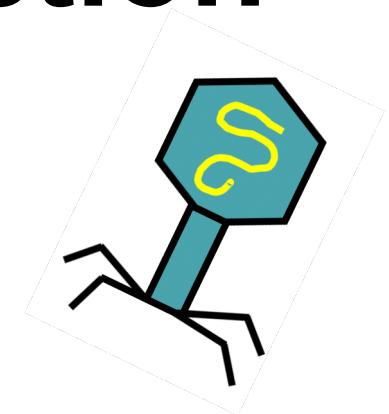


Personalized medicine for bone and joint infection

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

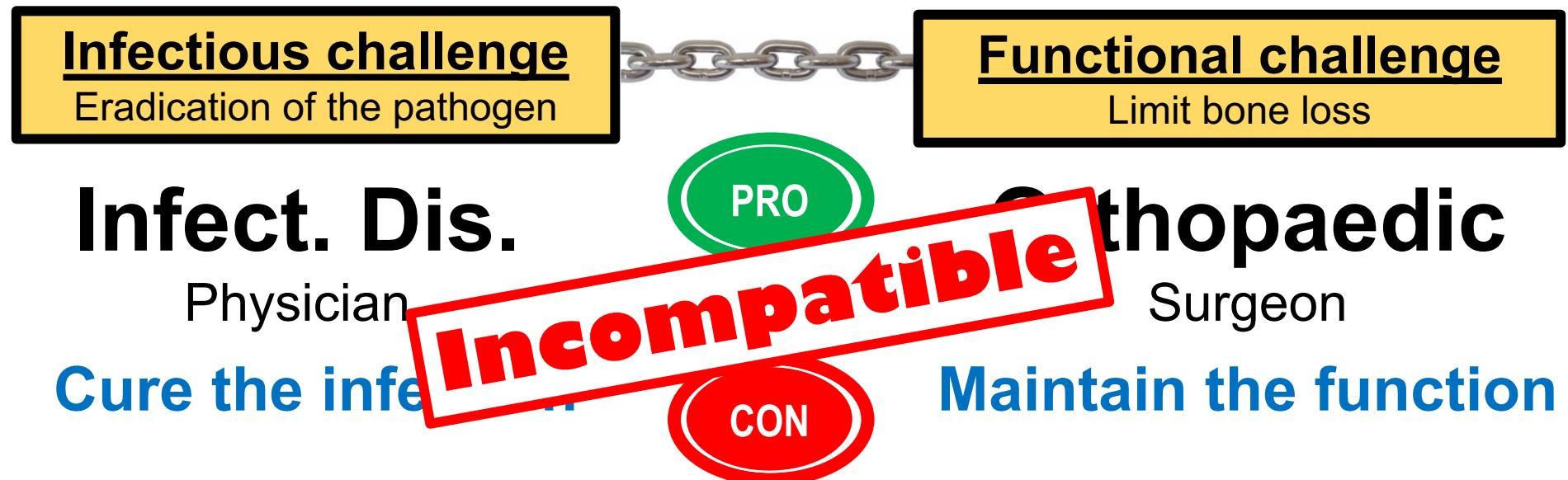
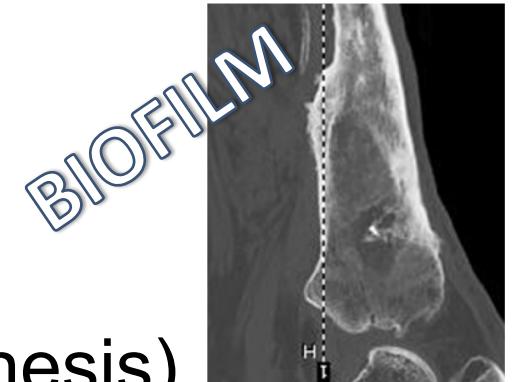
Centre International de Recherche en Infectiologie, CIRI, Inserm U1111, CNRS
UMR5308, ENS de Lyon, UCBL1, Lyon, France

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)



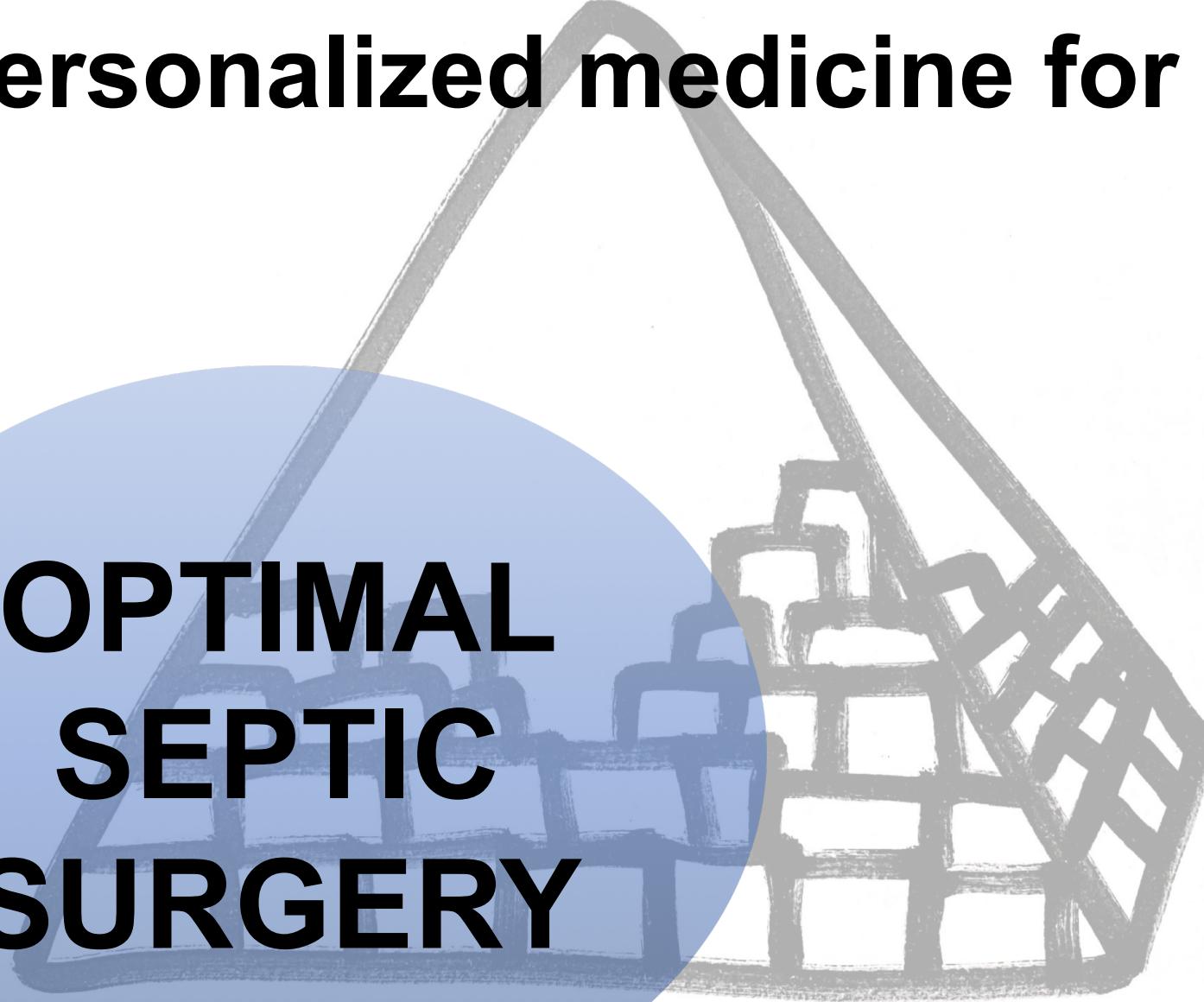
Personalized medicine for BJI



Personalized medicine for BJI



**OPTIMAL
SEPTIC
SURGERY**



Clinical case #1

Patient with nonunion (potentially septic)



1-stage material exchange,
bone grafting, antibiotics?



VS.



2-stage material
exchange, bone
grafting,
antibiotics?

1-stage resection
prosthesis



2-stage resection prosthesis
(1st stage with spacer)

Personalized medicine for BJI

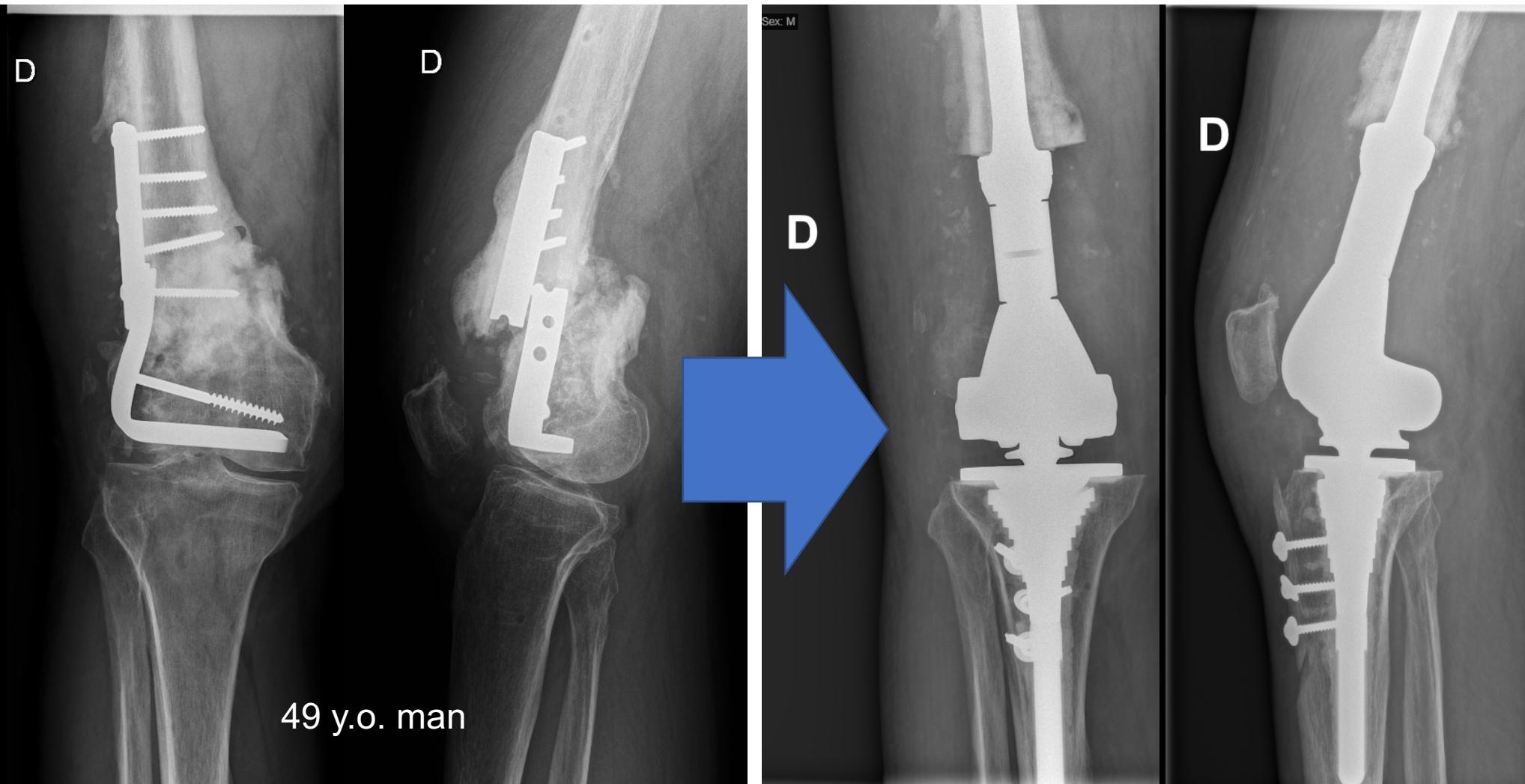
Empirical antimicrobial therapy

OPTIMAL
SEPTIC
SURGERY

TARGETED AND
OPTIMAL
ANTIMICROBIAL
THERAPY

Clinical case #1

Patient with nonunion (potentially septic)



