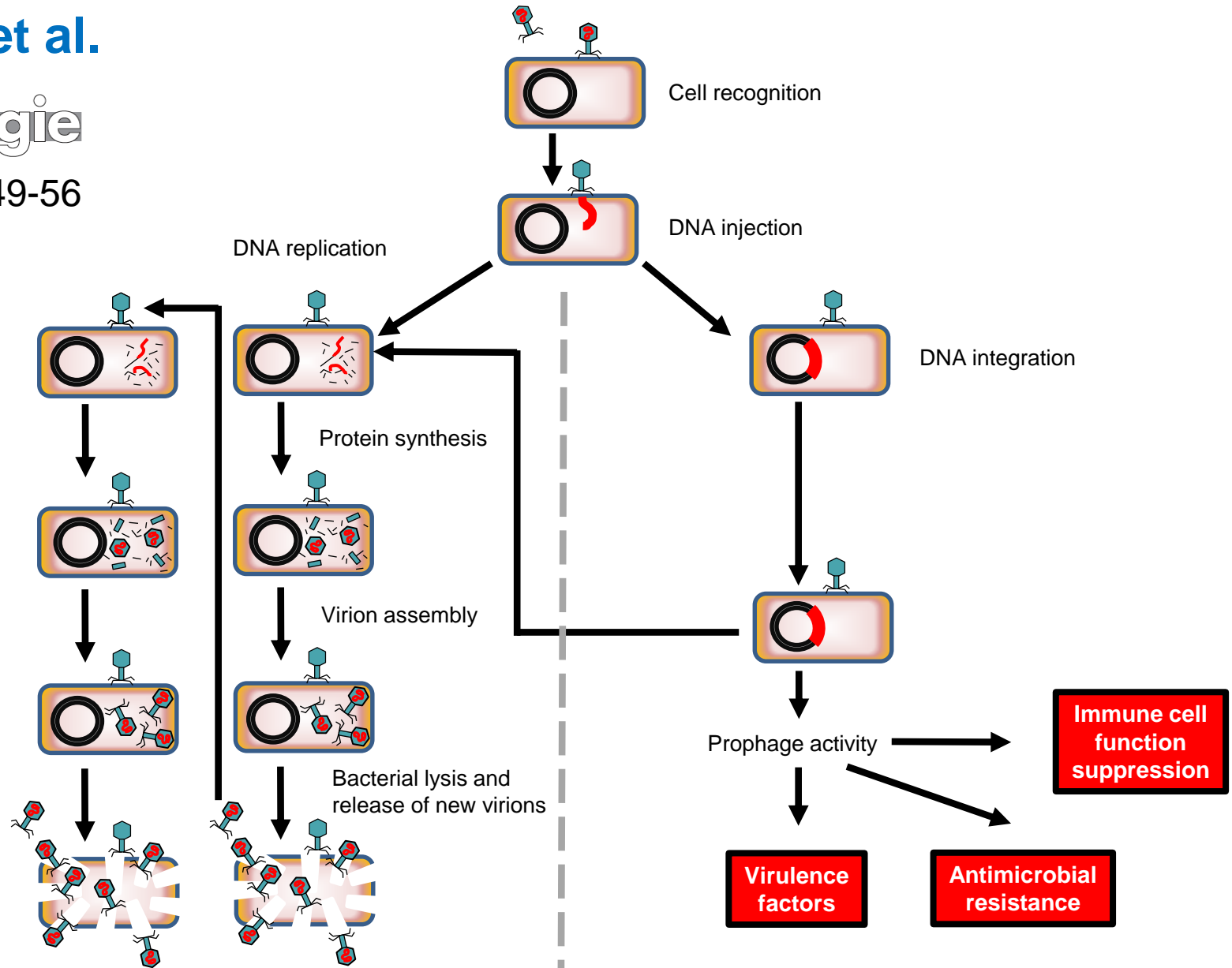


Lytic cycle

Self-maintained bacterial lysis

Lysogenic cycle

Bacterial genetic remodeling

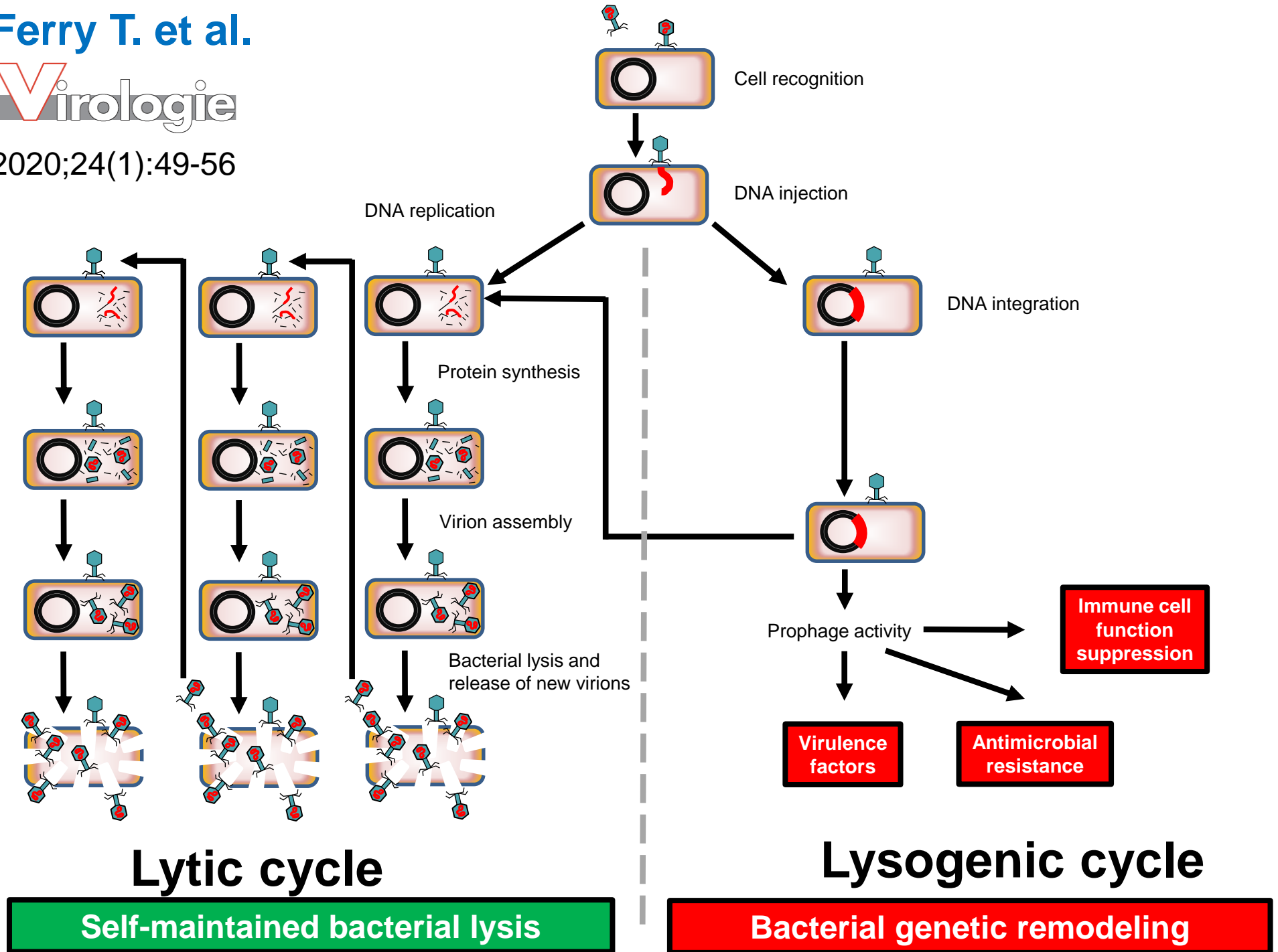


Lytic cycle

Self-maintained bacterial lysis

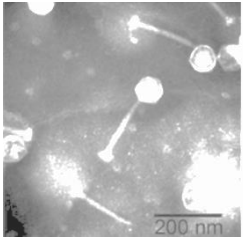
Lysogenic cycle

Bacterial genetic remodeling



A clear antibacterial activity!

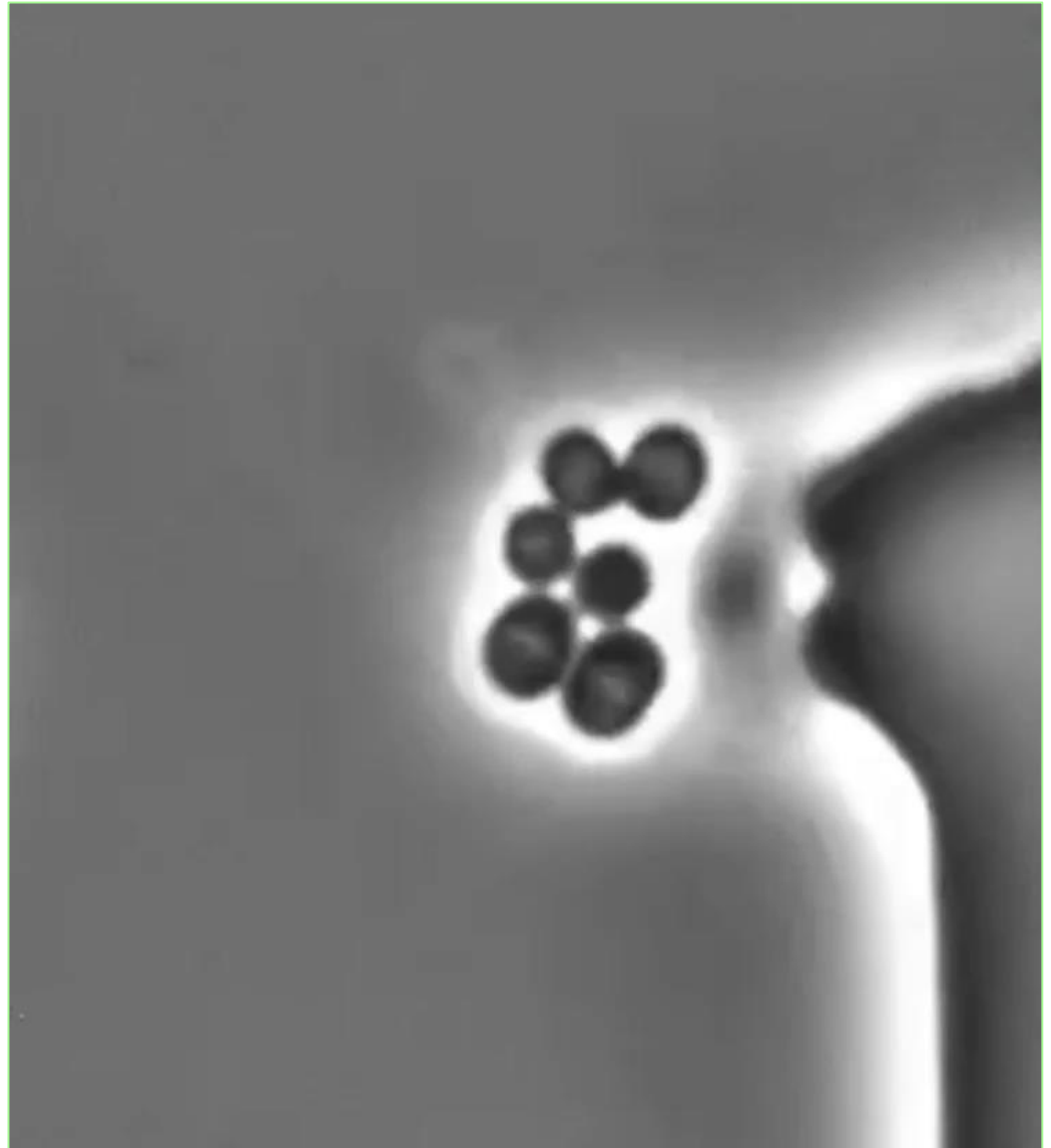
