Nouvelles approches dans le traitement des infections ostéoarticulaires

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

@FerryLyon

Conflict of interest

Intérêts financiers : Aucun
Liens durables ou permanents : Aucun
Interventions ponctuelles : Pfizer, Sanofi, Debiopharm, Contrafect, MaaT Pharma, Heraeus, Atlangram
Investigateur coordinateur d'essai thérapeutique : MaaT Pharma, Bonesuport
Intérêts indirects : Astellas, Pfizer, MSD

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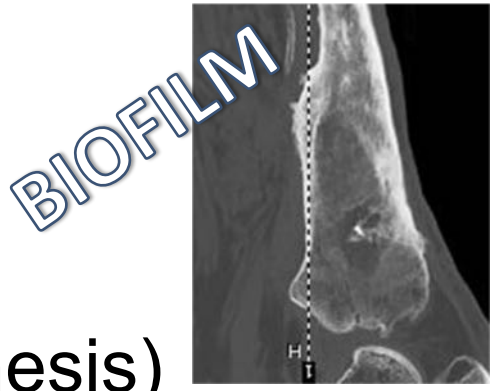
Chronic bone and joint infection

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



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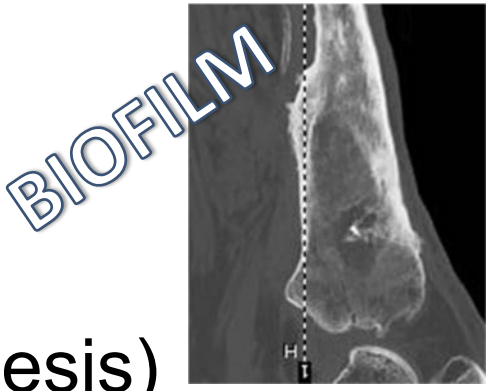


Infectious challenge
Eradication of the pathogen

Functional challenge
Limit bone loss

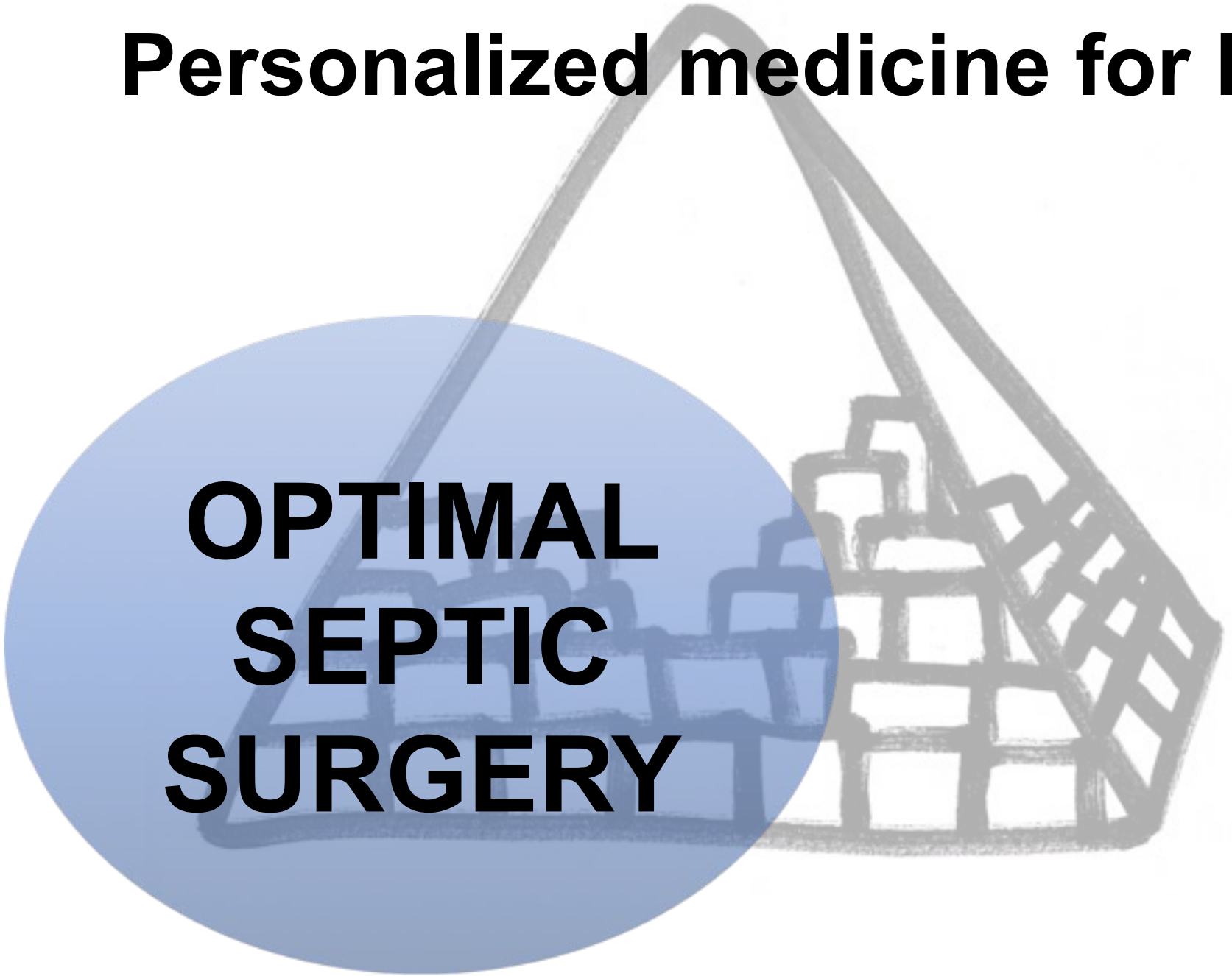
Infect. Dis.
Physician
Cure the infe

PRO
Incompatible
CON

thopaedic
Surgeon
Maintain the function

Personalized medicine for BJI

Personalized medicine for BJI



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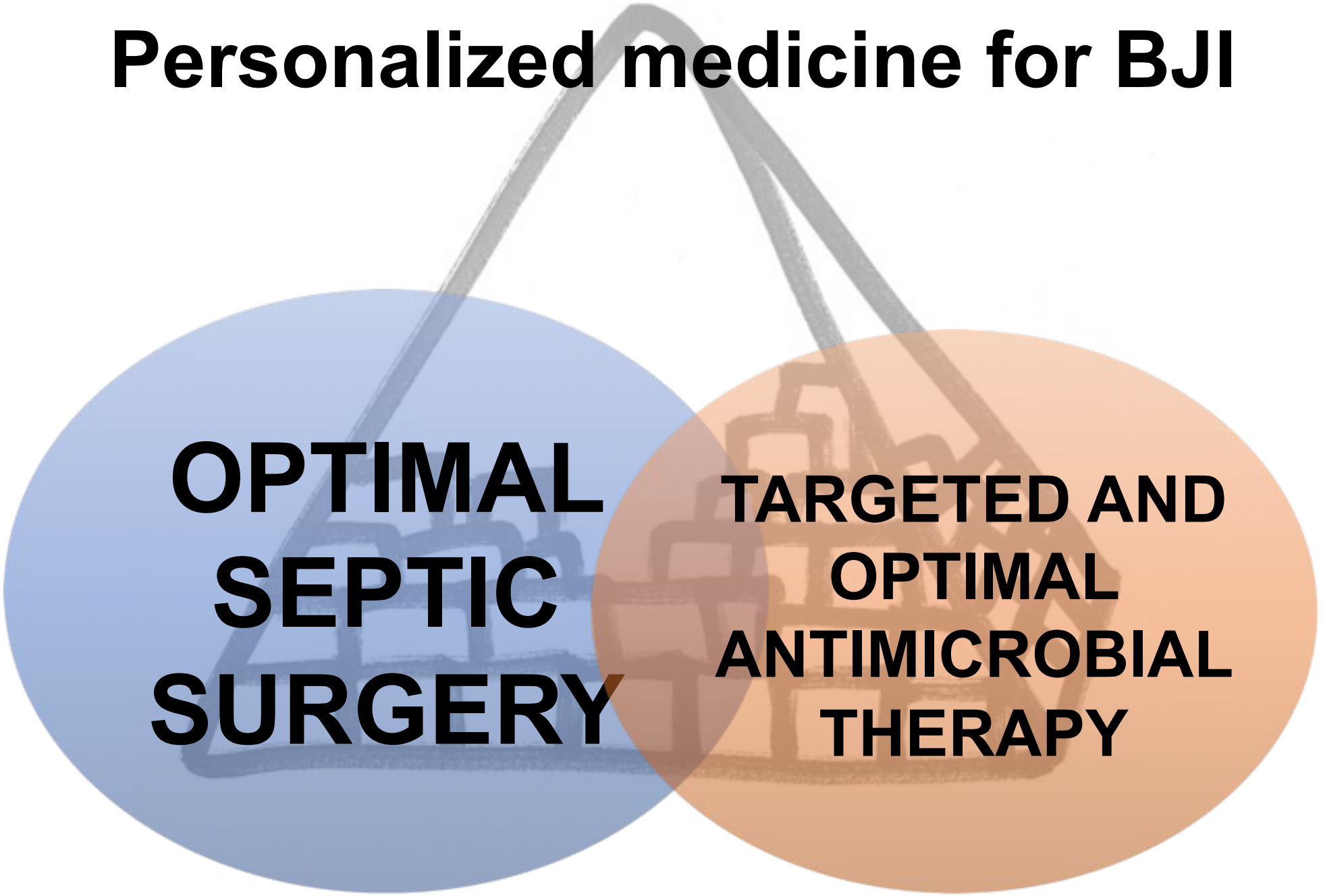