Use the antibiogram

	<i>Staphylococcus epidermidis</i>	CMI (mg/l)
Oxacilline		S
Kanamycine		S
Gentamicine		S
Tobramycine		S
Erythromycine		S
Lincomycine		S
Pristinamycine		S
Tétracycline		S
Ofloxacine		S
Cotrimoxazole		S
Nitrofurantoine		S
Rifampicine		S
Fosfomycine		R
Acide Fusidique		S
Vancomycine		S
Linézolide		S

To target the pathogen

To personnalize the antimicrobial therapy:

- Patient's profile (weight, allergy, comedication)
- Select an active and the most optimal regimen

Personalized medicine for BJI

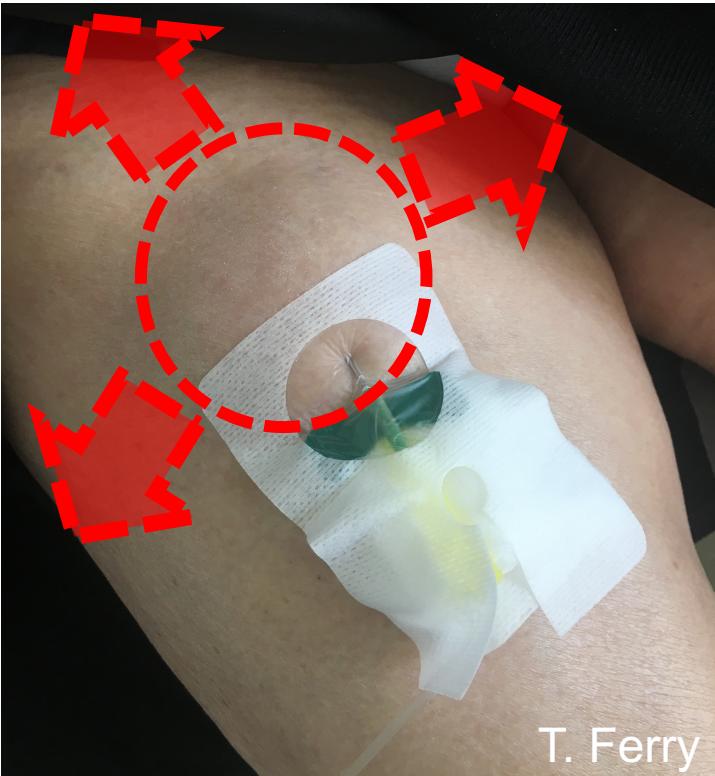
OPTIMAL
SEPTIC
SURGERY

TARGETED AND
OPTIMAL
ANTIMICROBIAL
THERAPY

Clinical case #2

85-year-old woman

Acute PJI resistant *K. pneumoniae*
‘DAIR’ & Subcutaneous ertapenem



Ertapenem
1g

50 mL
NaCl 9%

30 min
gravity
infusion



Clinical case #2

85-year-old woman

Ertapenem
1g

50 mL
NaCl 9%

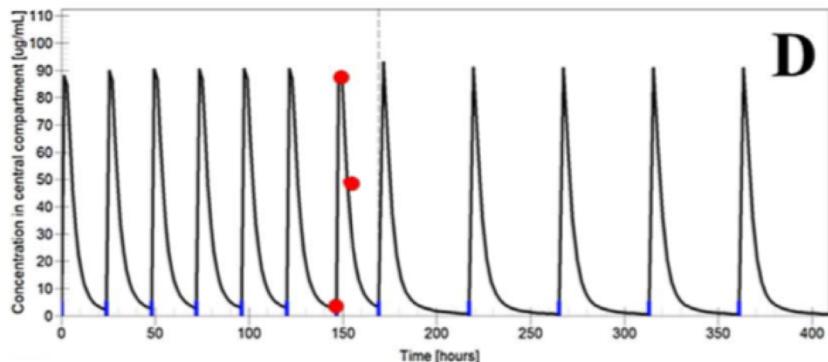
30 min
gravity
infusion

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

T. Ferry *SICOT-J* 2020, 6, 26

Persistence of the *K. pneumoniae*

**No explantation
To maintain the function**



**PK-based
suppressive therapy
SC injection each 48h**

Ertapenem MIC
0.064 mg/L



Personalized medicine for BJI

MULTIDISCIPLINAR MEETING

THE BEST INDIVIDUALIZED MEDICOSURGICAL STRATEGY

OPTIMAL
SEPTIC
SURGERY

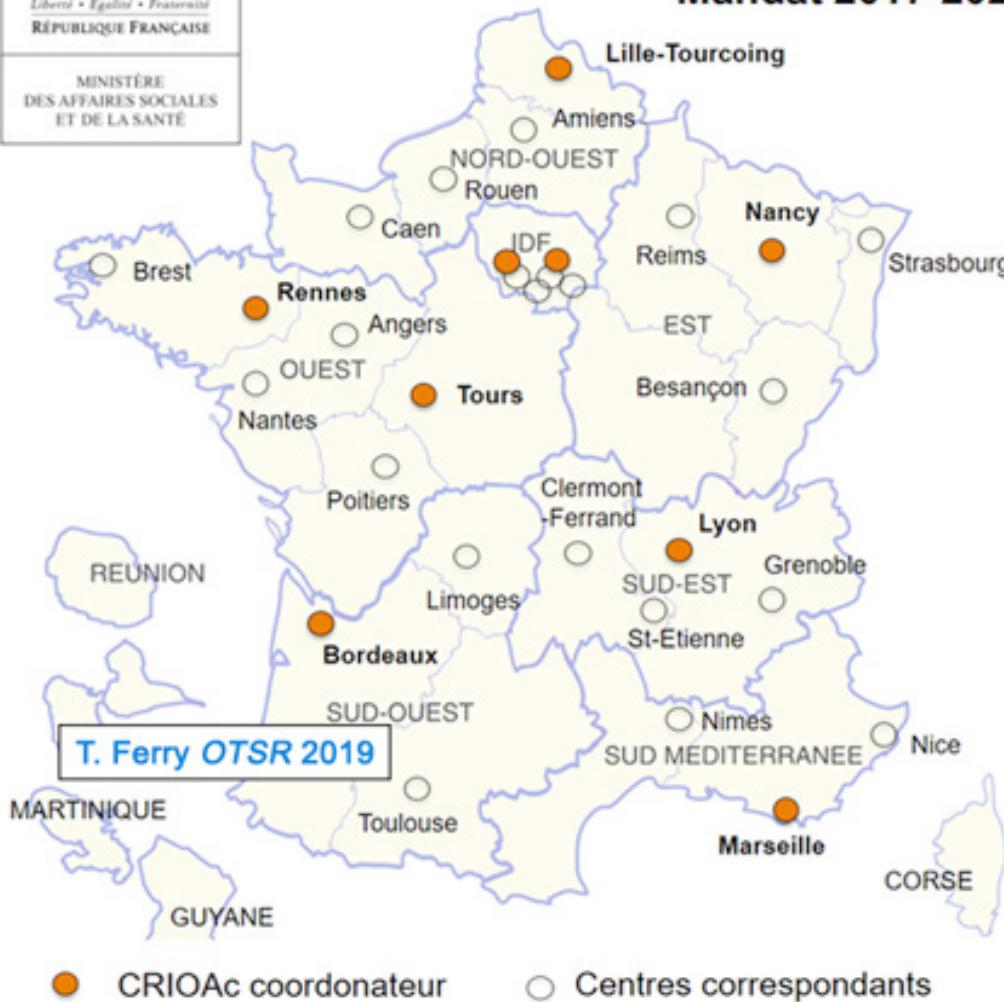
TARGETED AND
OPTIMAL
ANTIMICROBIAL
THERAPY



Centre de Référence des Infections Ostéo-Articulaires complexes



Réseau des CRIODc Mandat 2017-2022



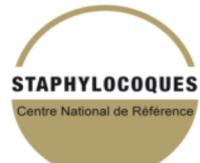


Centre de Référence des Infections Ostéo-Articulaires complexes



Réseau des Crioac

Mandat 2017-2022



Pr. Sébastien Lustig
MD, PhD
Orthopaedic surgeon

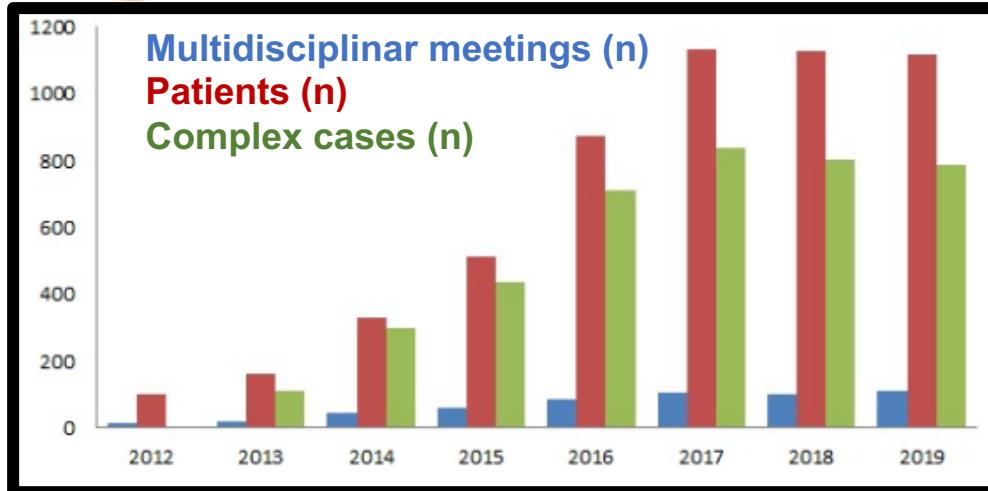
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Infectiologist