S. aureus being lysed by the Sa2 phage



Bacterial DNA appeared in green

Courtesy Pascal Maguin
Luciano Marraffini Lab

THE ROCKEFELLER UNIVERSITY



A clear antibacterial activity!

Phagogram

Phage

10^{10}

10^9

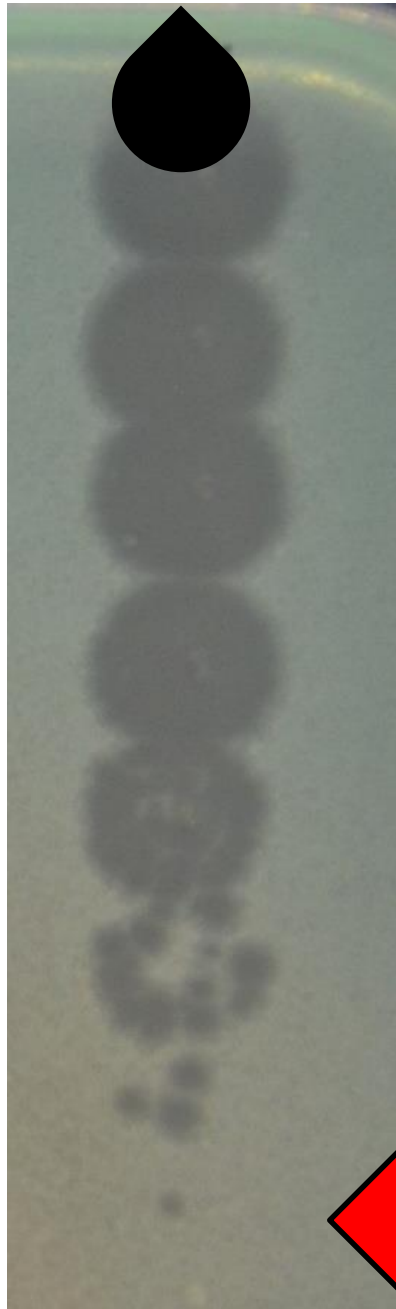
10^8

10^7

10^6

10^5

PFU/mL



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

Phage

A clear antibacterial activity!