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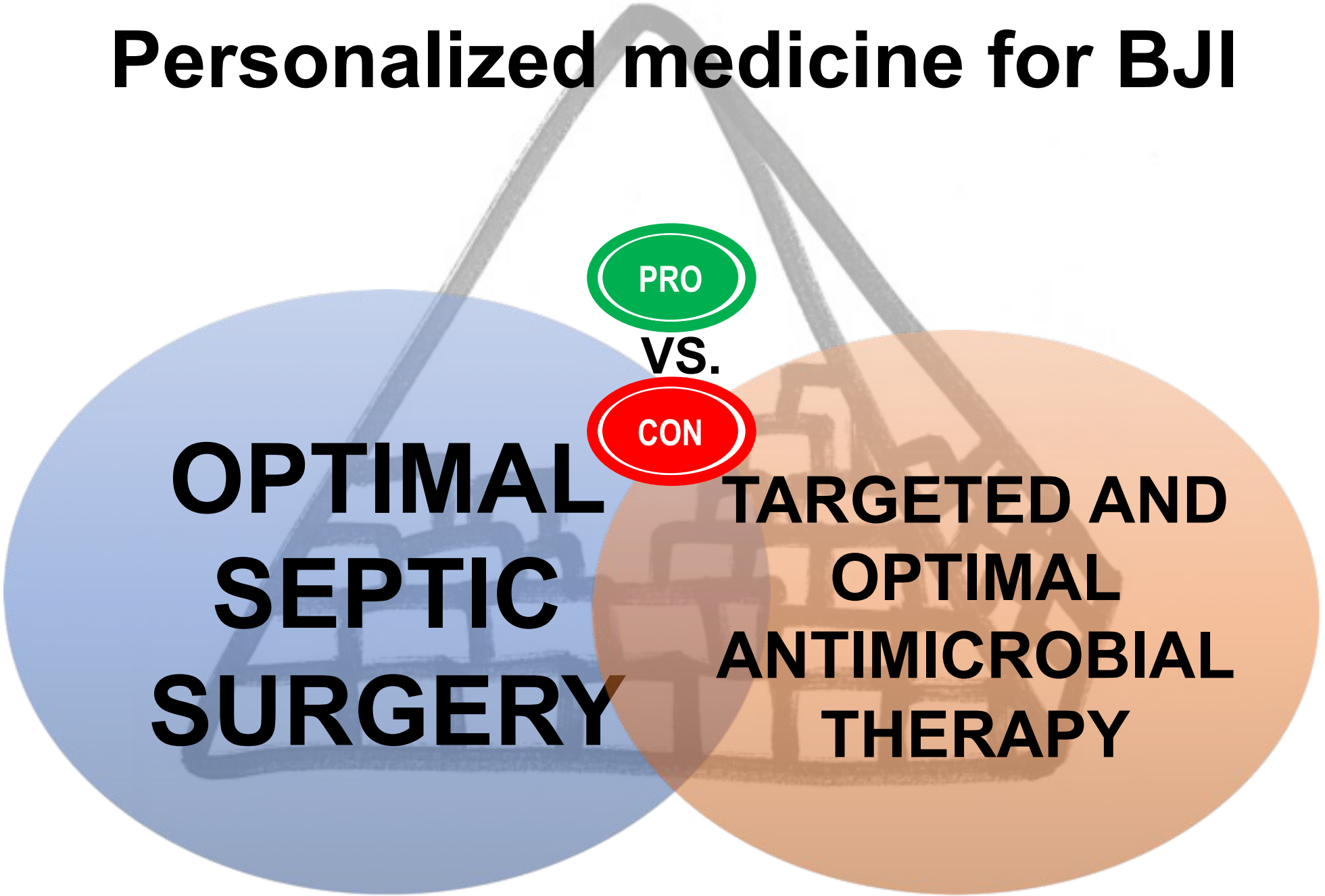

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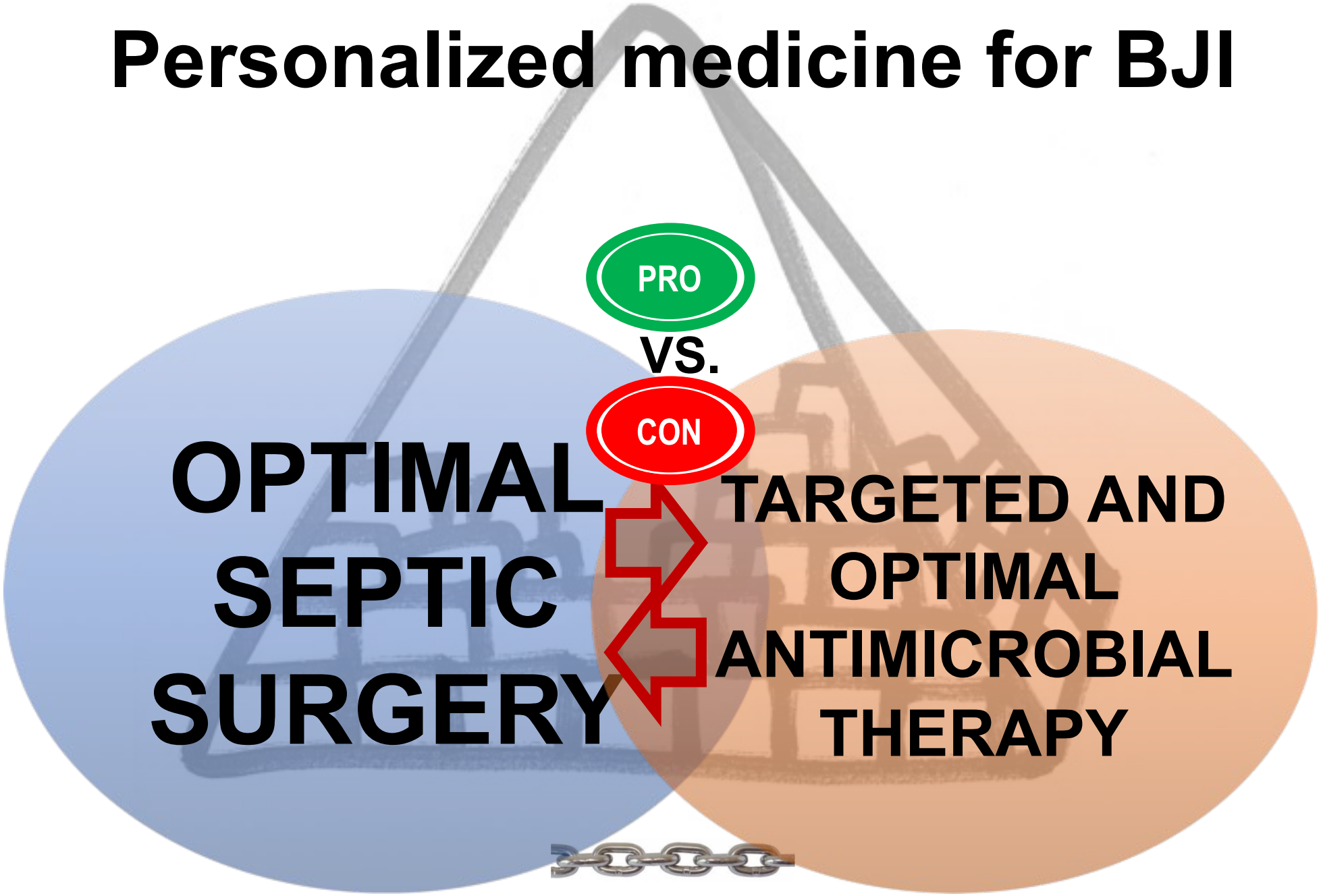