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Microbiologist

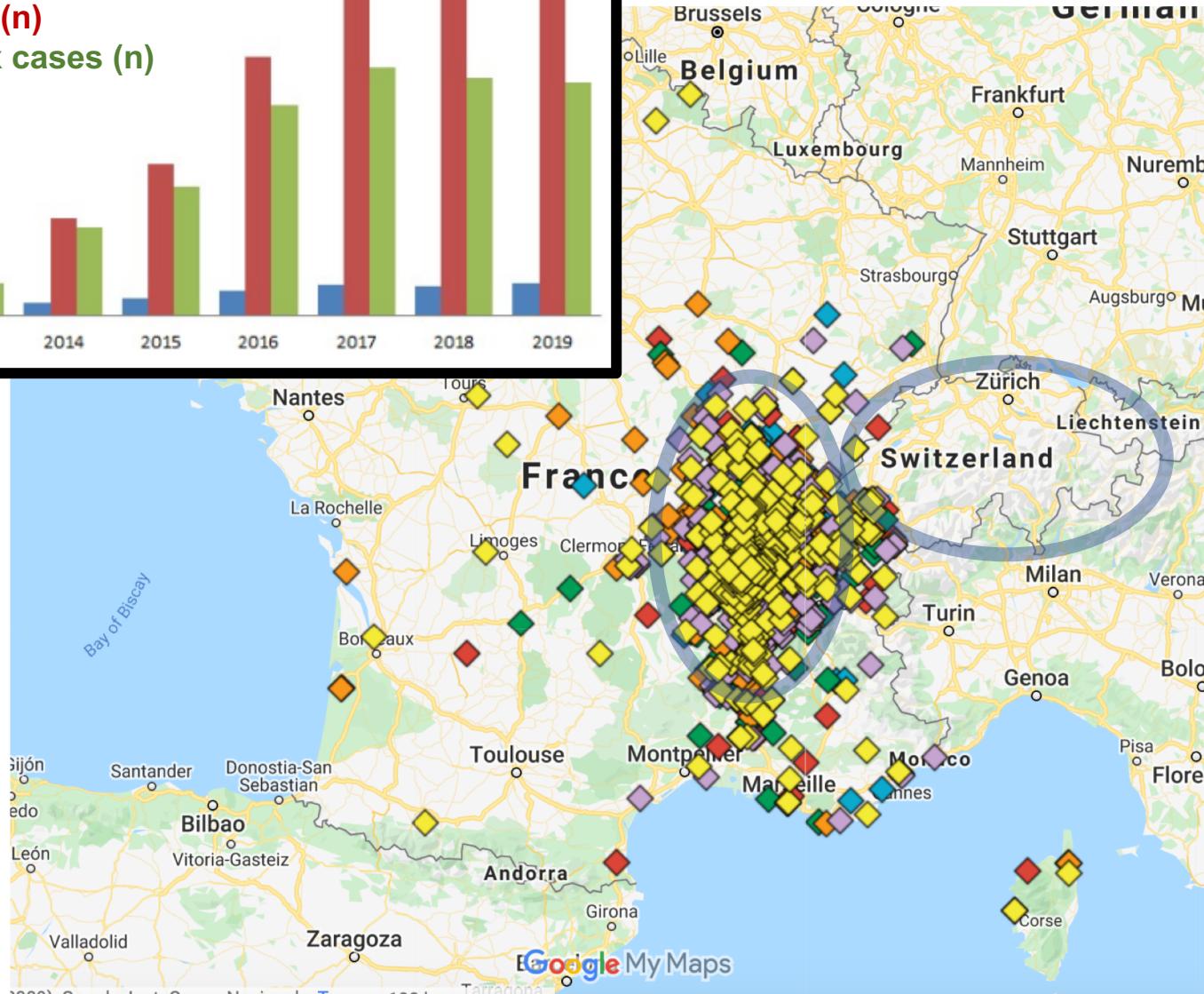


trois correspondants

Centre de Référence des Infections Ostéo-Articulaires complexes



- ◆ 2019
- ◆ 2018
- ◆ 2017
- ◆ 2016
- ◆ 2015





Centre de Référence des Infections Ostéo-Articulaires complexes



to develop
personnalized innovative approach

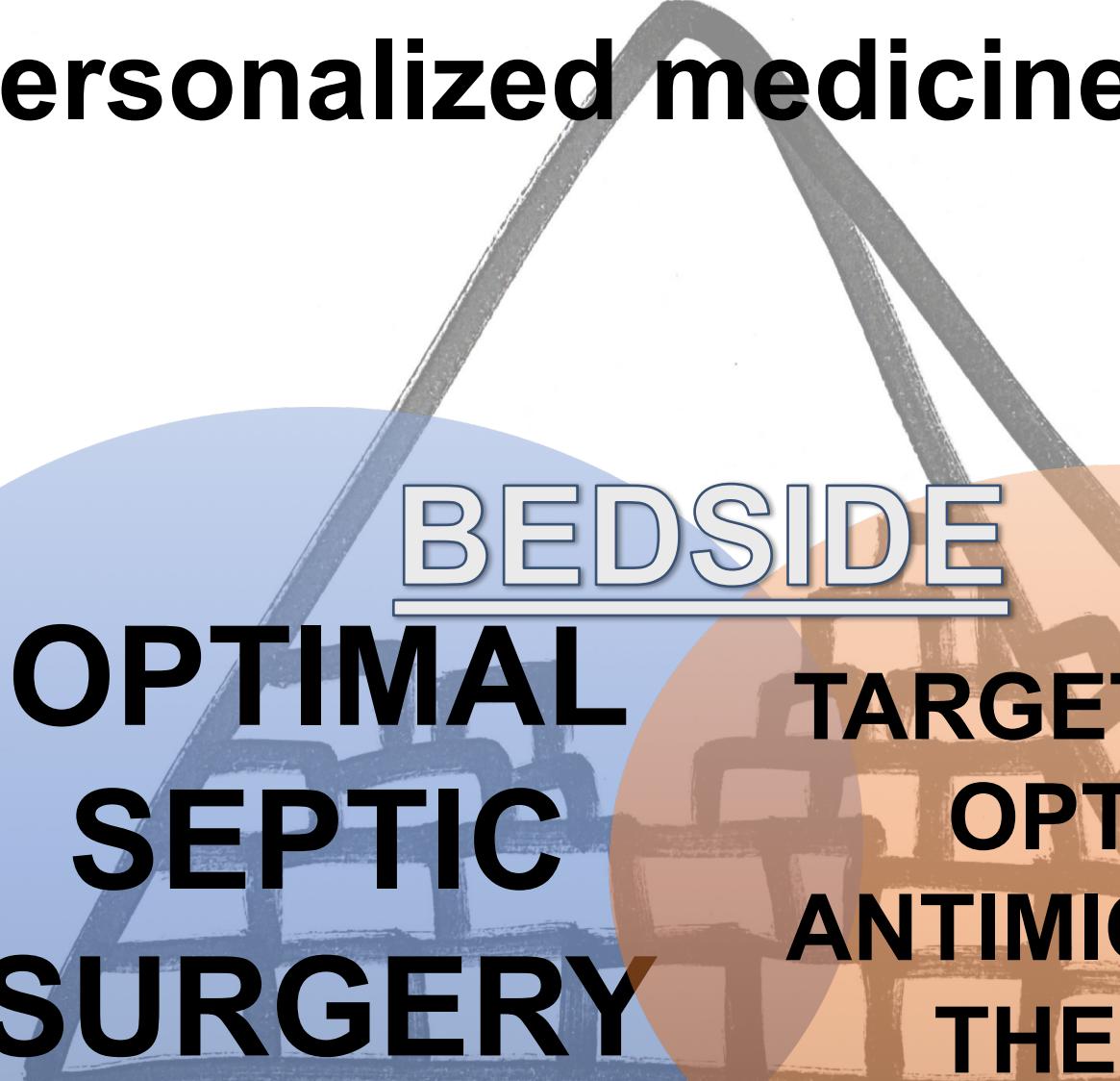


BEDSIDE

The norm to manage complex BJI

MULTIDISCIPLINAR MEETING

Personalized medicine for BJI



BEDSIDE



**OPTIMAL
SEPTIC
SURGERY**



**TARGETED AND
OPTIMAL
ANTIMICROBIAL
THERAPY**

MULTIDISCIPLINAR MEETING

Personalized medicine for BJI

AntibioticS-loaded
PMMA cements

Antibiotic-loaded
bone substitutes

Bacteriophages

Bacteriophage-
derived lysins

New antibiotics
targeting the biofilm

**ADJUVANT
INNOVATIVE ANTI-
INFECTIVE AGENTS
BEDSIDE**

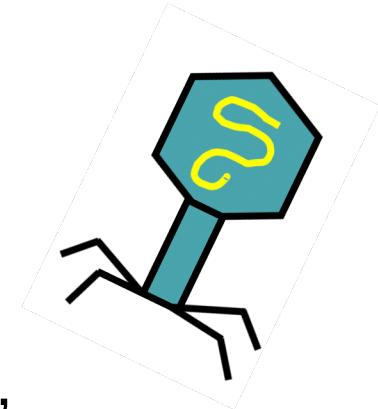
**OPTIMAL
SEPTIC
SURGERY**

**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

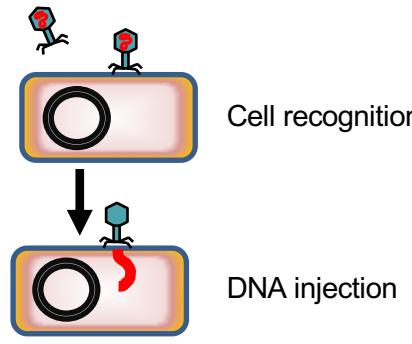


X million of ≠
BactériophageS !!!
(targeting environmental bacteria)