Phagogram

10^{10}

10^9

10^8

10^7

10^6

10^5

PFU/mL

1,0

0,8

0,6

0,4

0,2

0,0

OD 600 nm

S. aureus

**kinetic growth
in liquid
media**

+ Phage

0

1

2

3

4

5

6

7

8

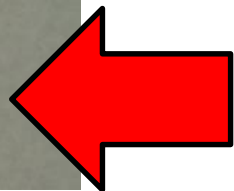
9

10

11

12

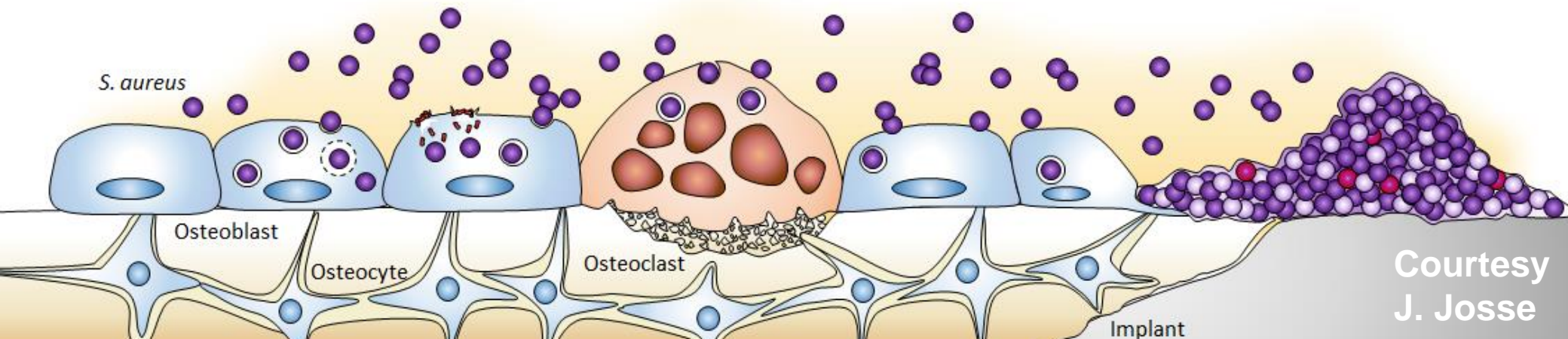
Hours of incubation



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

Persisters in chronic BJI

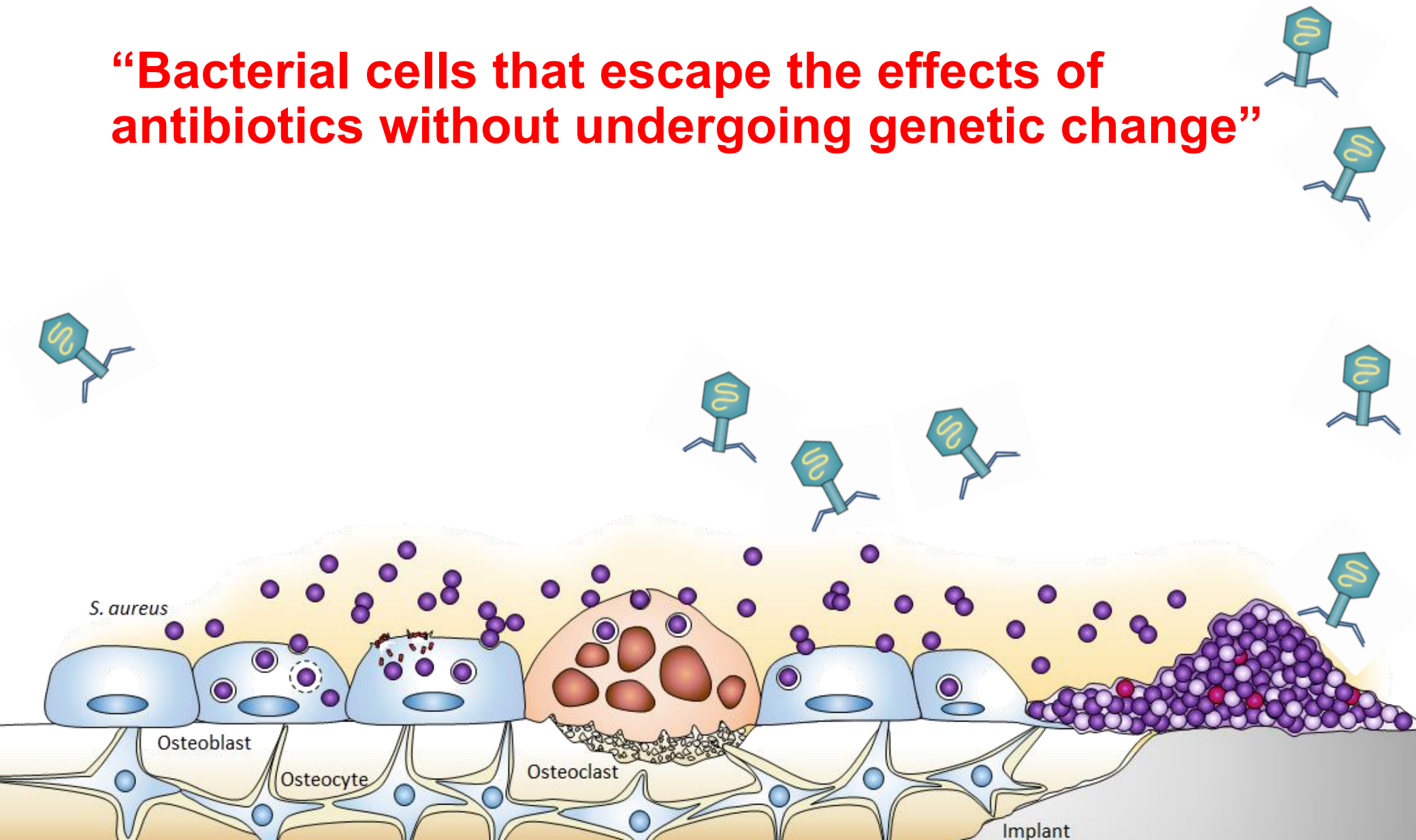
“Bacterial cells that escape the effects of antibiotics without undergoing genetic change”