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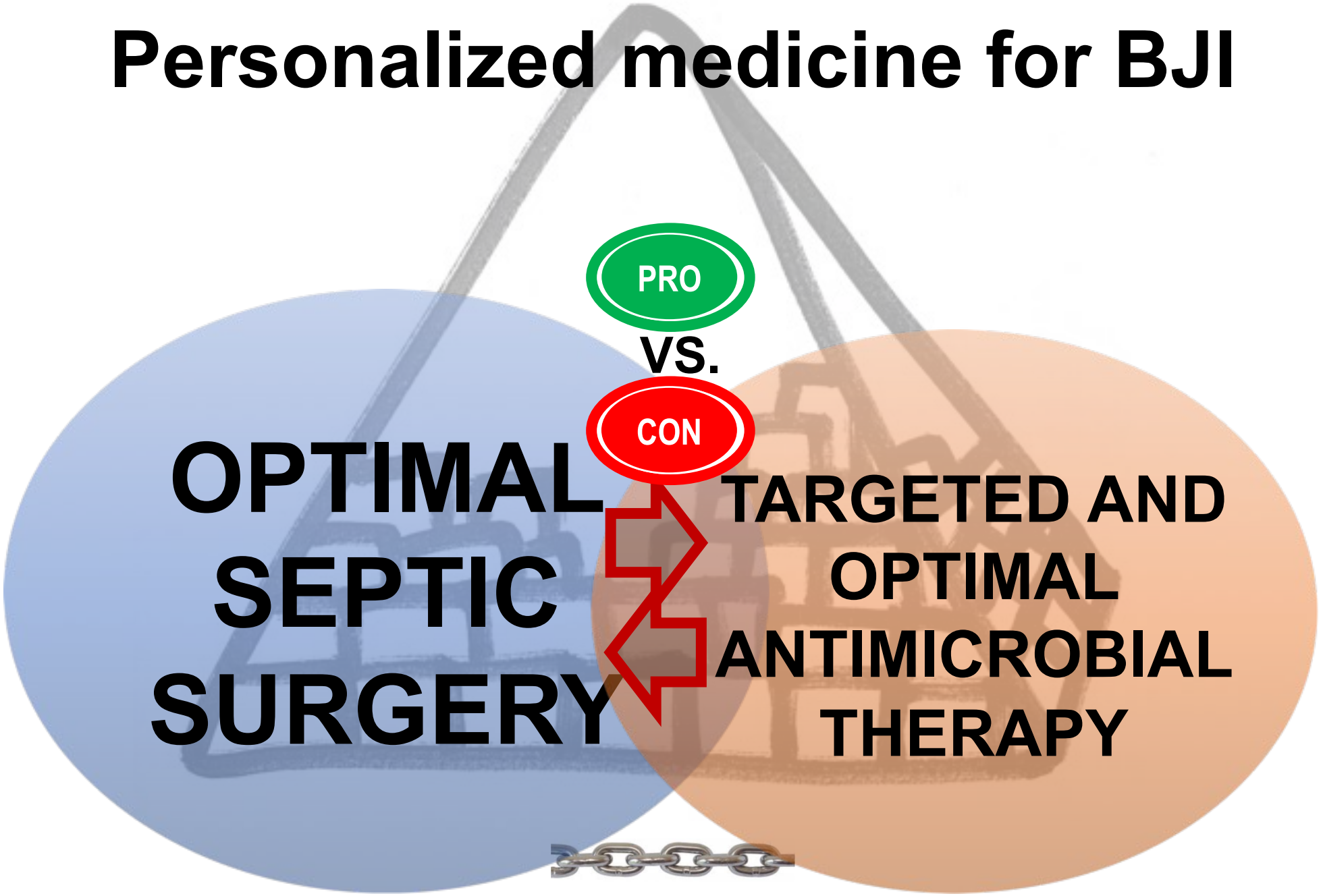
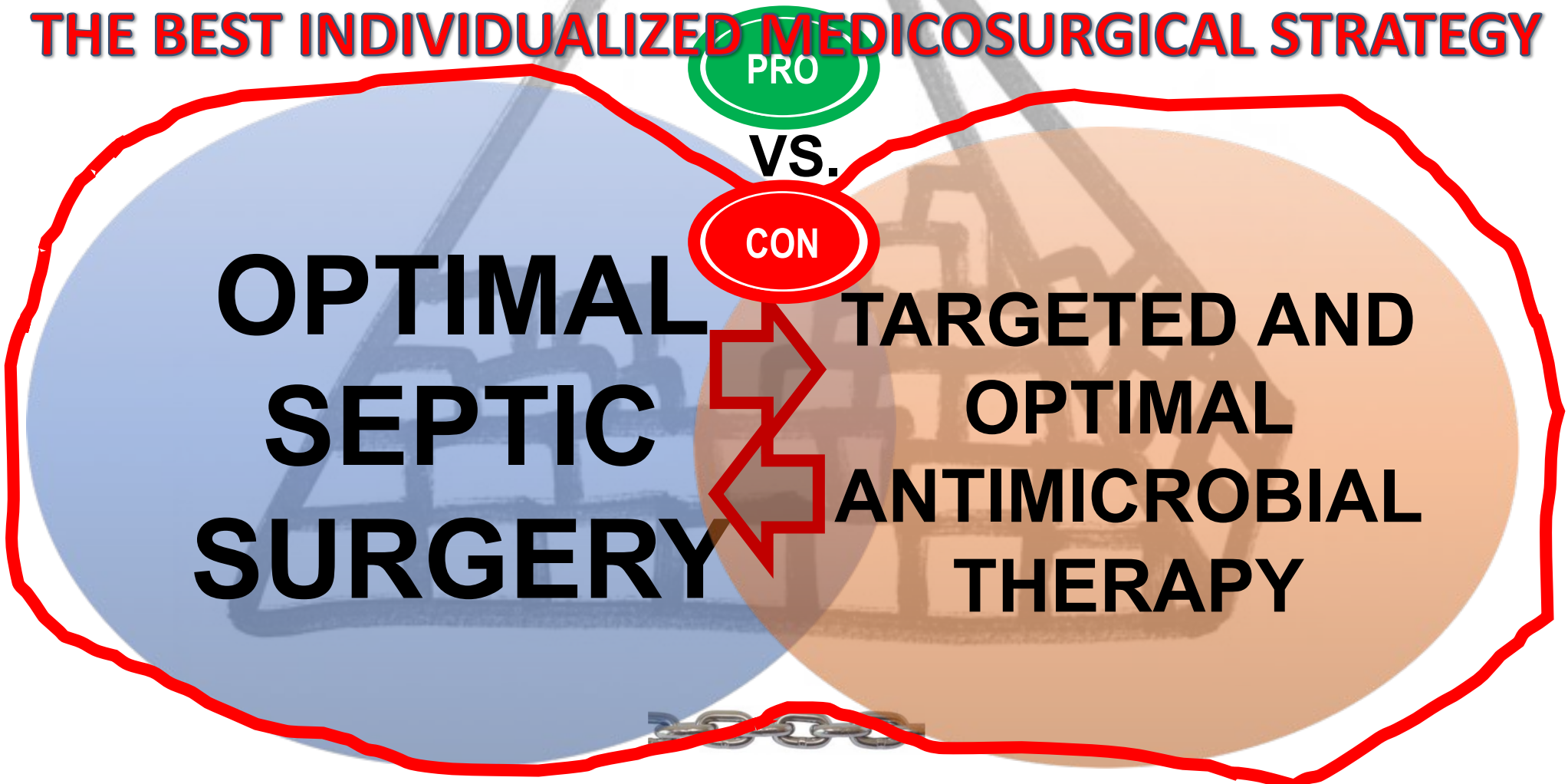