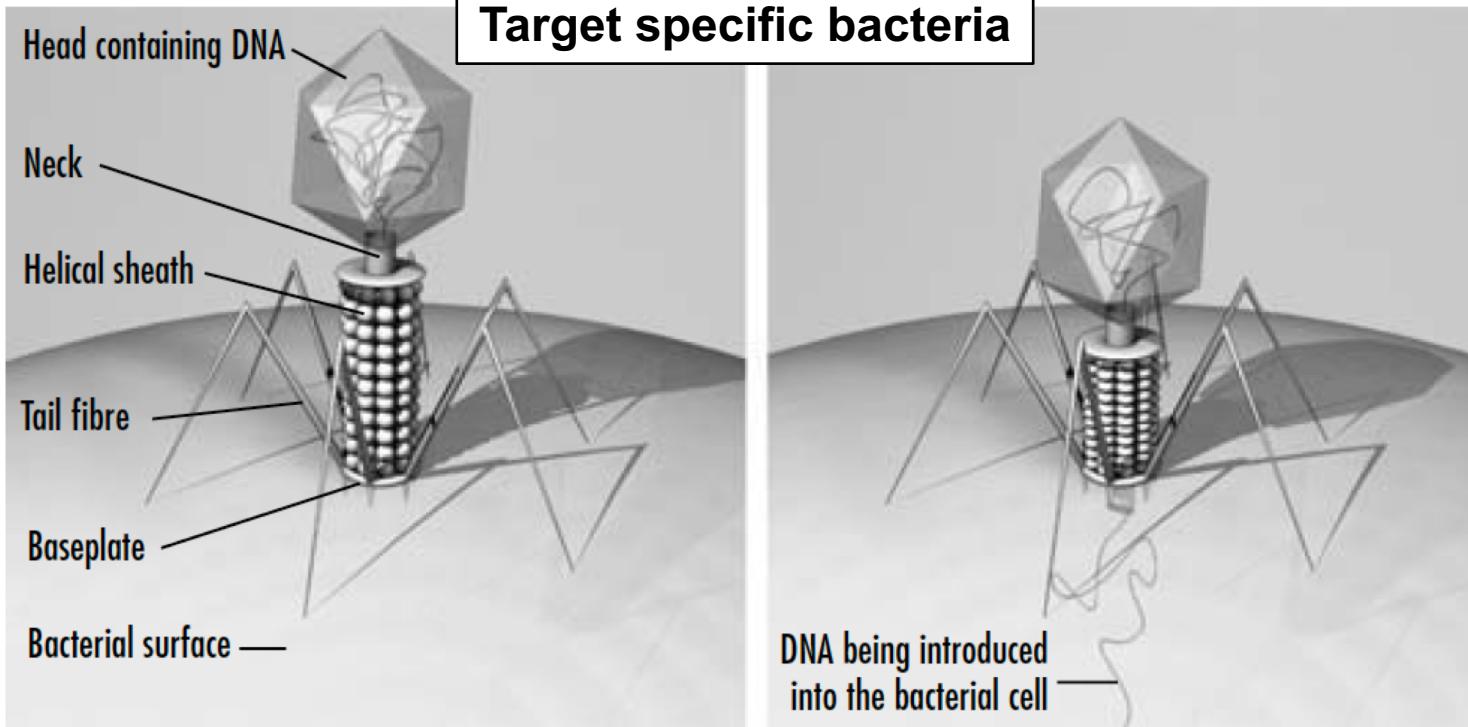


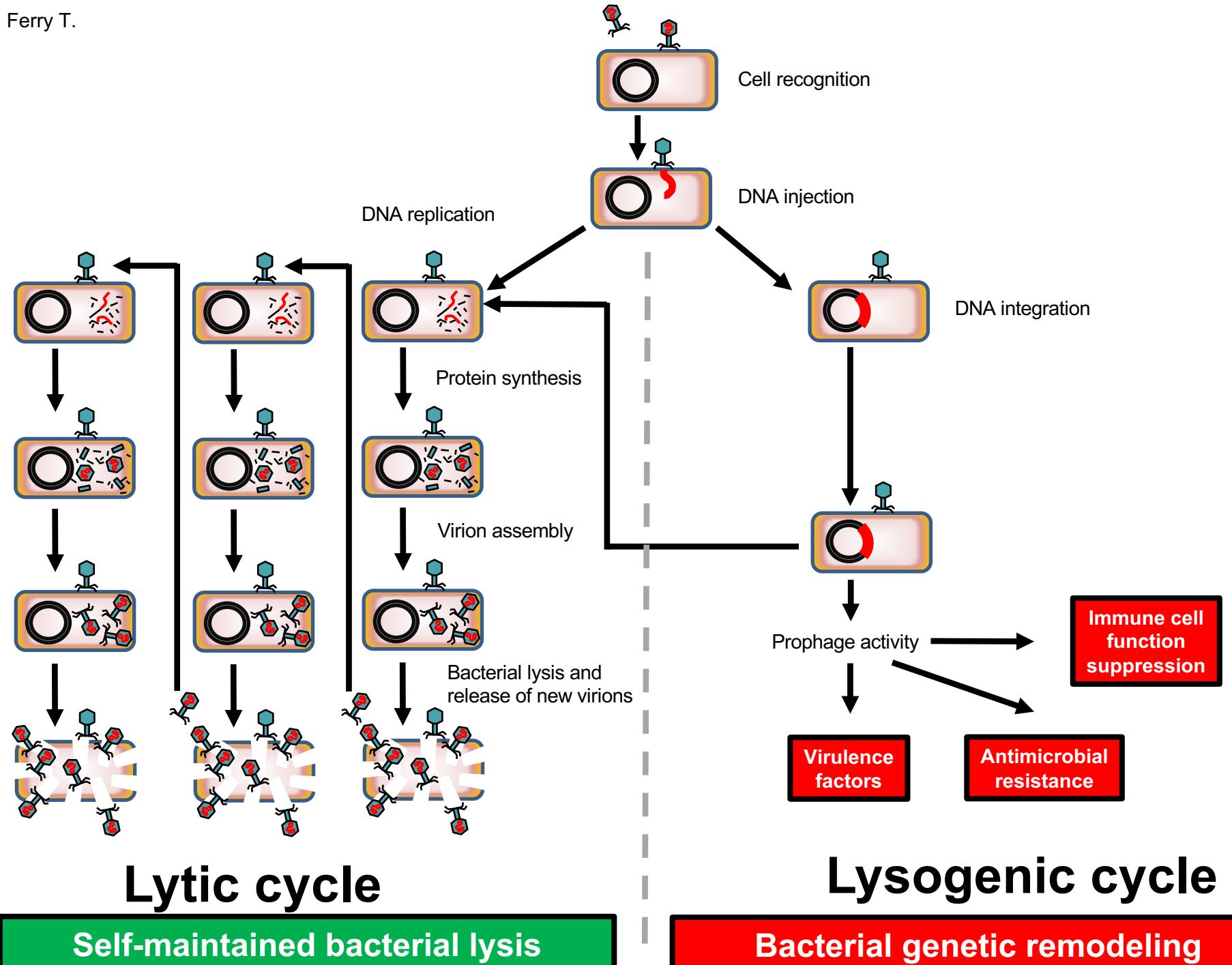
10⁸ of THREE
bacteriophages/mL
(targeting *S. aureus*)





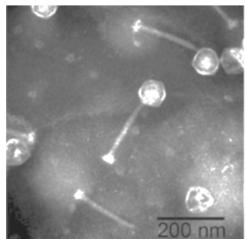
Environmental viruses Target specific bacteria





A clear antibacterial activity!

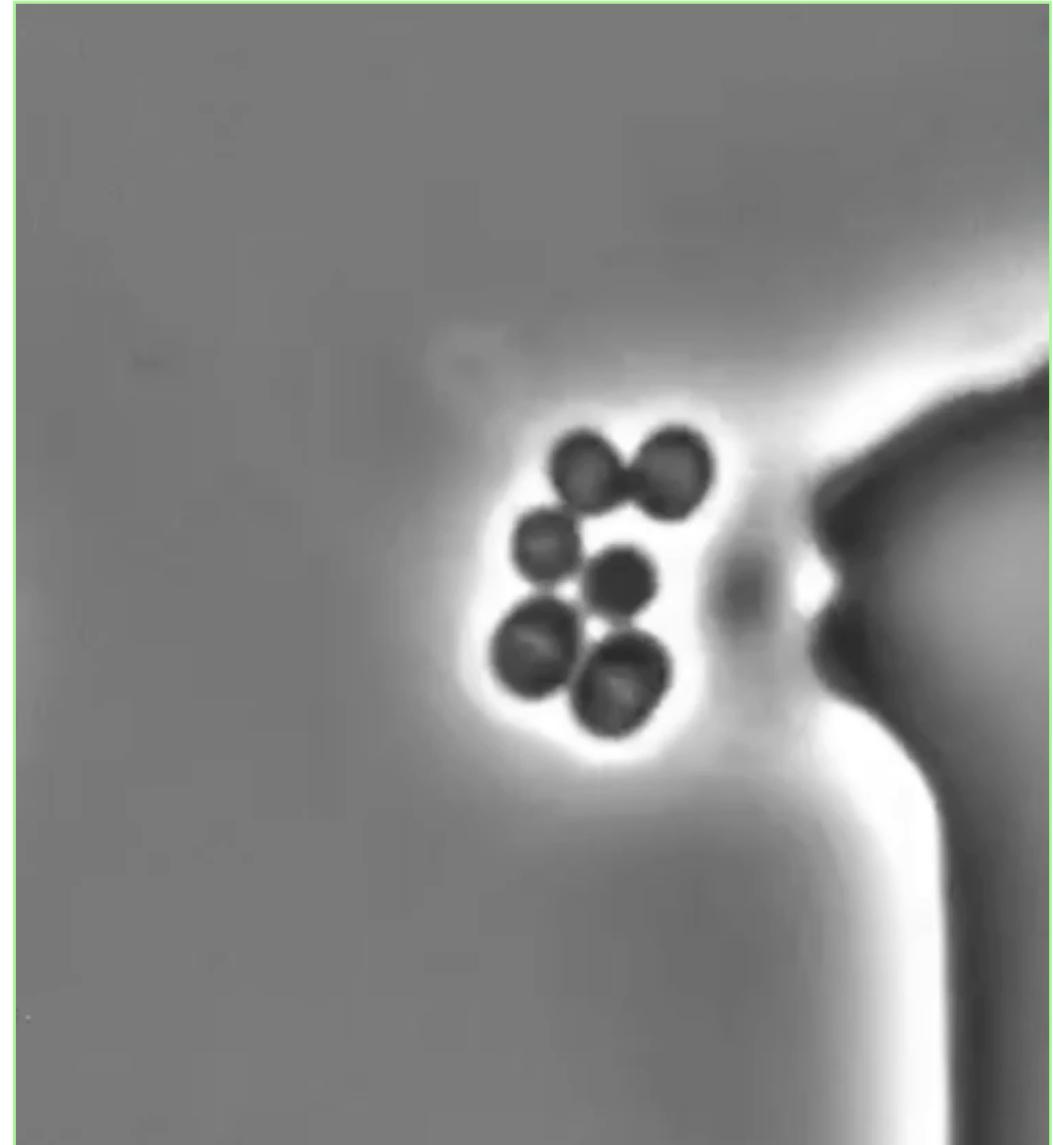
S. aureus being lysed by the Sa2 phage

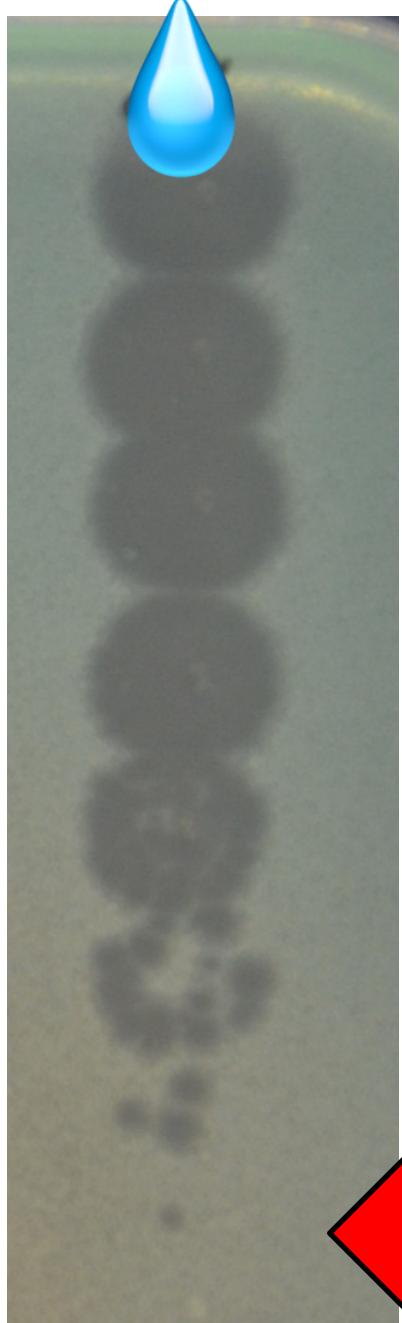


Bacterial DNA
appeared in
green

Courtesy Pascal Maguin
Luciano Marraffini Lab

THE ROCKEFELLER UNIVERSITY





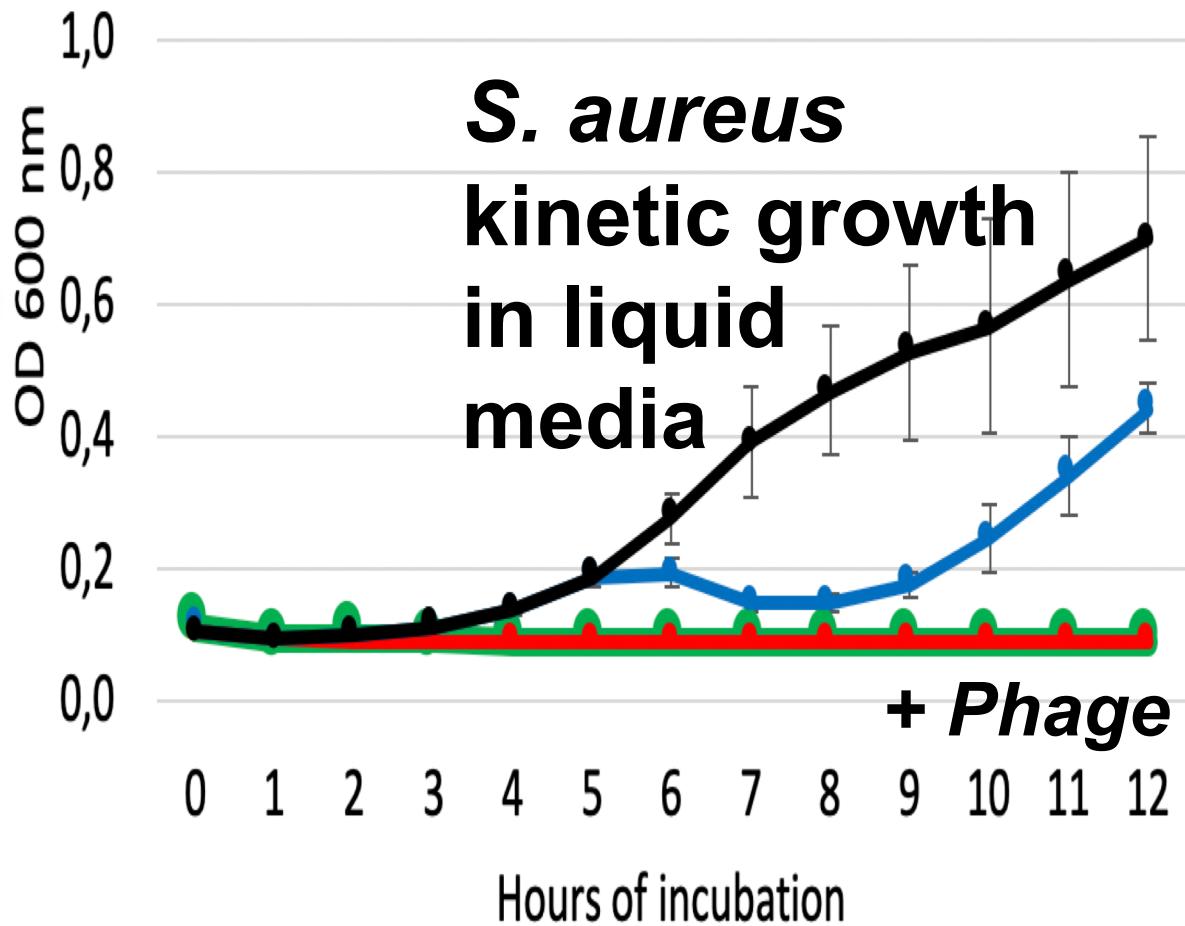
Phage

10^{10}
 10^9
 10^8
 10^7
 10^6
 10^5

PFU/mL

A clear antibacterial activity!