Courtesy
J. Josse

Persisters in chronic BJI

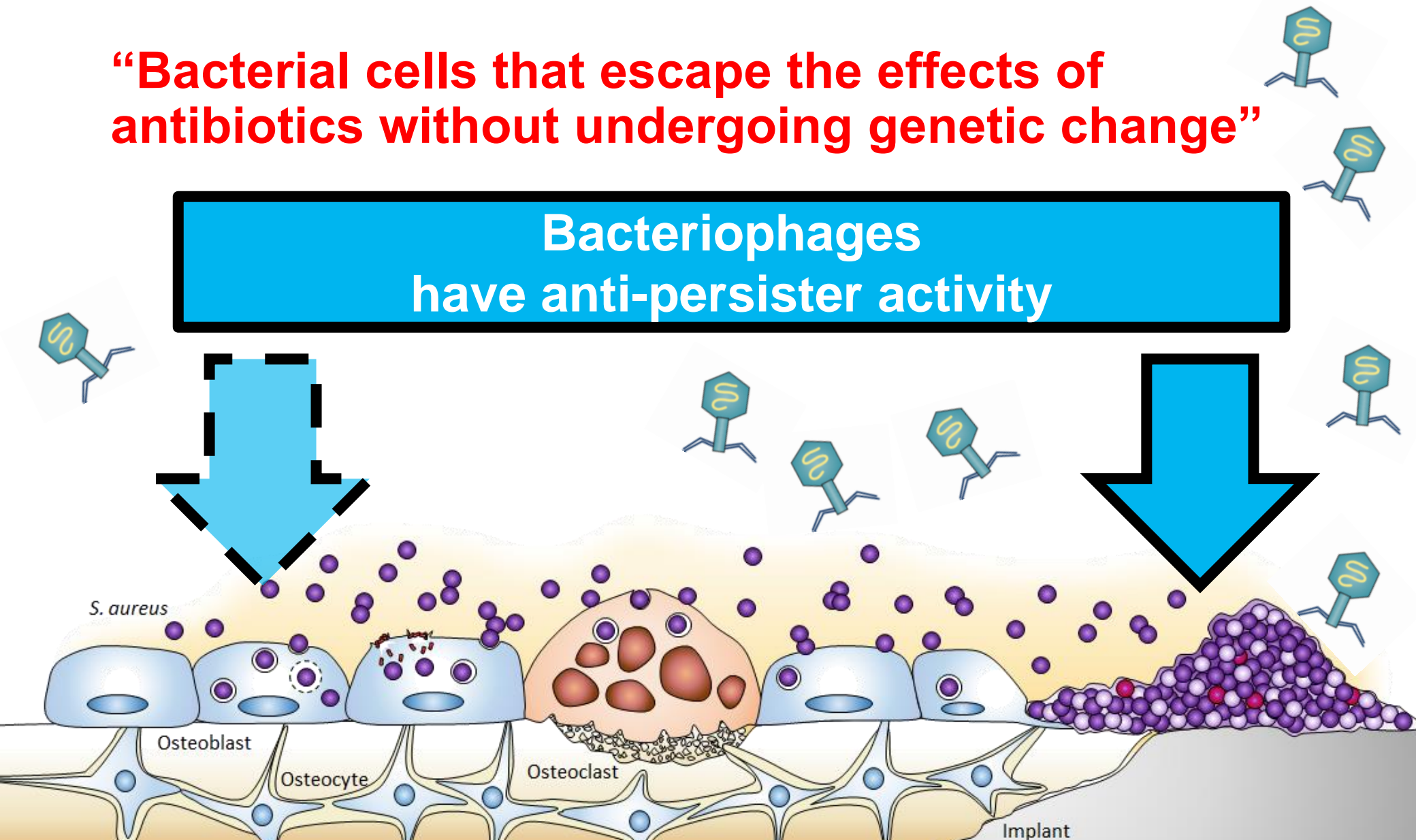
“Bacterial cells that escape the effects of antibiotics without undergoing genetic change”



Persisters in chronic BJI

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

**Bacteriophages
have anti-persister activity**



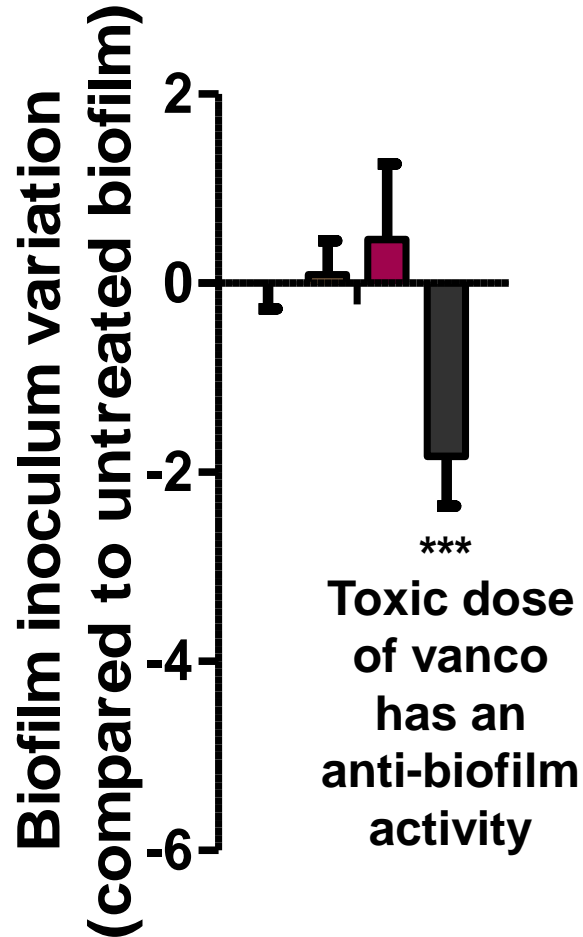
□ No Antibiotic

■ MIC

■ C_{bone} (4*MIC)