Personalized medicine for BJI

MULTIDISCILINAR MEETING

THE BEST INDIVIDUALIZED MEDICOSURGICAL STRATEGY



Centre de Référence des Infections Ostéo-Articulaires complexes

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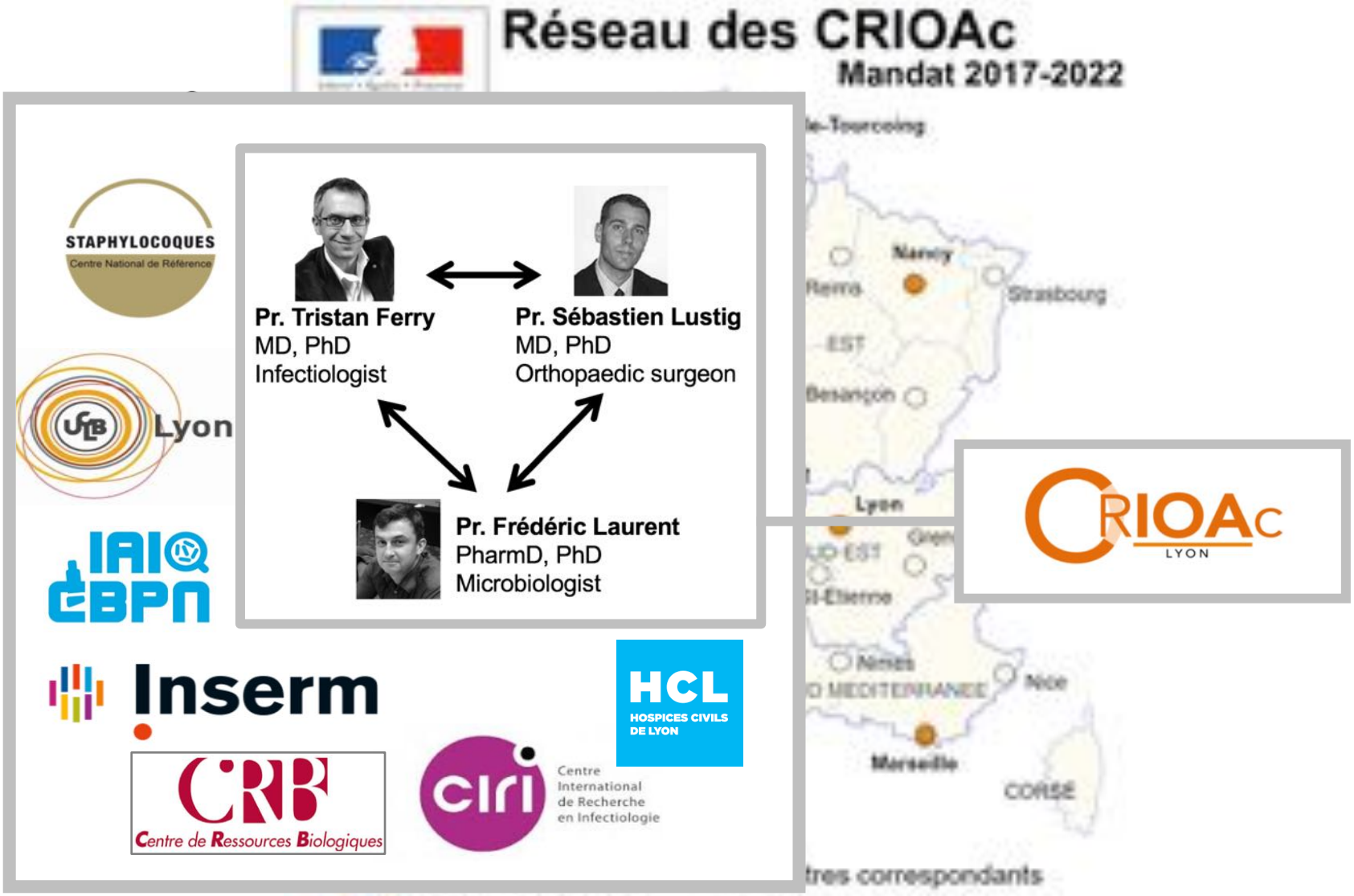


Centre de Référence des Infections Ostéo-Articulaires complexes

Réseau des CRIOAc

Mandat 2017-2022

Pr. Tristan Ferry
MD, PhD
Infectiologist

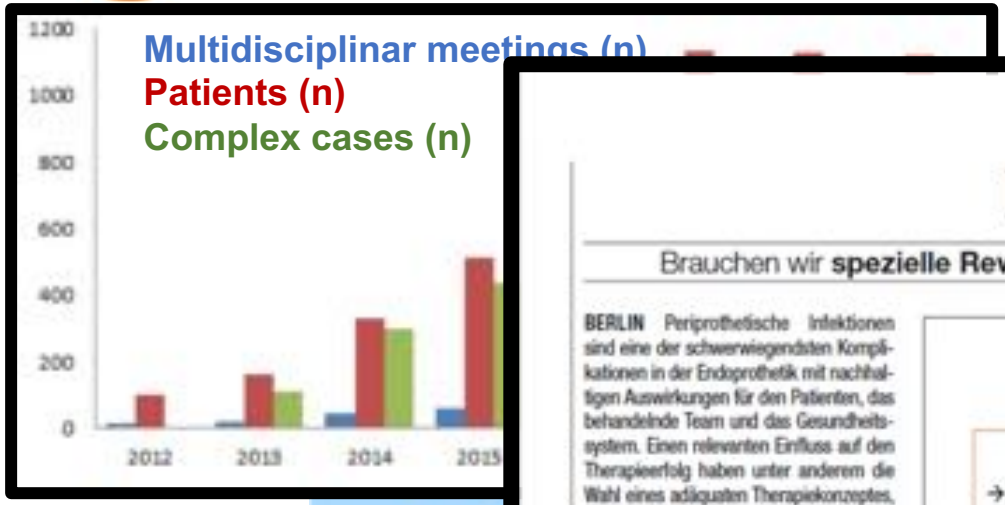
Pr. Sébastien Lustig
MD, PhD
Orthopaedic surgeon