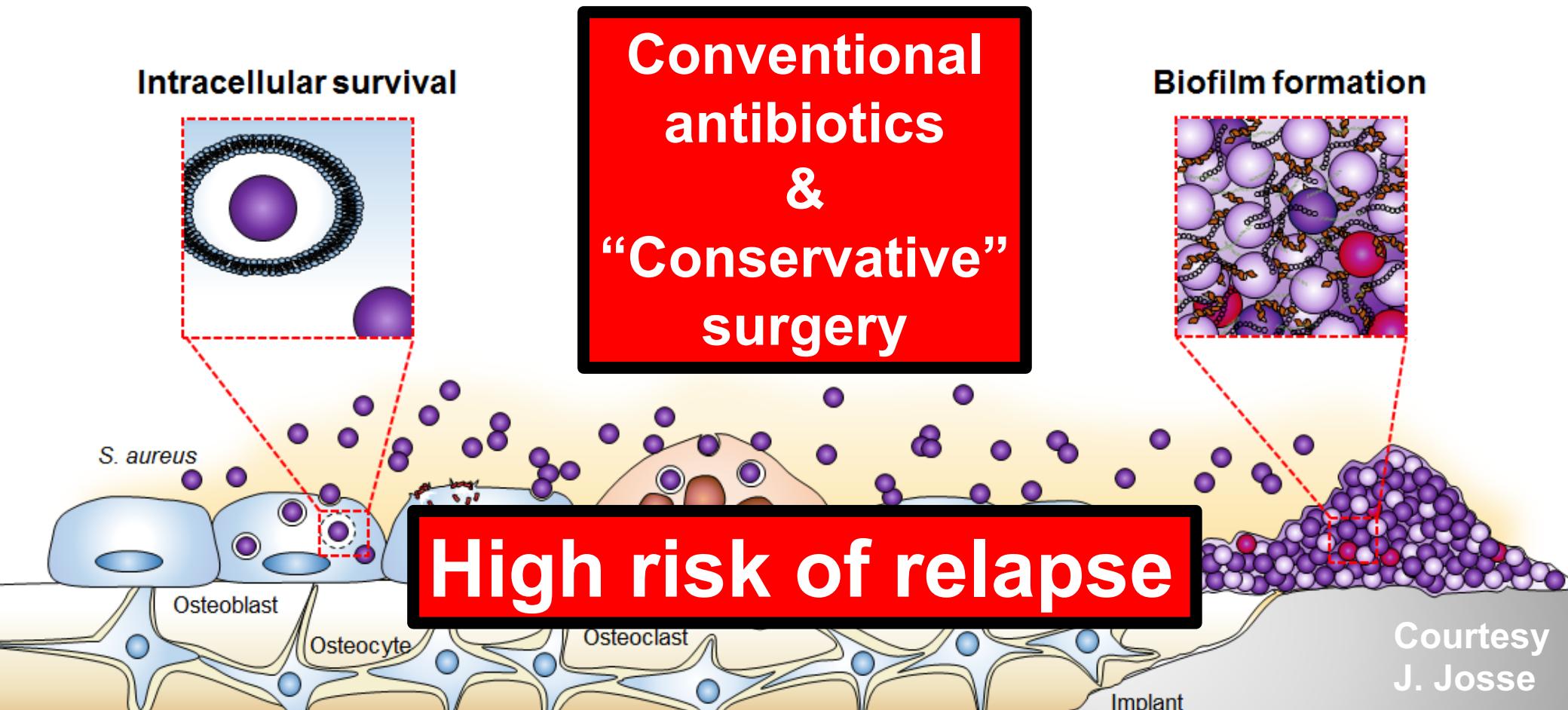
Phagogram



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

Persisters in chronic BJI

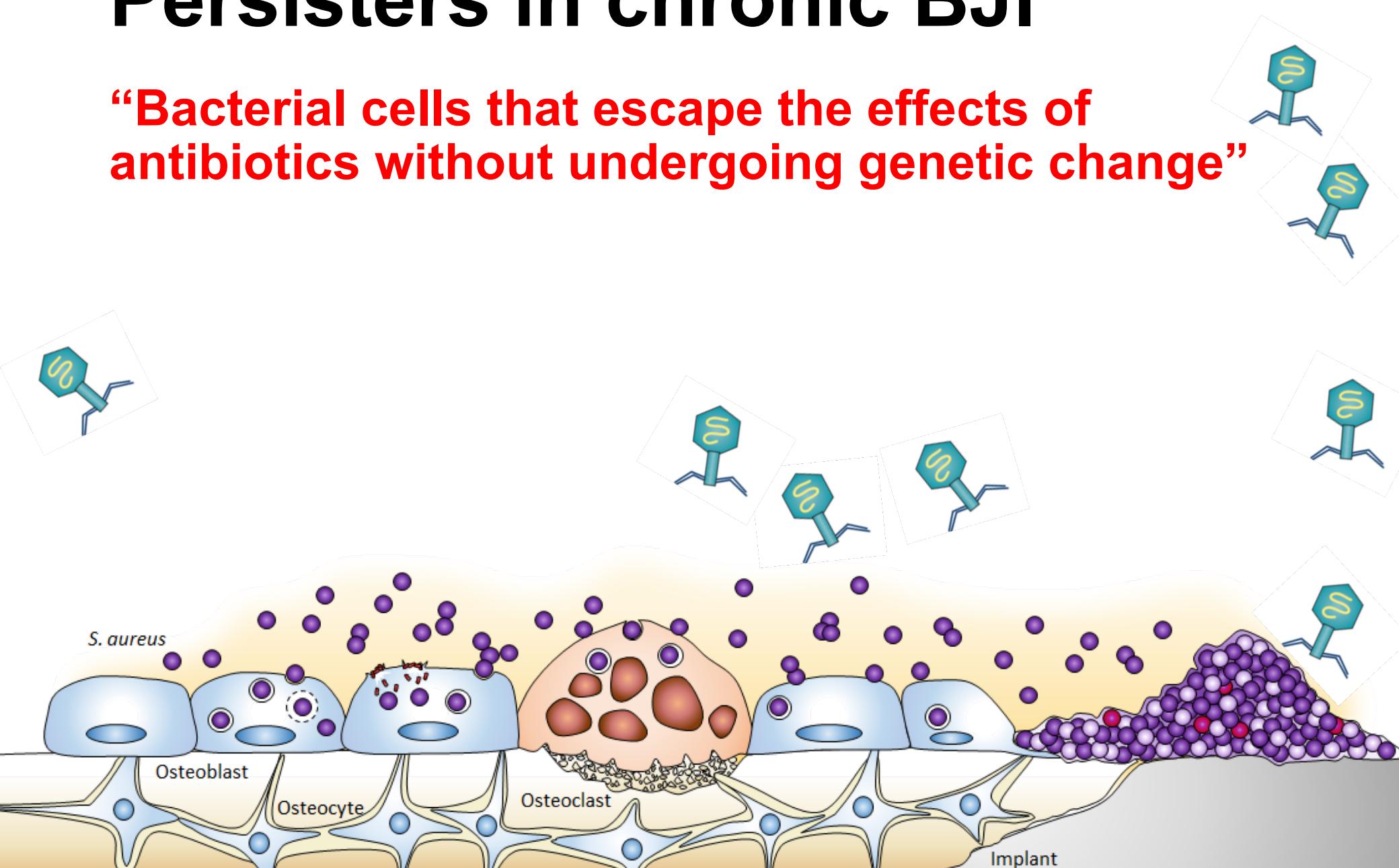
“Bacterial cells that escape the effects of antibiotics without undergoing genetic change”



Courtesy
J. Josse

Persisters in chronic BJI

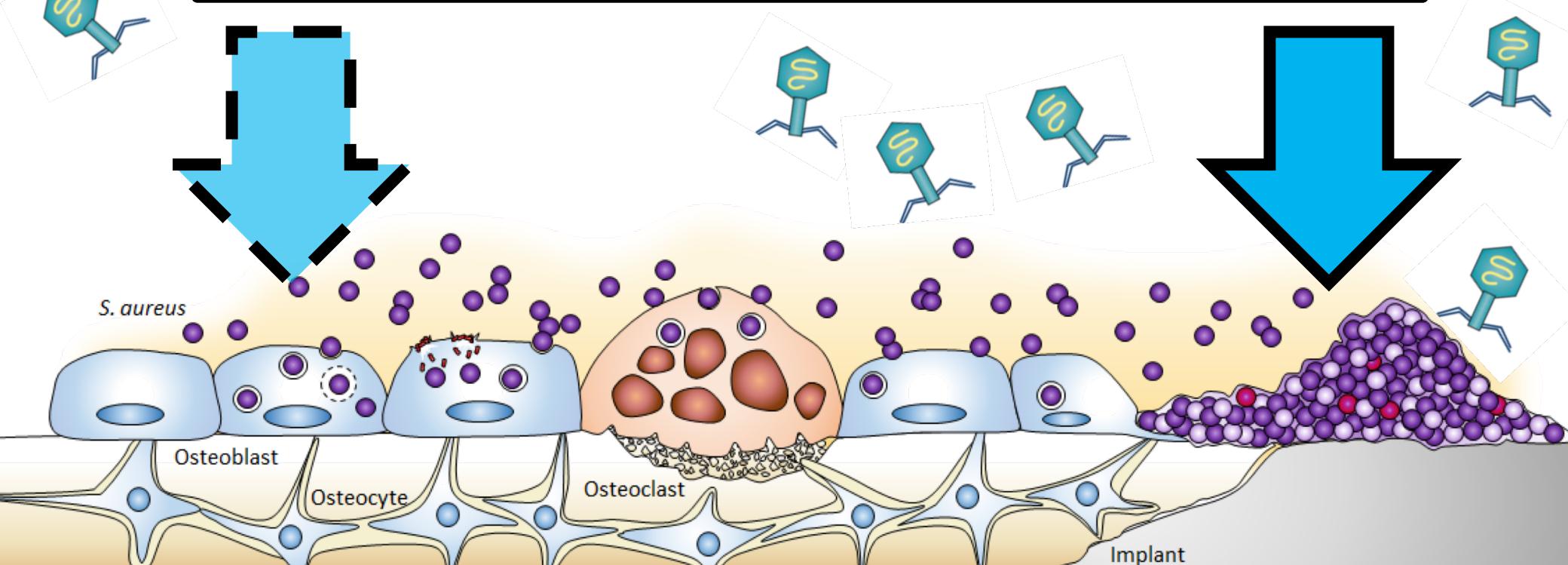
“Bacterial cells that escape the effects of antibiotics without undergoing genetic change”