■ 10*MIC

vancomycin



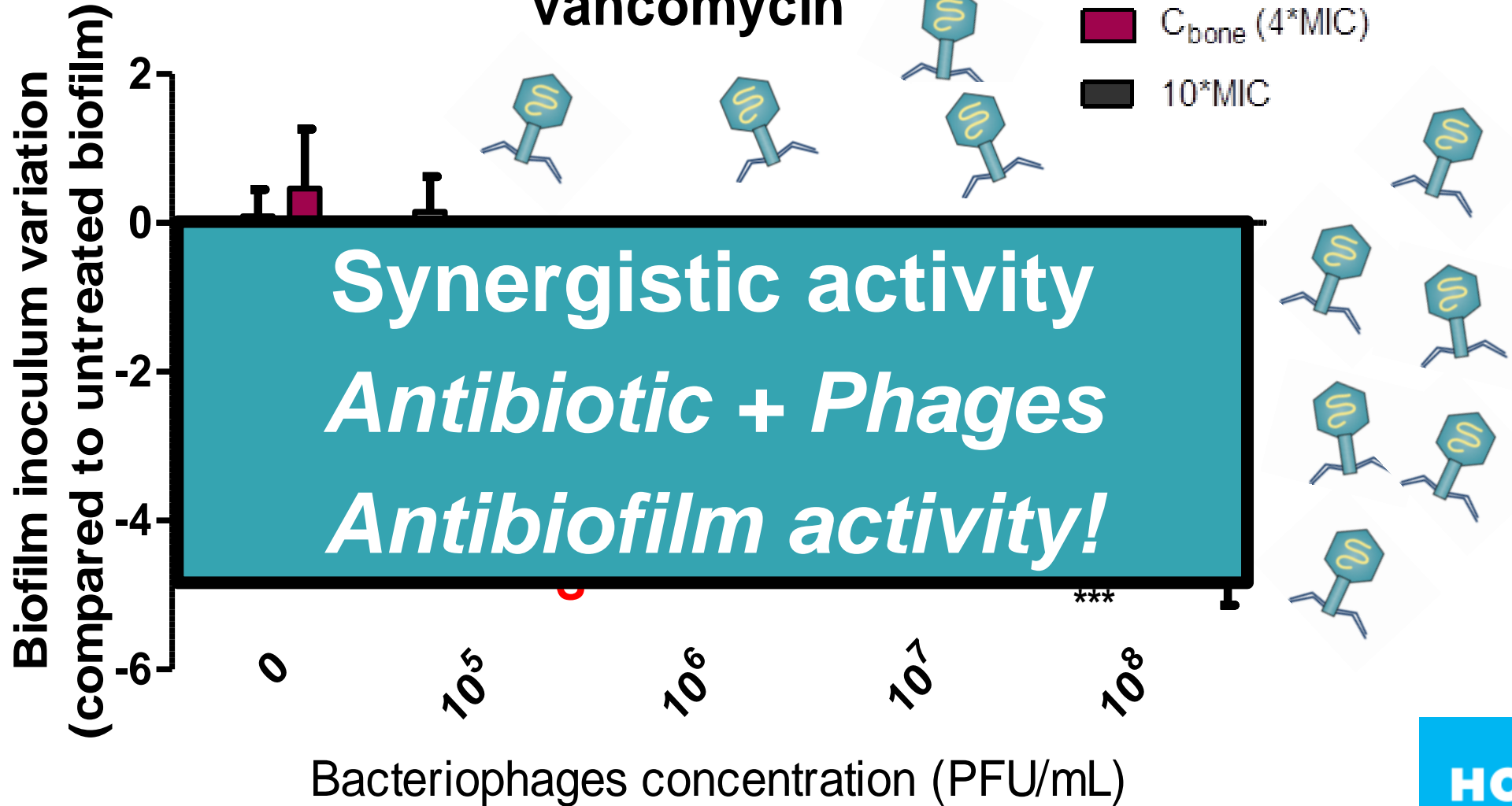
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■ 10*MIC