Pr. Frédéric Laurent
PharmD, PhD
Microbiologist

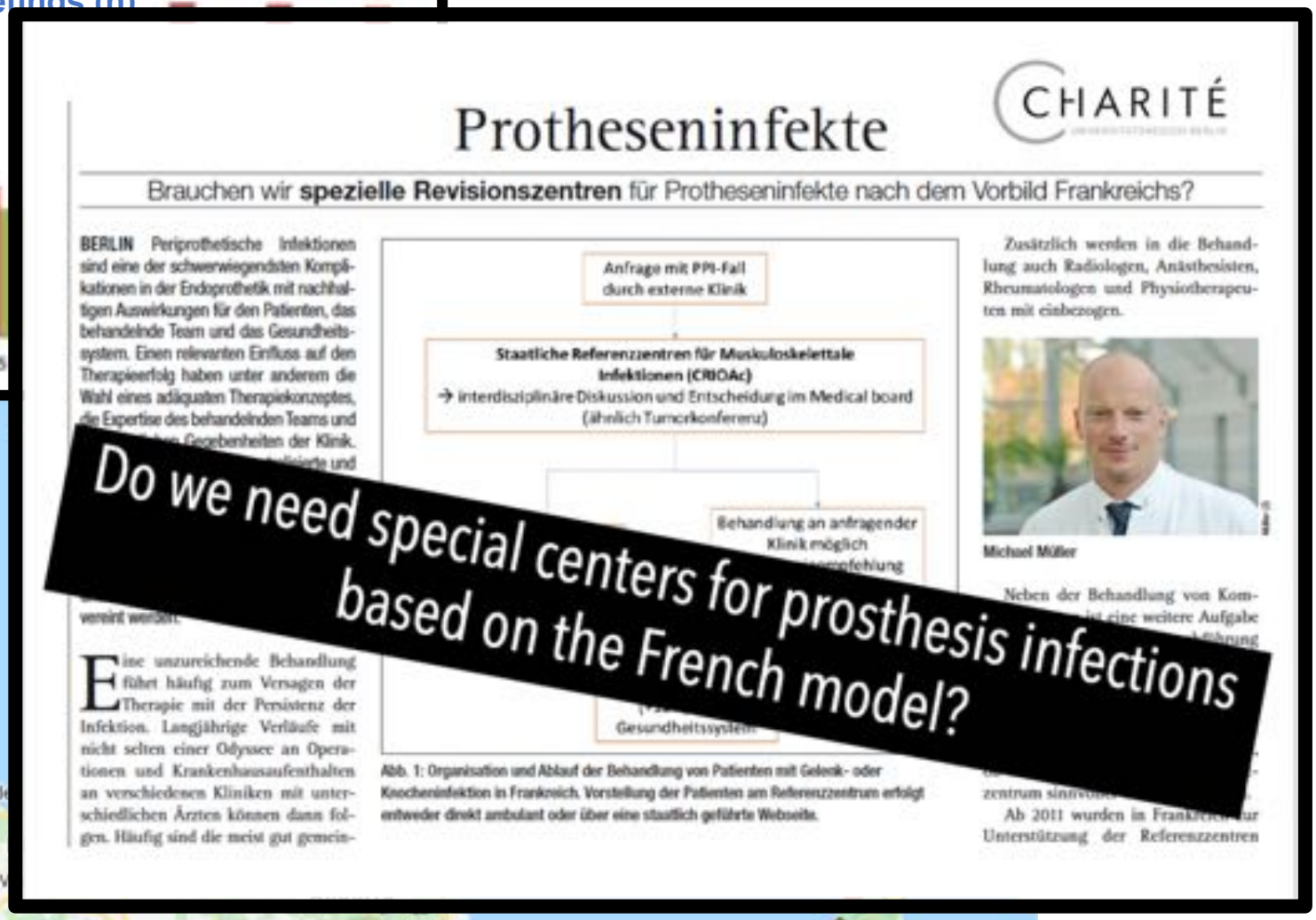
tres correspondants

Centre de Référence des Infections Ostéo-Articulaires complexes

CRIOAc LYON



2019
2018
2017
2016
2015



Prothese**n**infekte

CHARITÉ

Brauchen wir **spezielle Revisionszentren** für Prothese**n**infekte nach dem Vorbild Frankreichs?

BERLIN Periprothetische Infektionen sind eine der schwerwiegendsten Komplikationen in der Endoprothetik mit nachhaltigen Auswirkungen für den Patienten, das behandelnde Team und das Gesundheitssystem. Einen relevanten Einfluss auf den Therapieerfolg haben unter anderem die Wahl eines adäquaten Therapiekonzeptes, die Expertise des behandelnden Teams und [illegible] der Klinik. [illegible] vereint werden.

Eine unzureichende Behandlung führt häufig zum Versagen der Therapie mit der Persistenz der Infektion. Langjährige Verläufe mit nicht selten einer Odyssee an Operationen und Krankenhausaufenthalten an verschiedenen Kliniken mit unterschiedlichen Ärzten können dann folgen. Häufig sind die meist gut gemein-

Abb. 1: Organisation und Ablauf der Behandlung von Patienten mit Gelenk- oder Knocheninfektion in Frankreich. Vorstellung der Patienten am Referenzzentrum erfolgt entweder direkt ambulant oder über eine staatlich geführte Webseite.

Zusätzlich werden in die Behandlung auch Radiologen, Anästhesisten, Rheumatologen und Physiotherapeuten mit einbezogen.

Michael Müller

Neben der Behandlung von Kom- [illegible] eine weitere Aufgabe [illegible] zentrum sind [illegible]

Ab 2011 wurden in Frankreich [illegible] Unterstützung der Referenzzentren

Do we need special centers for prosthesis infections based on the French model?

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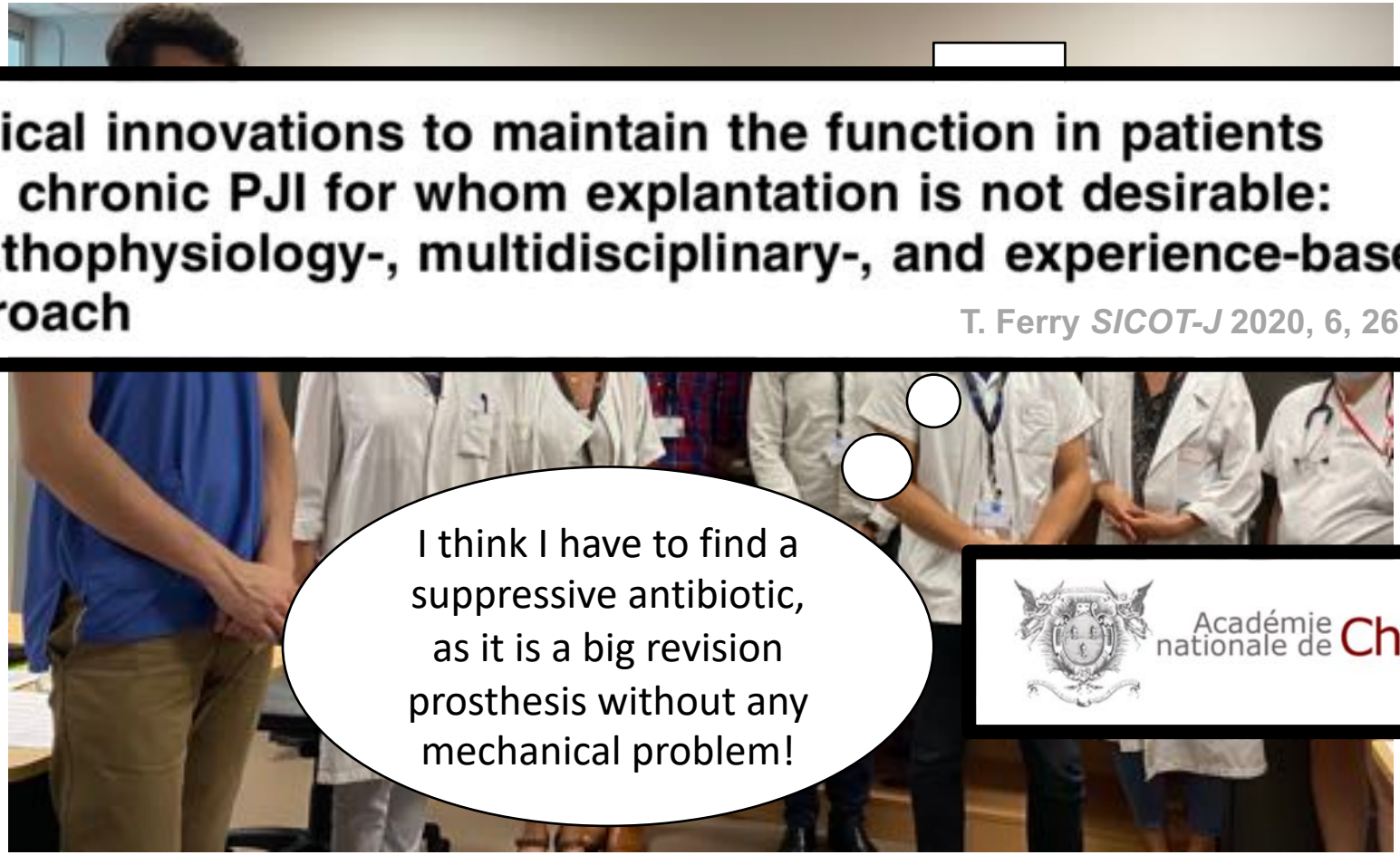
Centre de Référence des Infections Ostéo-Articulaires complexes

MULTIDISCILINAR MEETING

CRIOAc LYON

Centre de Référence des Infections Ostéo-Articulaires complexes

MULTIDISCILINAR MEETING



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

I think I have to find a suppressive antibiotic, as it is a big revision prosthesis without any mechanical problem!