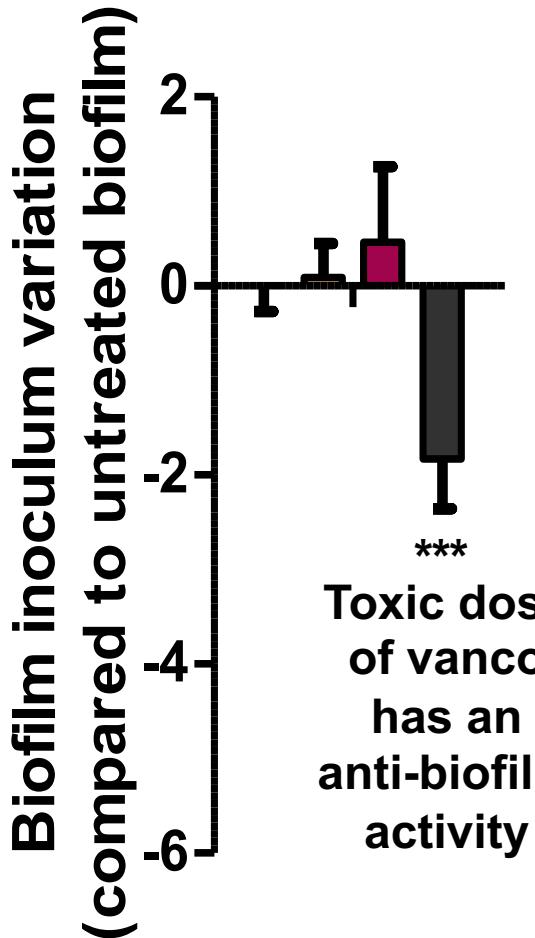


Persisters in chronic BJI

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

Bacteriophages
have anti-persister activity

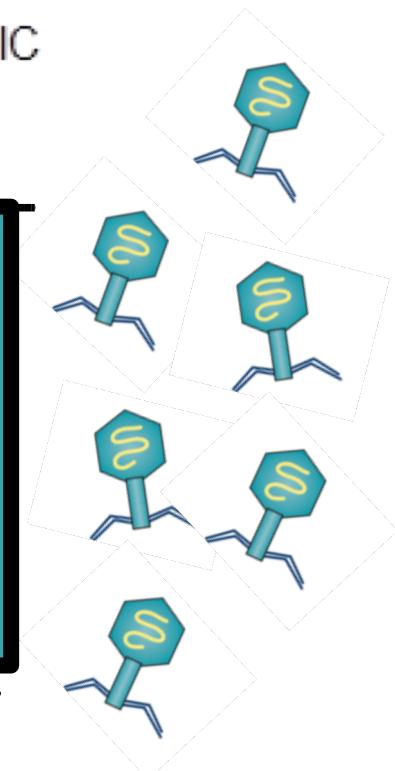
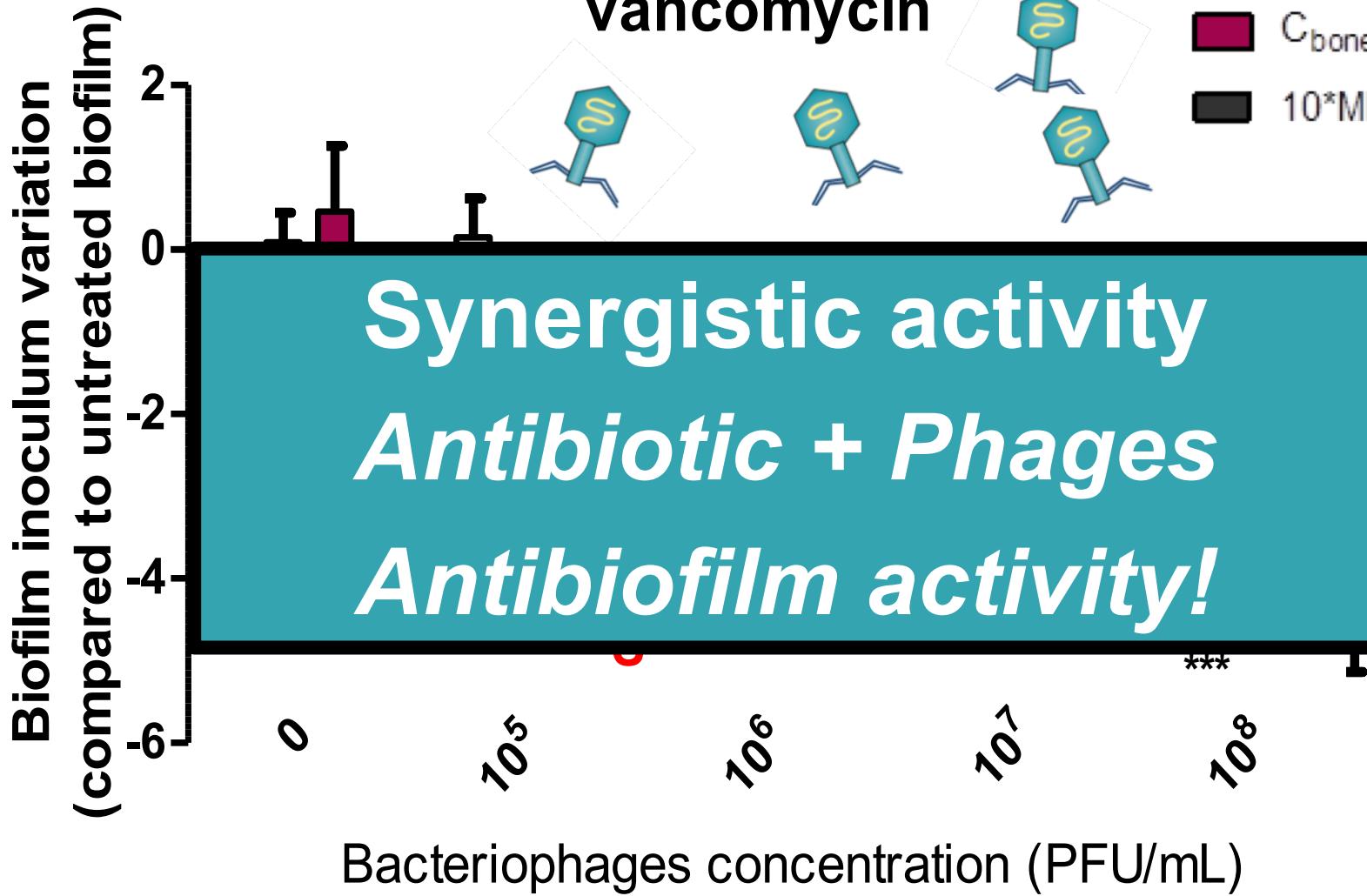




- No Antibiotic
- MIC
- $C_{bone} (4^*MIC)$
- 10^*MIC



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



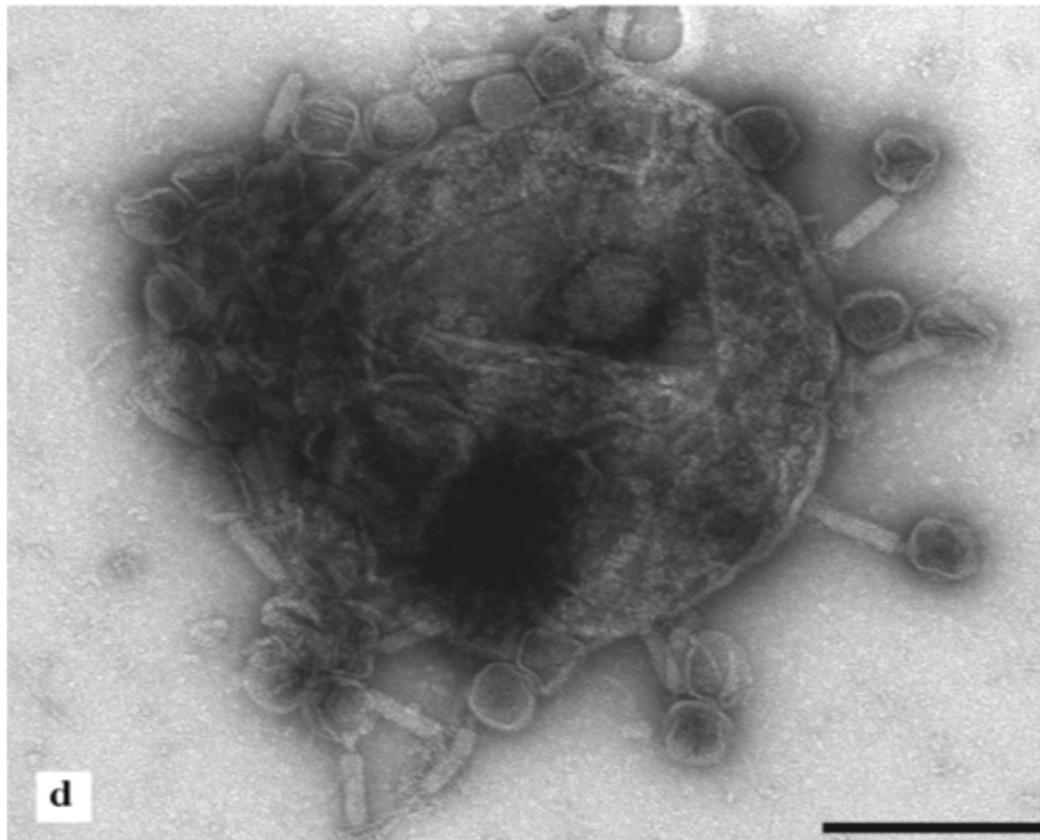
Cocktails produced in 2020 by the Eliava Institute

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



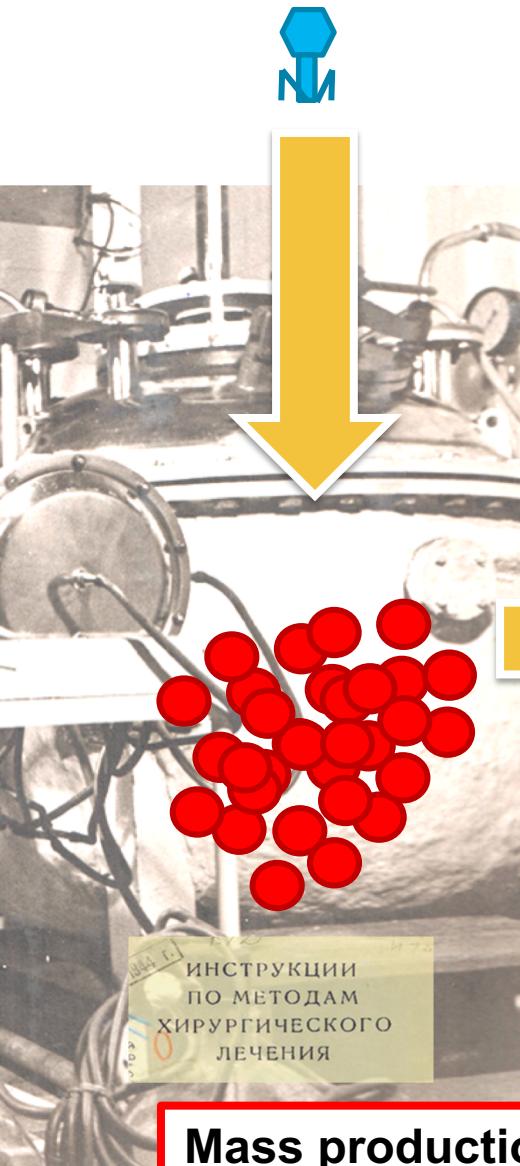
T. Ferry

Bacteriophage ISP (*Myoviridae*)

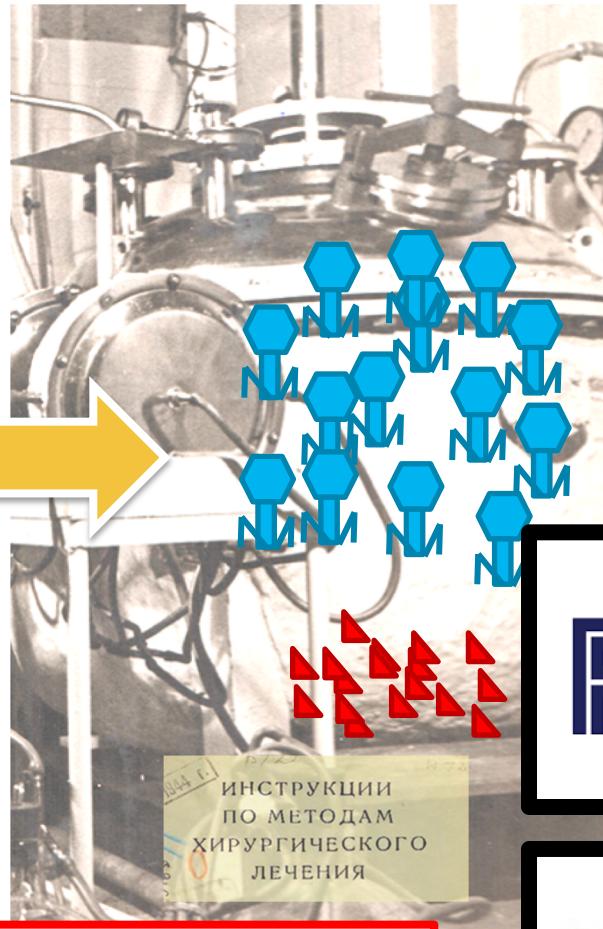


Merabishvili et al. PloS ONE 2009

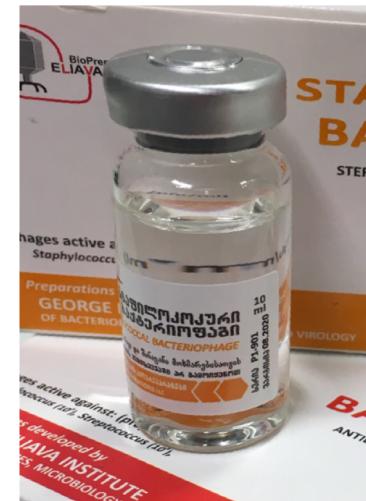
Not meeting Good Manufacturing Practices (GMP)



Mass production of bacteriophages
in Soviet Union during WWII



Pyrogenic
Bacterial
remnant?