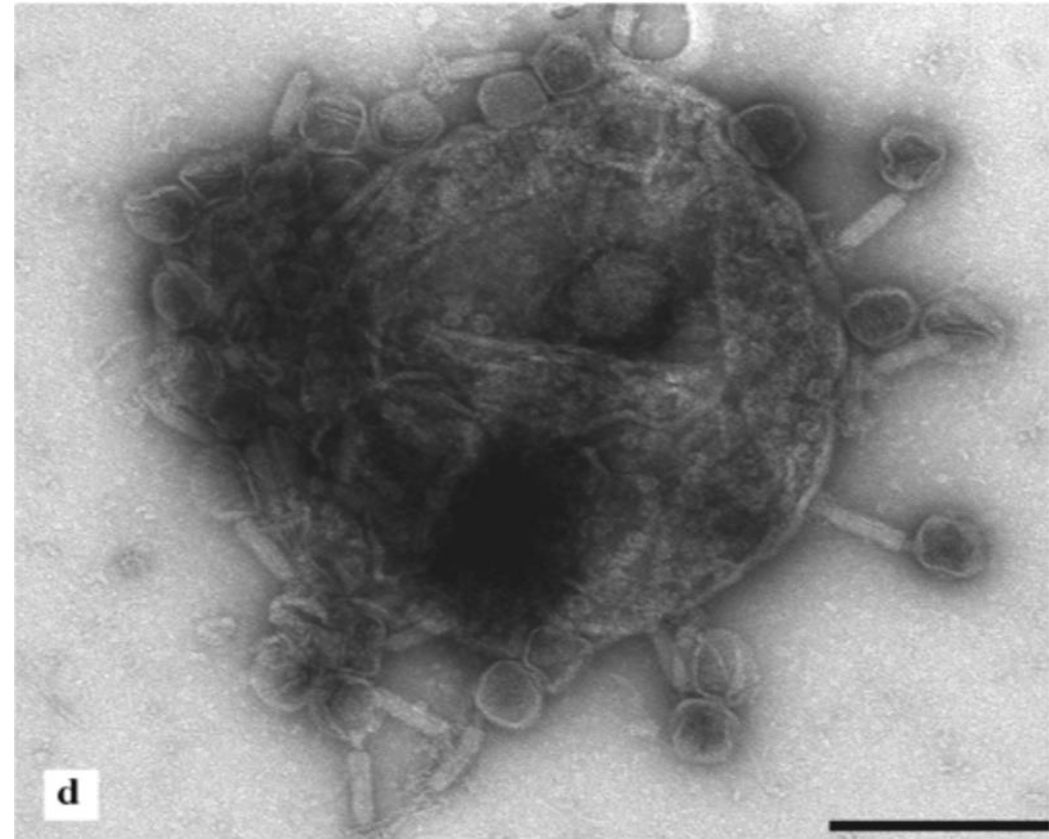
vancomycin



Cocktails produced in 2021 by the Eliava Institute

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

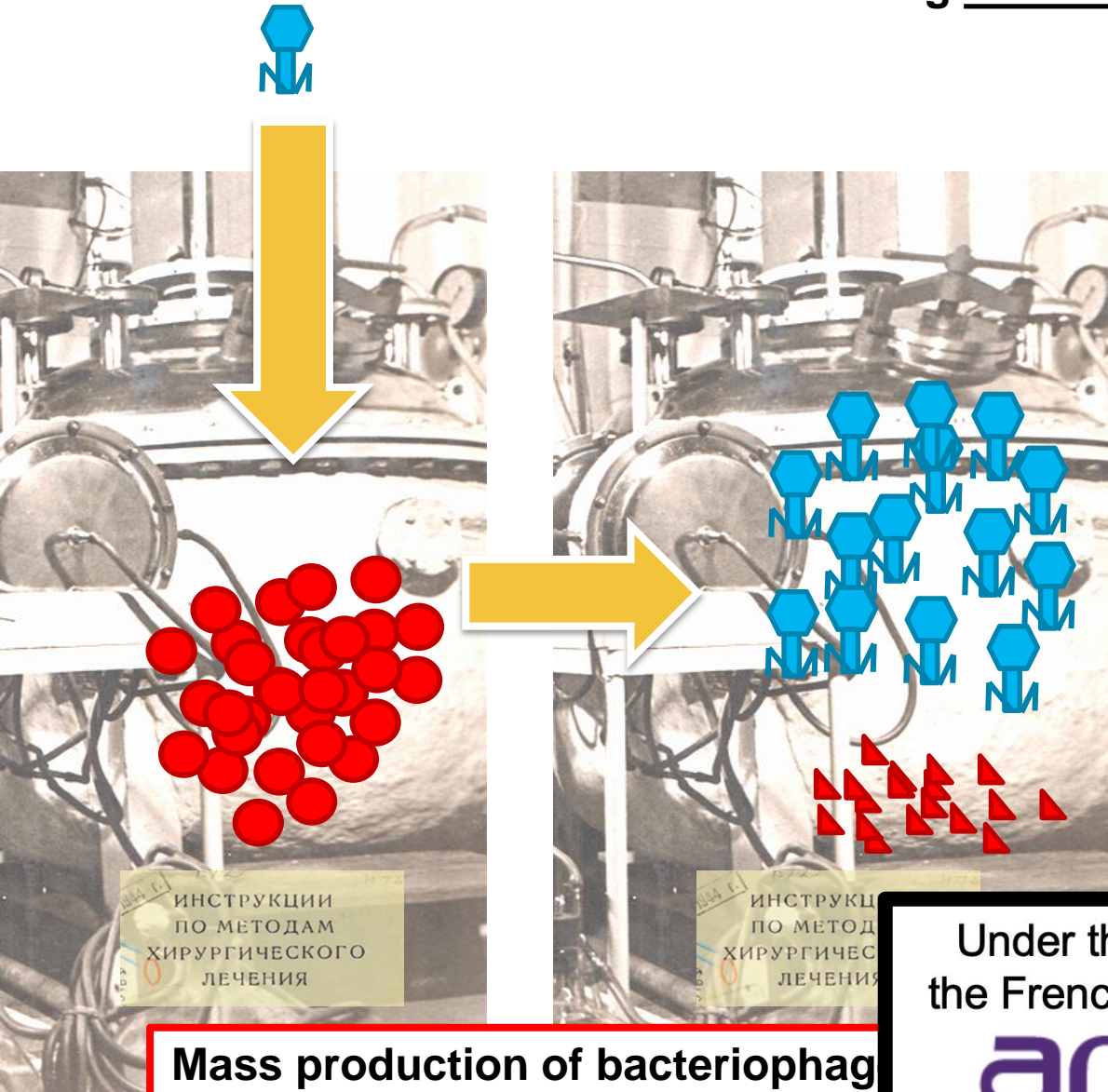
Bacteriophage ISP (*Myoviridae*)



Merabishvili et al. PloS ONE 2009



Not meeting Good Manufacturing Practices (GMP)



Pyrogenic
Bacterial
remnant?



10^6 phages/mL



GMP

**Purified and
produced as
a drug**

10^6 phages/mL

Under the supervision of
the French Health Authority

ansm

Agence nationale de sécurité du médicament
et des produits de santé



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?

Ferry T. 2018 *Open Forum Infectious Diseases*



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 ✉, 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,

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 Fevre*⁷,
Jérôme Josse^{2,3,4,5}, *Charlotte Petitjean*⁷, *Christian Chidiac*^{1,2,3,4}, *Gilles Leboucher*⁸ and
Frédéric Laurent^{2,3,4,5} on behalf of the Lyon BJI Study group

#PhagoDAIR

Clinical case #2

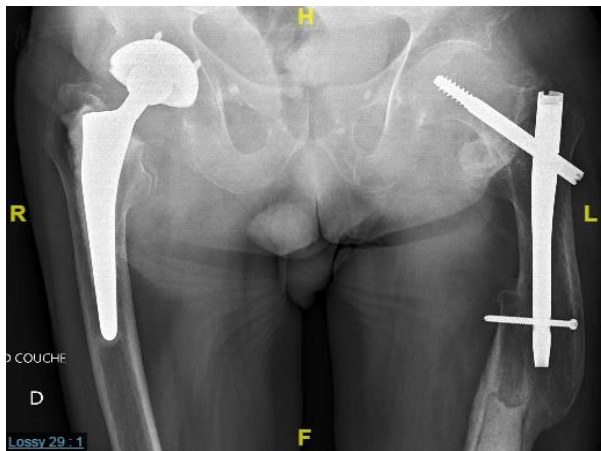
80-year-old man

Relapsing MSSA prosthetic left knee infection (past revision)

Failure under suppressive antimicrobial therapy

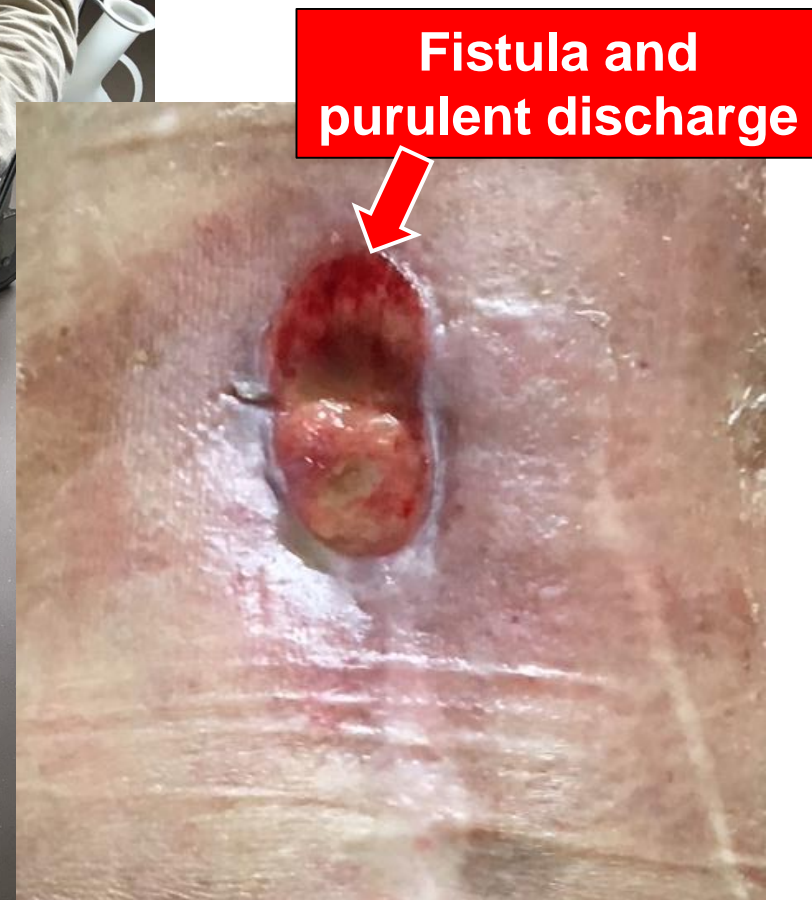
Complex orthopaedic situation with past femoral fracture

Impossible to walk (painful knee)





Septic arthritis



**Fistula and
purulent discharge**

Clinical case #2

Amputation
(but not feasible !) ?



VS.