Académie nationale de Chirurgie

Suppressive antimicrobial therapy

Consensus document

Management of prosthetic joint infections. Clinical practice guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)

2017

Some patients may be considered **unsuitable for implant removal**, either because they present with **too many baseline conditions**, or because a **poor functional outcome is foreseen**. In these patients, prolonged or **indefinite antimicrobial therapy aiming to control the infection may be considered**. This strategy is known as **SAT (suppressive antimicrobial therapy).**

Suppressive antimicrobial therapy

Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America[a]

2013

IDSA
Infectious Diseases Society of America

Douglas R. Osmon,[1] Elie F. Berbari,[1] Anthony R. Berendt,[2] Daniel Lew,[3] Werner Zimmerli,[4] James M. Steckelberg,[1] Nalini Rao,[5,6] Arlen Hanssen,[7] and Walter R. Wilson[1]

Table 3. Common Antimicrobials Used for Chronic Oral Antimicrobial Suppression (B-III Unless Otherwise Stated in Text)[a,b]

Microorganism	Preferred Treatment	Alternative Treatment
Staphylococci, oxacillin-susceptible	Cephalexin 500 mg PO tid or qid or Cefadroxil 500 mg PO bid	Dicloxacillin 500 mg PO tid or qid Clindamycin 300
Staphylococci, oxacillin-resistant	Cotrimoxazole 1 DS tab PO bid Minocycline or doxycycline	
β-hemolytic streptococci		Cephalexin 500 mg PO tid or qid
	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	
Pseudomonas aeruginosa	Ciprofloxacin 250–500 mg PO bid	
Enterobacteriaceae	Cotrimoxazole 1 DS tab PO bid	β-lactam oral therapy based on in vitro susceptibilities
Propionibacterium spp	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	Cephalexin 500 mg PO tid or qid Minocycline or doxycycline 100 mg PO bid

Beta-lactam, clindamycin, cotrimoxazole, tetracycline

Clinical Infectious Diseases 2013;56(1):e1–25

Clinical case #1

71-year-old man
Vitiligo, myocardial disaese

Chronic relapsing PJI
(resection prosthesis)

Puncture: *S. epidermidis*
only susceptible to vancomycine, daptomycine, linézolide

X-ray: asymptomatic partial tibial loosening

Clinical status: fistula, walk without help and without pain

Ferry T. *et al.*
Open Forum Infectious Diseases 2018

Clinical case #1

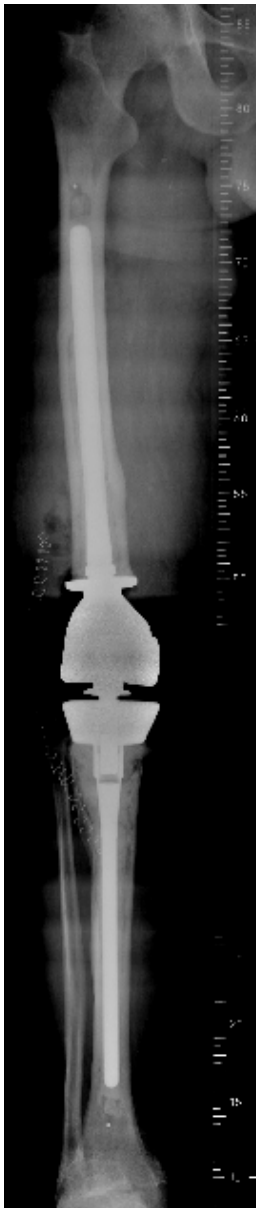
PRO

VS.

CON

‘DAIR’
Debridement
Antibiotics and
Implant Retention
+
Primary ATBx
then
SAT

Linezolid then **Tedizolid** 1 pill/day	Long acting Antibiotic **Dalbavancin** 1 injection/month



Ferry T. *et al.*
Open Forum Infectious Diseases 2018

Open Forum Infectious Diseases
ID CASE

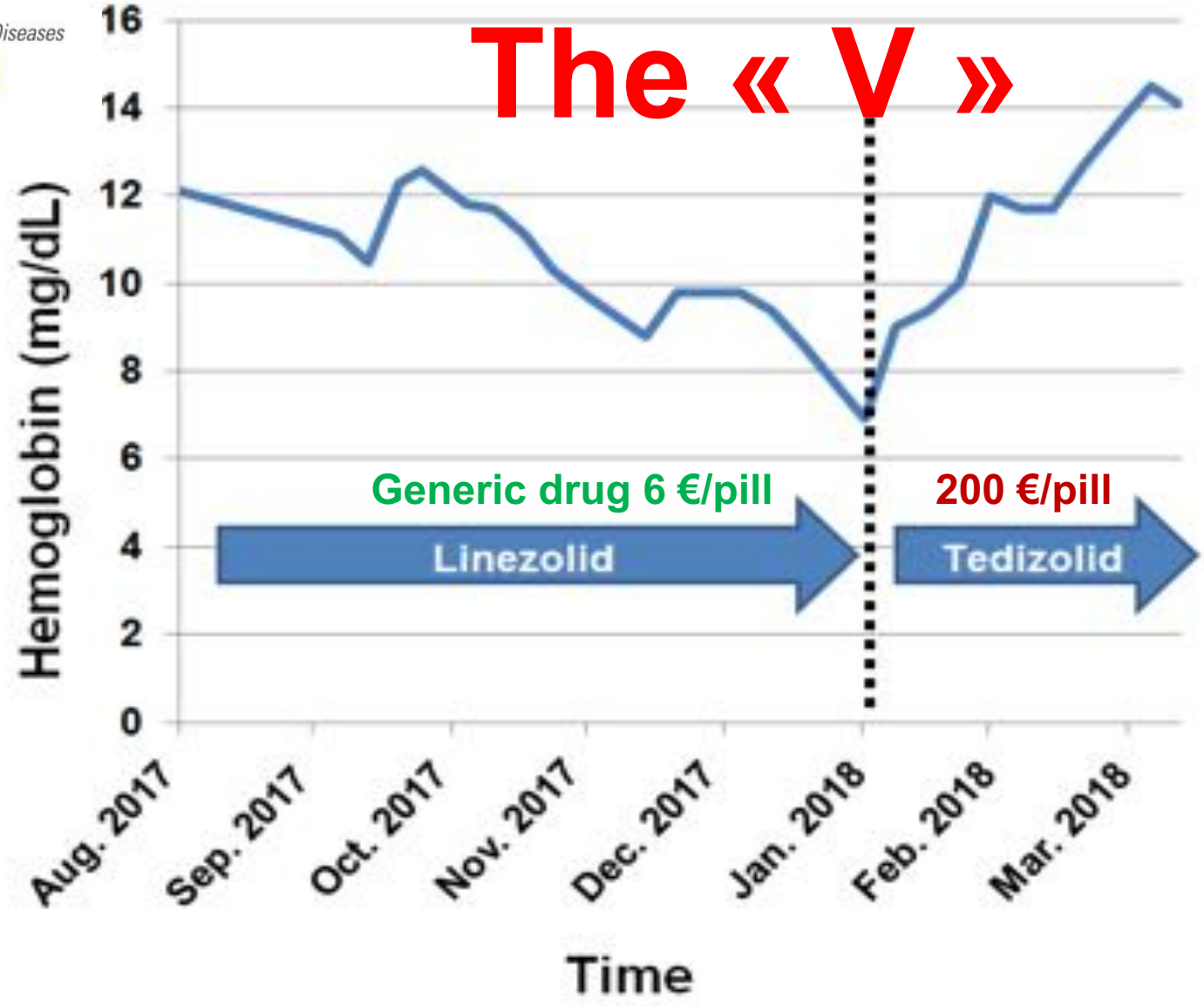


Figure 1. Hemoglobin during time, with continuous decrease under linezolid therapy, followed by a continuous increase after the switch to tedizolid.