10^6 phages/mL



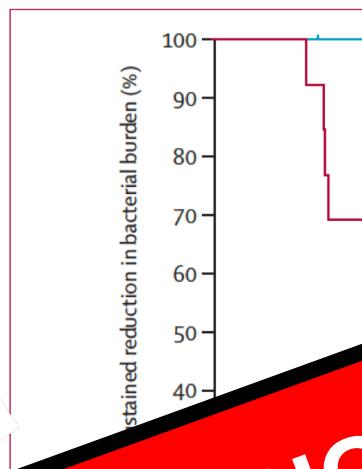
T. Ferry. *The story of Phage therapy*



GMP

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**

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



osa

RECYDES
RMA

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

• 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.**

JAMA 2013
The Journal of the American Medical Association

In France: **compassionate use, magistral preparation** by the hospital pharmacist

Clinical case #3

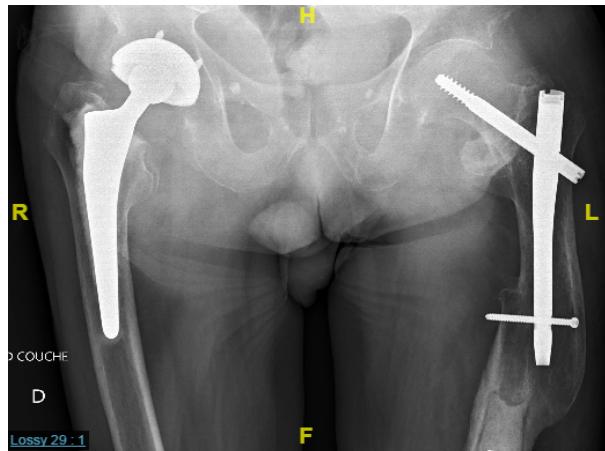
80-year-old man

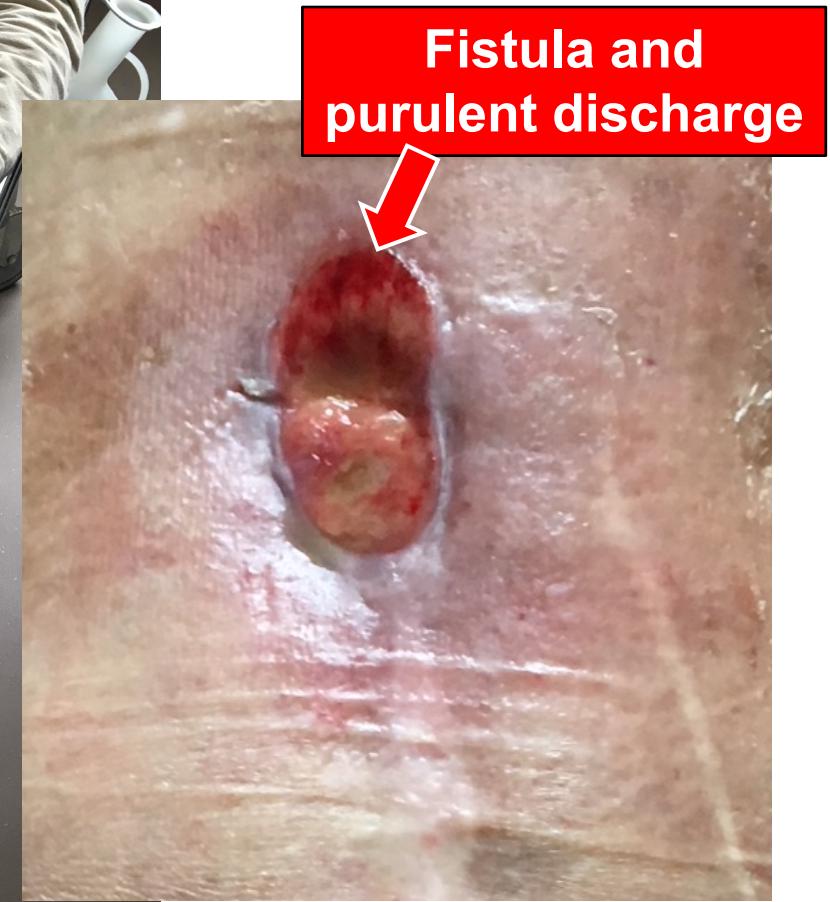
Relapsing MSSA prosthetic left knee infection (past revision)

Failure under suppressive oral antimicrobial therapy

Complex orthopaedic situation
with past femoral fracture

Impossible to walk (painful knee)





Fistula and
purulent discharge



Clinical case #3

Amputation
(but not feasible !) ?



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



Centre
International
de Recherche
en Infectiologie

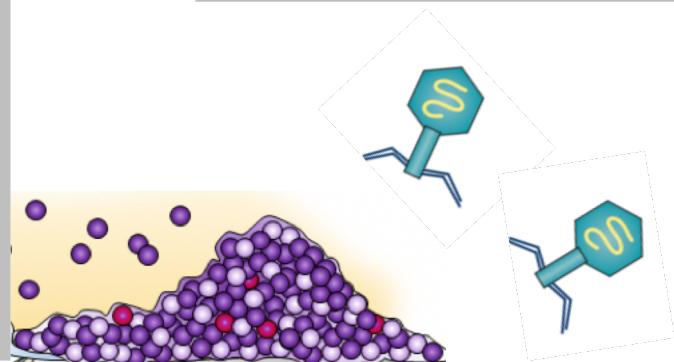
Pr. Sébastien Lustig
MD, PhD
Orthopaedic surgeon

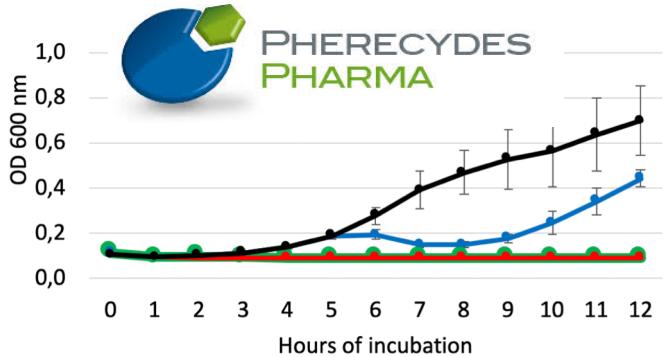
Pr. Tristan Ferry
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Microbiologist

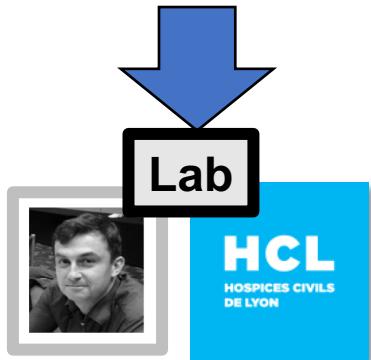


Dr. Gilles Leboucher
PharmD
Pharmacist





Phagogram Selection of active bacteriophages



Under the supervision of

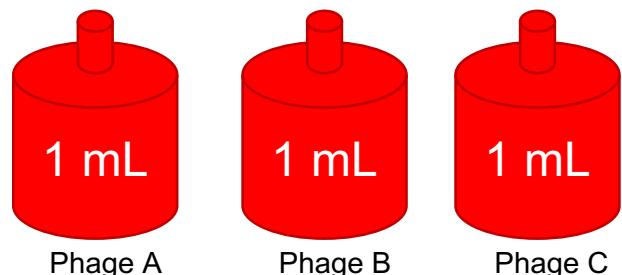


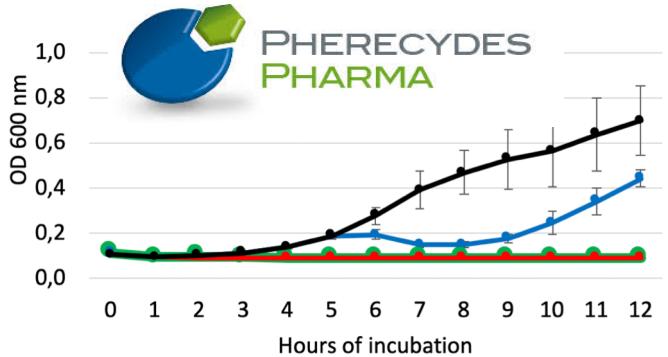
French Health Authority



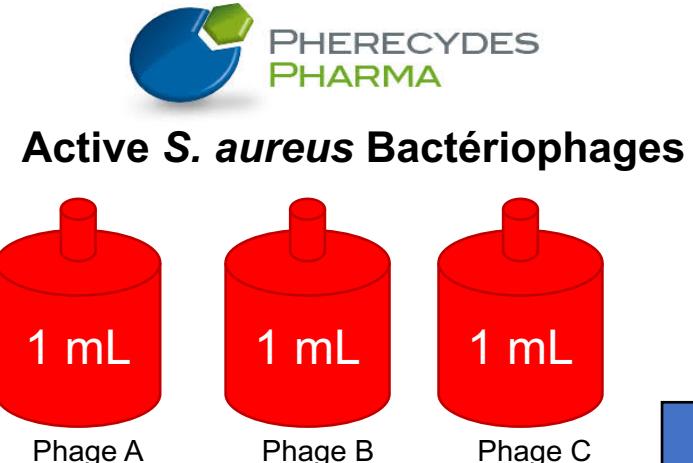
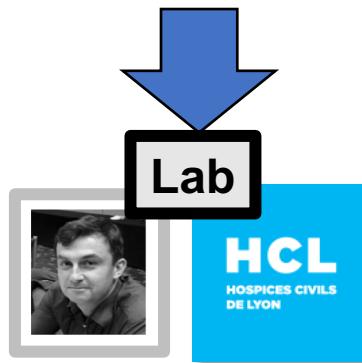
PHERECYDES PHARMA

Active *S. aureus* Bactériophages





Phagogram Selection of active bacteriophages



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







**“Debridement And Implant
Retention” (DAIR)**





“PhagoDAIR”



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



Clinical case #3

Post-operative antibiotics:

Daptomycin + Rifampin

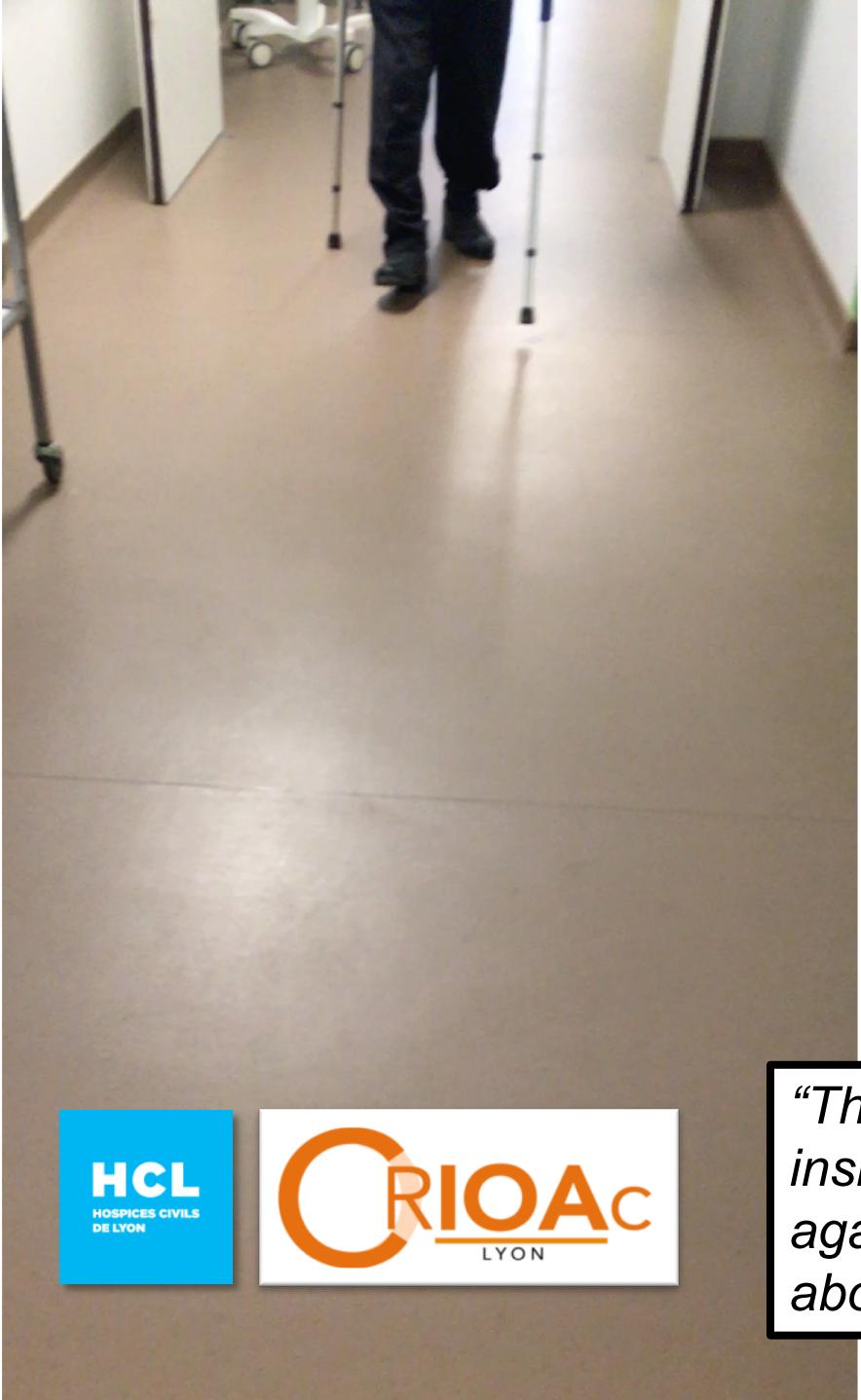
At day 4 (only MSSA in all intraoperative samples):

Levofloxacin + Rifampin

Then:

Cefalexin as suppressive antimicrobial therapy



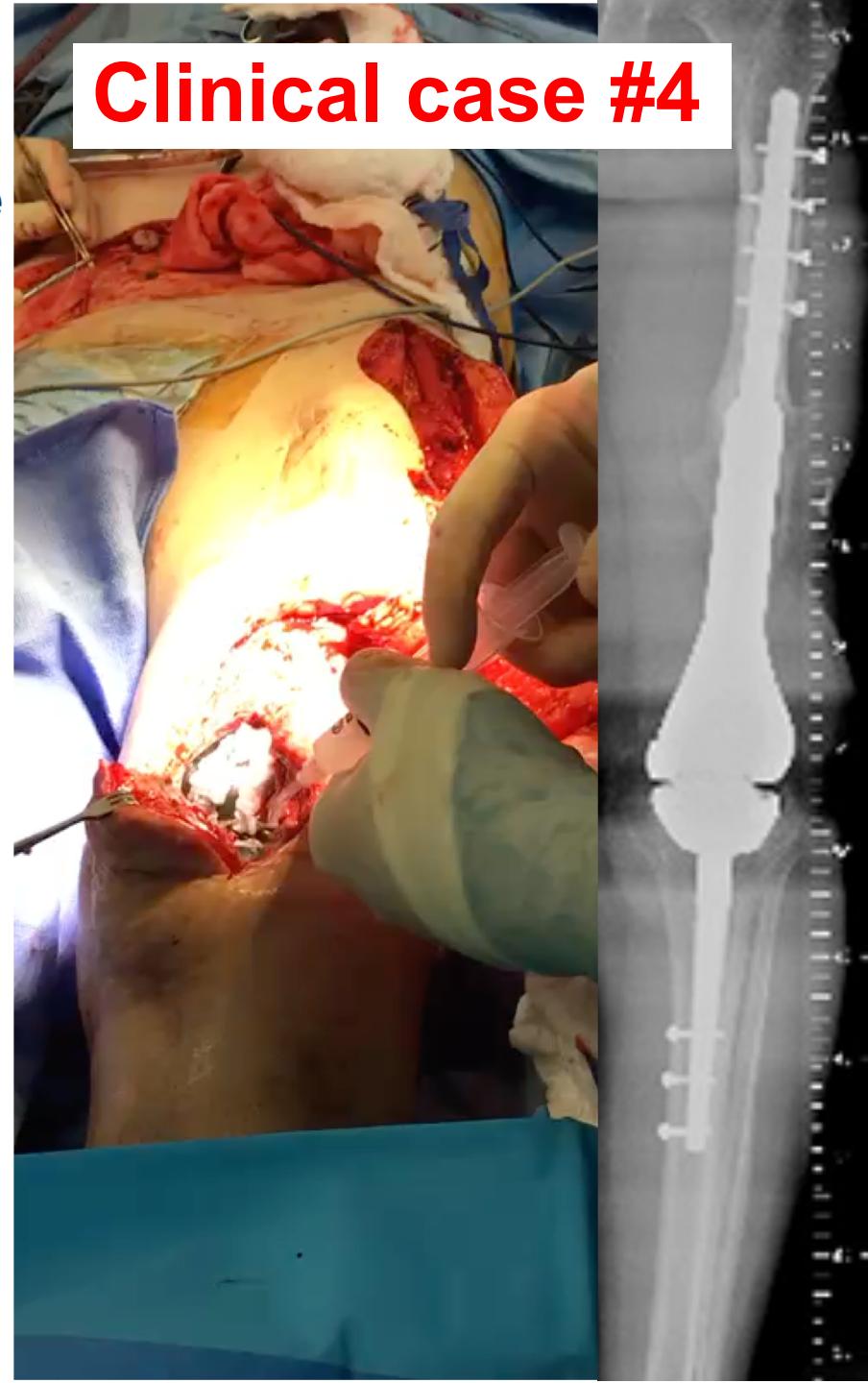
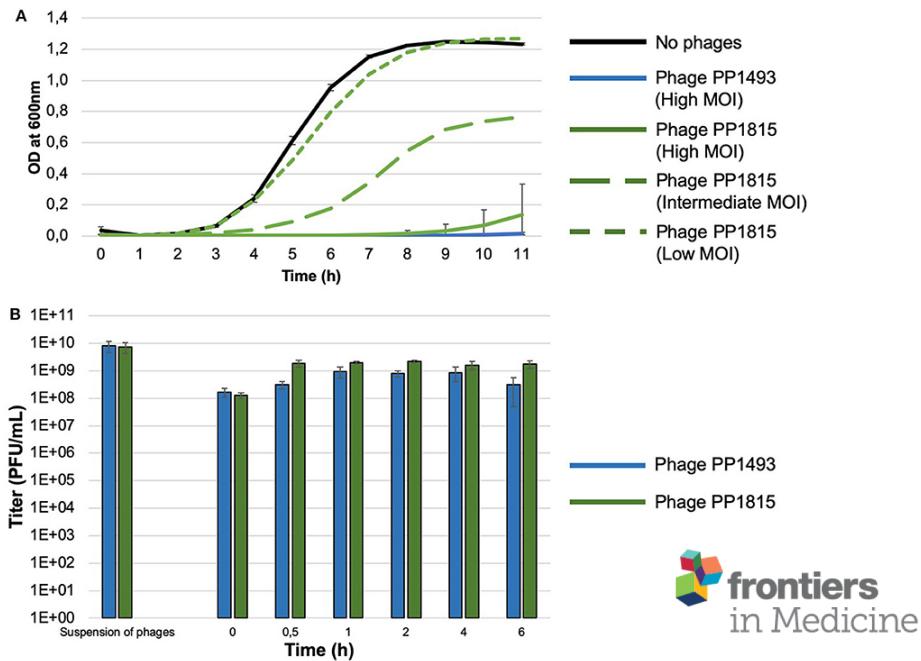


"The bacteriophages saved my life, he insists. I never thought one day to walk again. And to say that doctors were talking about cutting my leg off!"

R.N.

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



Lyon 1

C₁RCIOAc
LYON



Centre
International
de Recherche
en Infectiologie



- 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 multidisciplinar meeting**
- **ID 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 development** of therapeutic phages (discovery, banking, susceptibility testing) in connexion with health care authorities
- Need to **perform clinical trials** to evaluate if phage therapy improve the outcome



Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE



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

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, Elliott 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

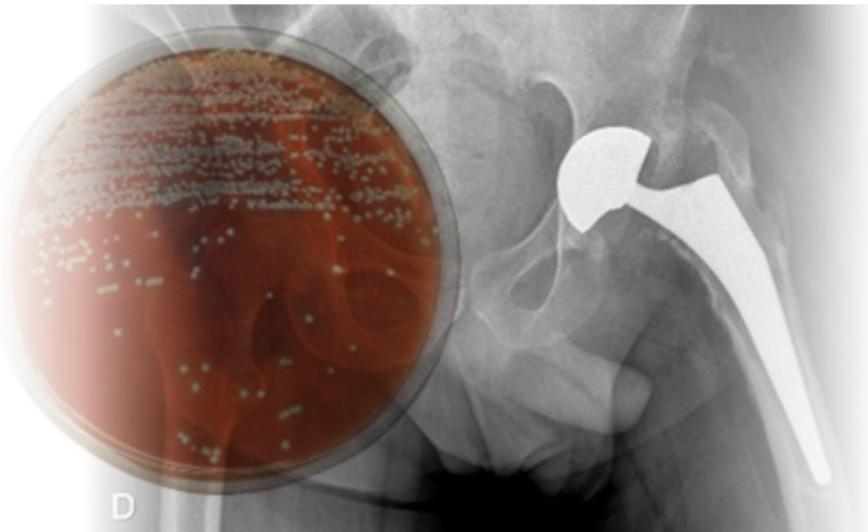
Nuclear Medicine – Isabelle Morelec, Marc Janier, Francesco Giammarile

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

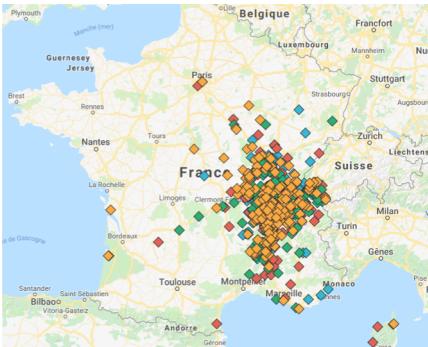
Clinical Research Assistant – Eugénie Mabrut



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



[@CrioacLyon](#)



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