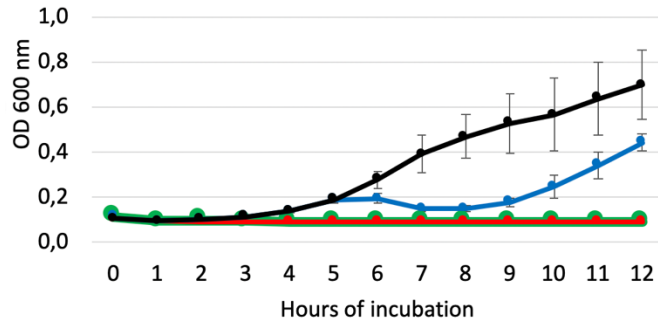
Doing nothing, but poor clinical situation with risk of complication and death

Conservative surgery
“Debridement And Implant Retention” (DAIR) +
innovative approach to disrupt biofilm

+

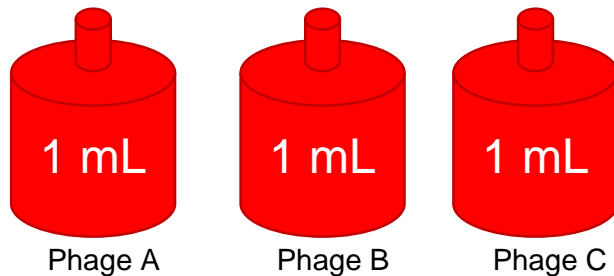
Suppressive antimicrobial therapy

Lyon Phage team



Phagogram
Selection of active bacteriophages

Active GMP *S. aureus* Bactériophages



ID Clinic



HCL
HOSPICES CIVILS
DE LYON

CRIAOC
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

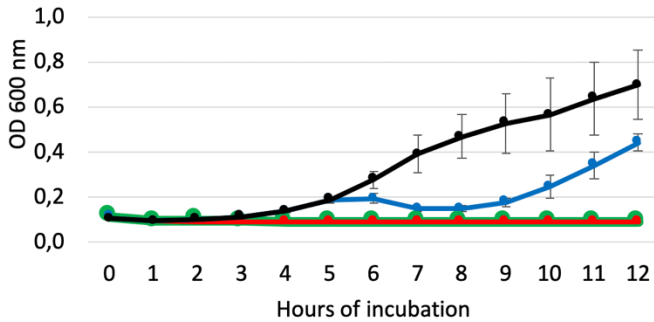
Pharmacy



HCL
HOSPICES CIVILS
DE LYON

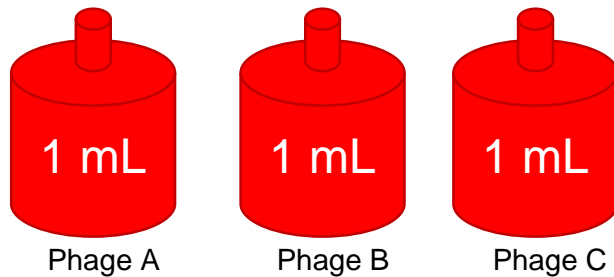
**Extemporaneous
magistral
preparation of the
mix of
bacteriophages**

Lyon Phage team



Phagogram
Selection of active bacteriophages

Active GMP
***S. aureus* Bactériophages**



ID Clinic



HCL
HOSPICES CIVILS
DE LYON

CRIAAC
LYON



Surgery



HCL
HOSPICES CIVILS
DE LYON

Lab



HCL
HOSPICES CIVILS
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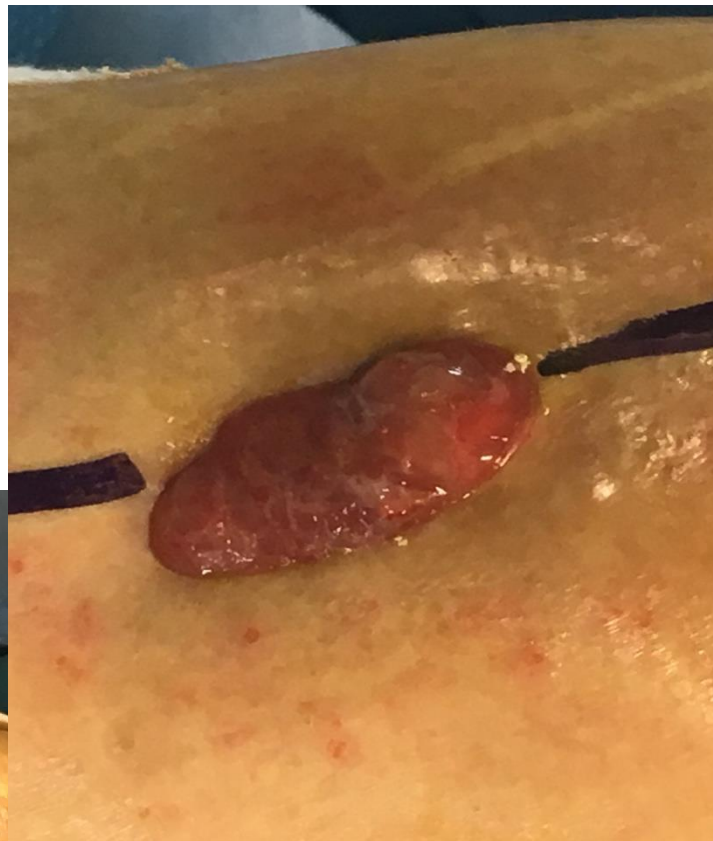
Pharmacy



HCL
HOSPICES CIVILS
DE LYON

**Extemporaneous
magistral
preparation of the
mix of
bacteriophages**











“PhagoDAIR”