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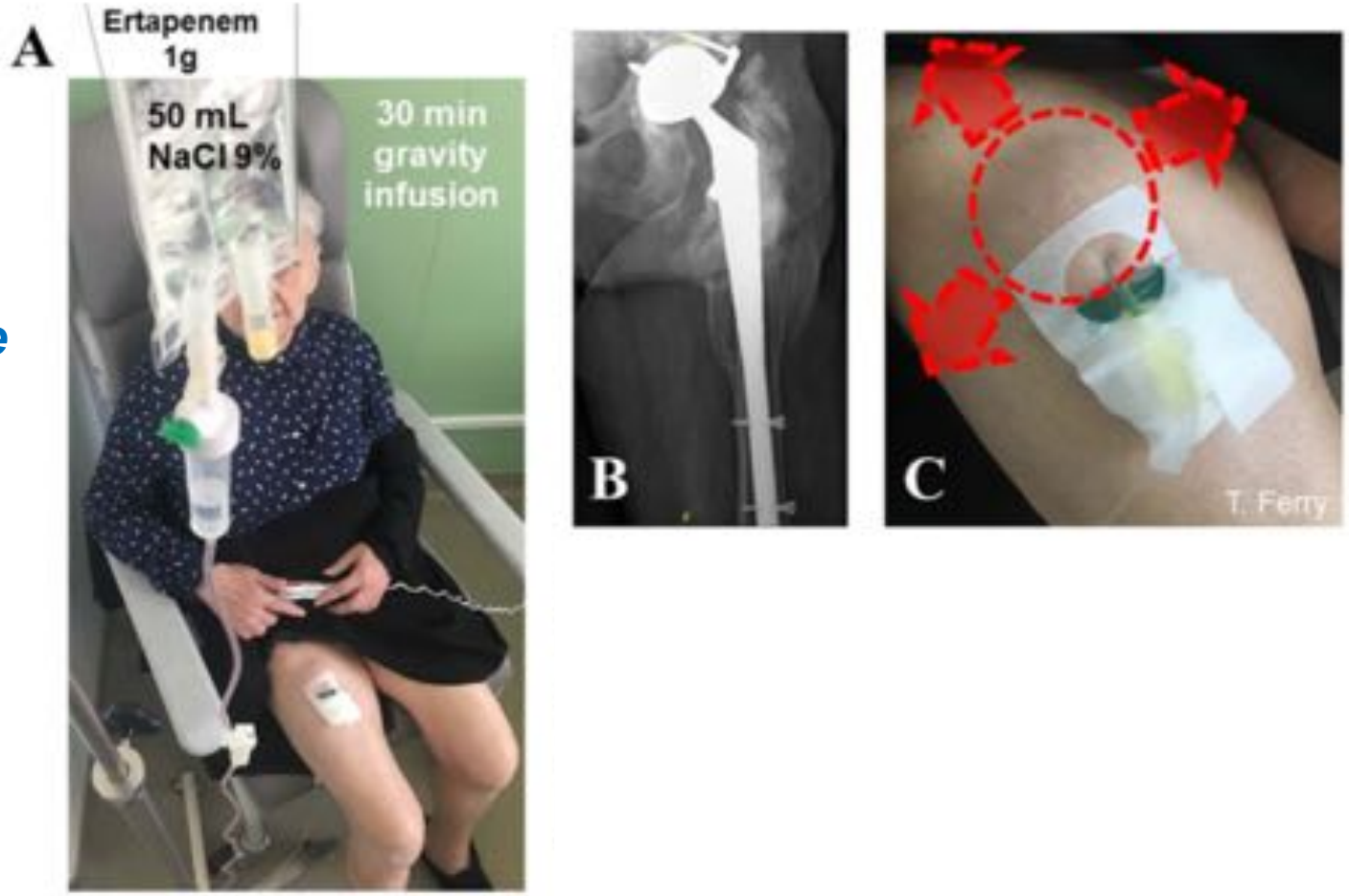
Subcutaneous suppressive antibiotic therapy for bone and joint infections: safety and outcome in a cohort of 10 patients

Cécile Pouderoux[1–3]*, Agathe Becker[1–3], Sylvain Goutelle[2–4], Sébastien Lustig[2,3,5], Claire Triffault-Fillit[1–3], Fatiha Daoud[1,3], Michel Henry Fessy[2,3,6], Sabine Cohen[2,7], Frédéric Laurent[2,3,8,9], Christian Chidiac[1–3], Florent Valour[1–3,9] and Tristan Ferry[1,3,9] on behalf of the Lyon Bone and Joint Infection

Journal of Antimicrobial Chemotherapy

Clinical case #2

78 y.o.
Relapsing PJI
MDR *E. Cloacae*
Iterative DAIR
Bacterial persistence
Long stem
No loosening



Ertepenem
SC
administration

T. Ferry JAC 2019 & SICOT-J 2020

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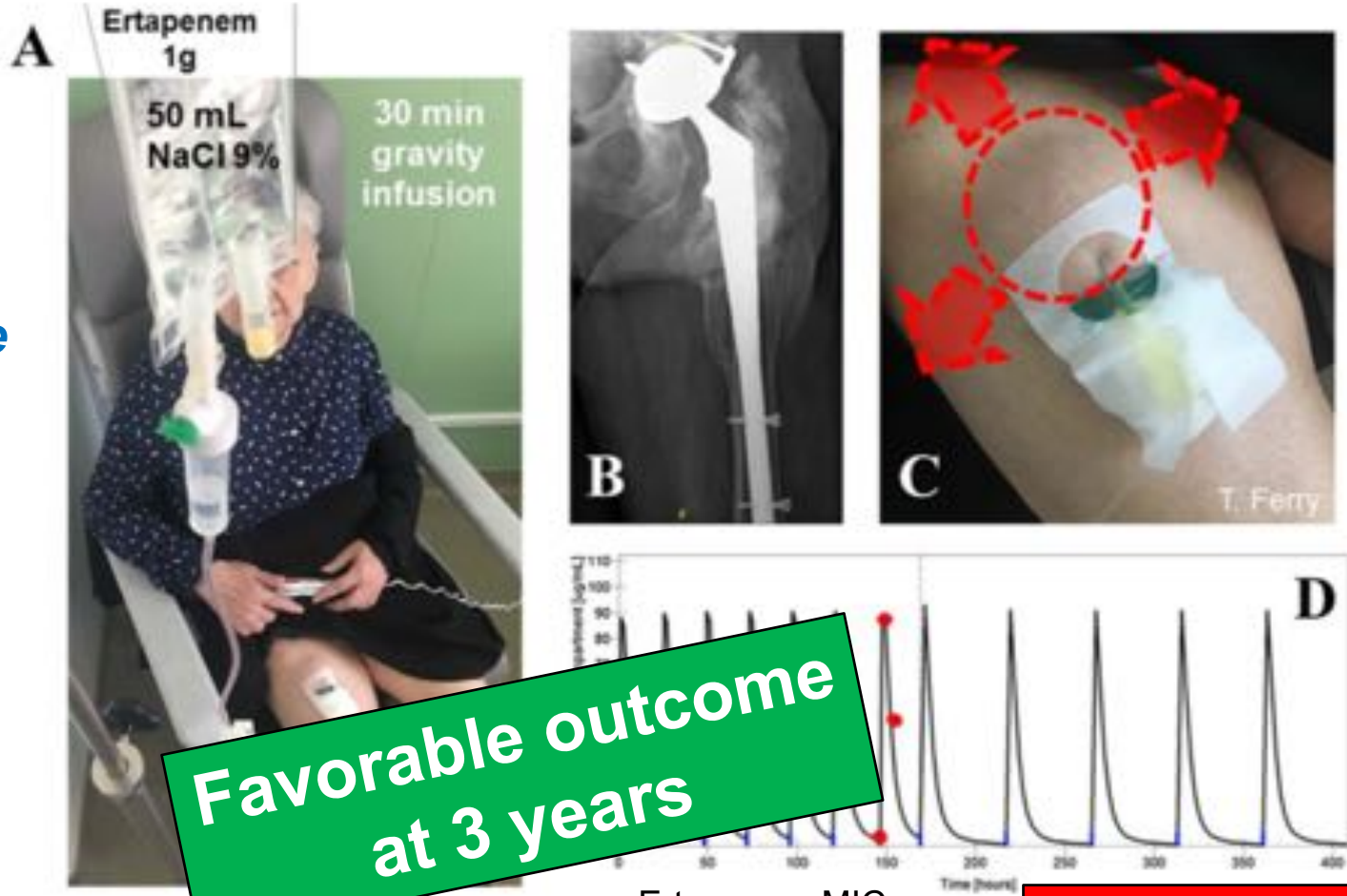