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

HCL
HOSPICES CIVILS
DE LYON

CRIOAc
LYON

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





**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.



**Favorable outcome
at 1 year**



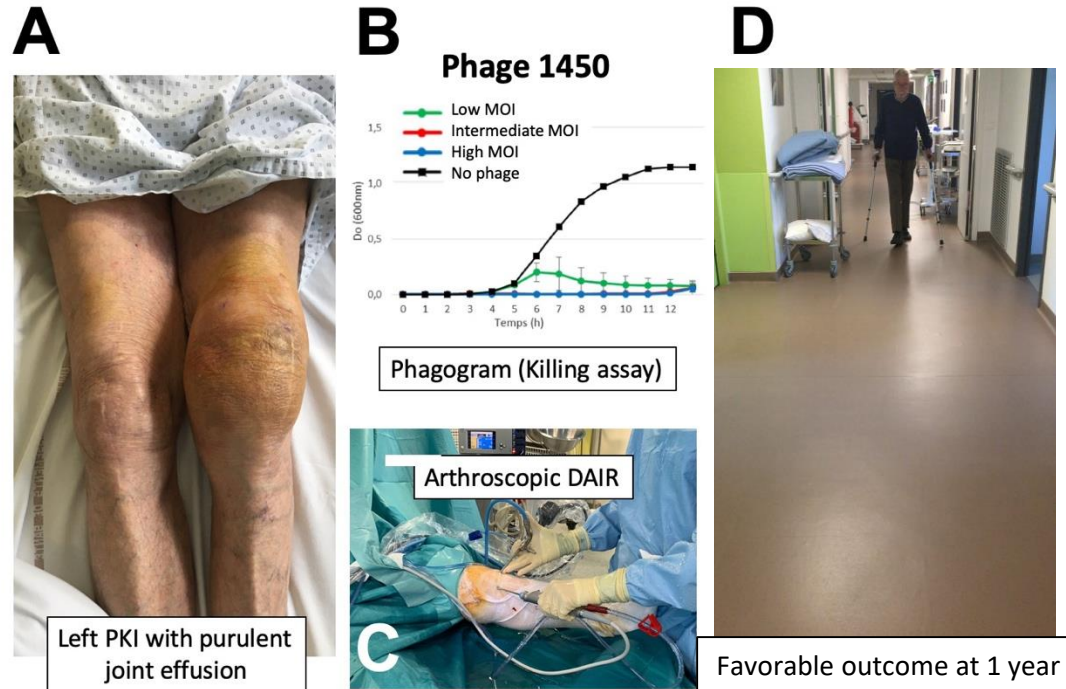




**Favorable outcome
at 1 year**

Arthroscopic “Debridement Antibiotics and Implant Retention” with local injection of **personalized phage therapy** to salvage a relapsing *Pseudomonas aeruginosa* prosthetic knee infection

**Phago
DAIR**



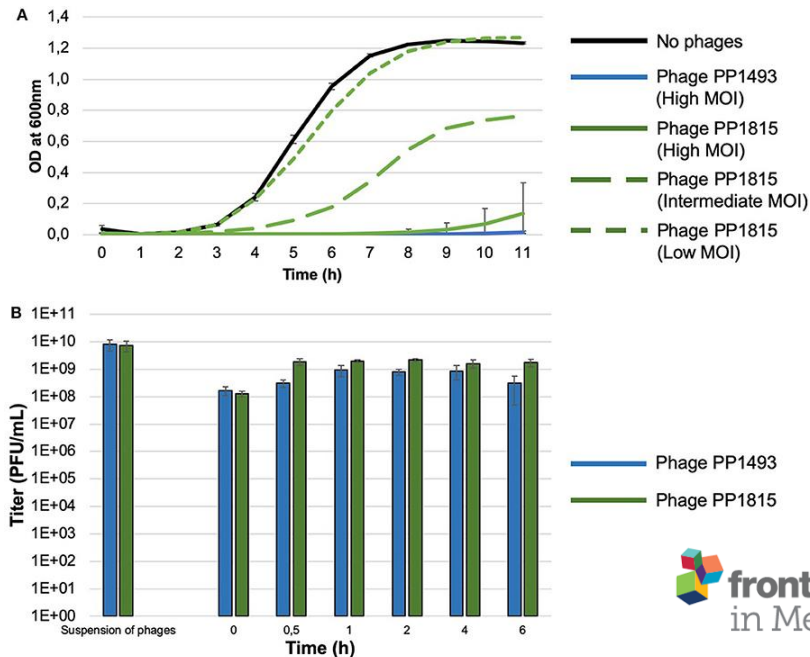
Submitted
30th
ECCMID
Paris, France
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Conclusions: The **PhagoDAIR** procedure by **arthroscopy** has the potential to be used **as salvage therapy** for patients with *P. aeruginosa* relapsing PJI, in combination with suppressive antimicrobial therapy. **A Phase II clinical study deserves to be performed to confirm this hypothesis.**

The Potential Innovative Use of Bacteriophages Within the DAC[®] Hydrogel to Treat Patients With Knee Megaprosthesis 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



Conclusion



- Creation of regional **reference centers** in France (funded by health ministry) transformed the patient approach
- **Personalized** clinical care is the **base of the pyramid** for the management of complex BJI with **bedside multidisciplinary meeting**
- **Infectious Disease physicians have potential great roles:**
 - Can help to keep the function!
 - Have to develop and propose **adjuvant personalized innovative anti-infective agents** for selected **relevant indications**
- **Phages** have a **real potential** in prosthetic-joint infection
- Need for **industrial and academic developement** of therapeutic phages (discovery, banking, susceptibility testing) in connexion with health care authorities
- Need to **perform clinical trials** to evaluate the ability of these innovations to improve the outcome



Lyon BJI Study group

Coordinator: Tristan Ferry

Infectious Diseases Specialists – Tristan Ferry, Florent Valour, Thomas Perpoint, Florence Ader, Sandrine Roux, Claire Triffault-Filit, Agathe Becker, Anne Conrad, Marielle Perry, Cécile Pouderoux, Nicolas Benech, Pierre Chauvelot, Johanna Lippman, Evelyne Braun, Christian Chidiac

Surgeons – Sébastien Lustig, Elvire Servien, Cécile Batailler, Stanislas Gunst, Axel Schimdt, Matthieu Malatray, Eliott Sappey-Marinier, Michel-Henry Fessy, Anthony Viste, Jean-Luc Besse, Philippe Chaudier, Lucie Louboutin, Quentin Ode, Adrien Van Haecke, Marcelle Mercier, Vincent Belgaid, Arnaud Walch, Sébastien Martres, Franck Trouillet, Cédric Barrey, Ali Mojallal, Sophie Brosset, Camille Hanriat, Hélène Person

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

Nuclear Medicine – Isabelle Morelec, Marc Janier, Francesco Giammarile

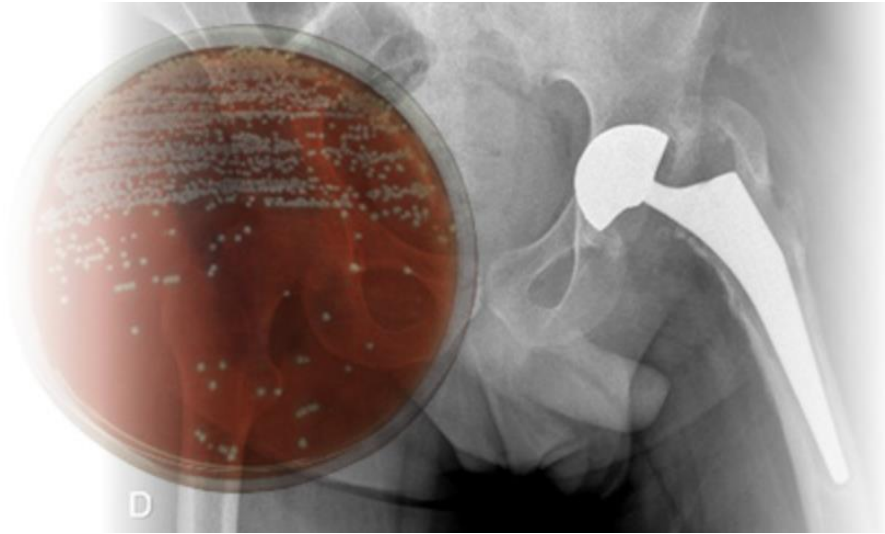
PK/PD specialists – Michel Tod, Marie-Claude Gagnieu, Sylvain Goutelle

Clinical Research Assistant – Eugénie Mabrut



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