Ertepenem

SC

administration

T. Ferry JAC 2019 & SICOT-J 2020

PK-based suppressive therapy SC injection each 48h

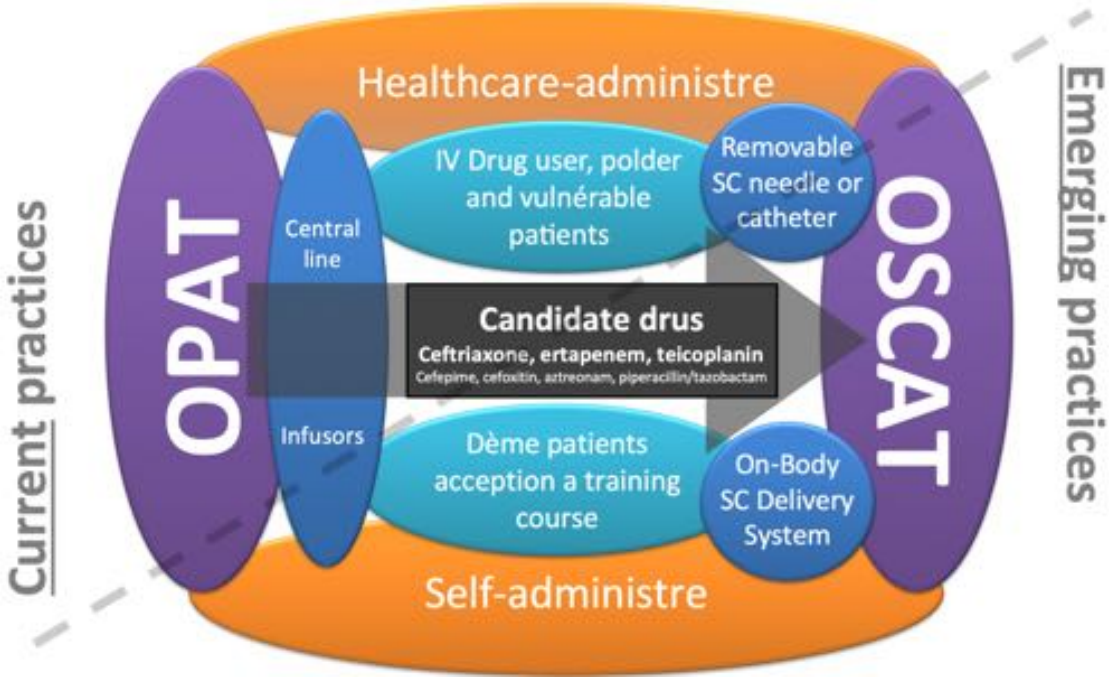
frontiers

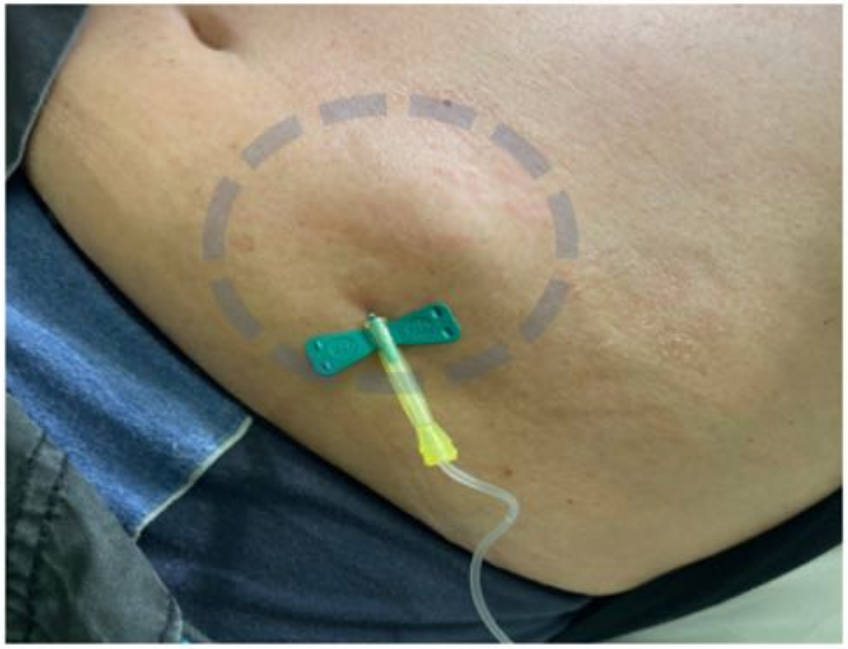
#OSCAT

In Press

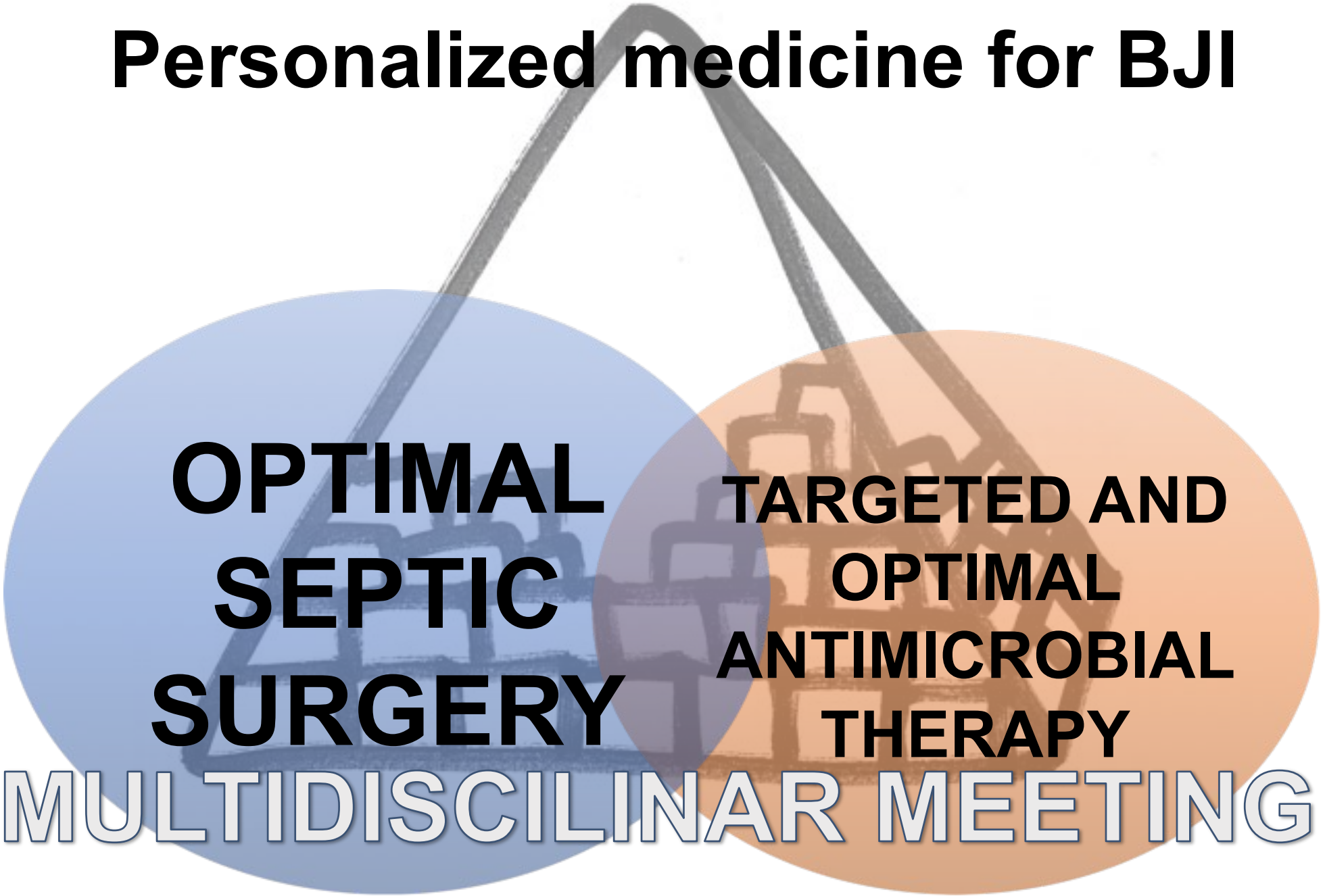
Outpatient SubCutaneous Antimicrobial Therapy (OSCAT) as a Measure to Improve the Quality and Efficiency of Healthcare Delivery for Patients with Serious Bacterial Infections

Tristan Ferry,[1,2,3,4] Thomas P. Lodise,[5] Jason Gallagher,[6] Emmanuel Forestier,[7] Sylvain Goutelle,[8,9] Vincent H. Tam,[10] John F. Mohr, III,[11] Claire Roubaud-Baudron[12,13]





Personalized medicine for BJI



Personalized medicine for BJI

AntibioticS-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

MULTIDISCILINAR 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

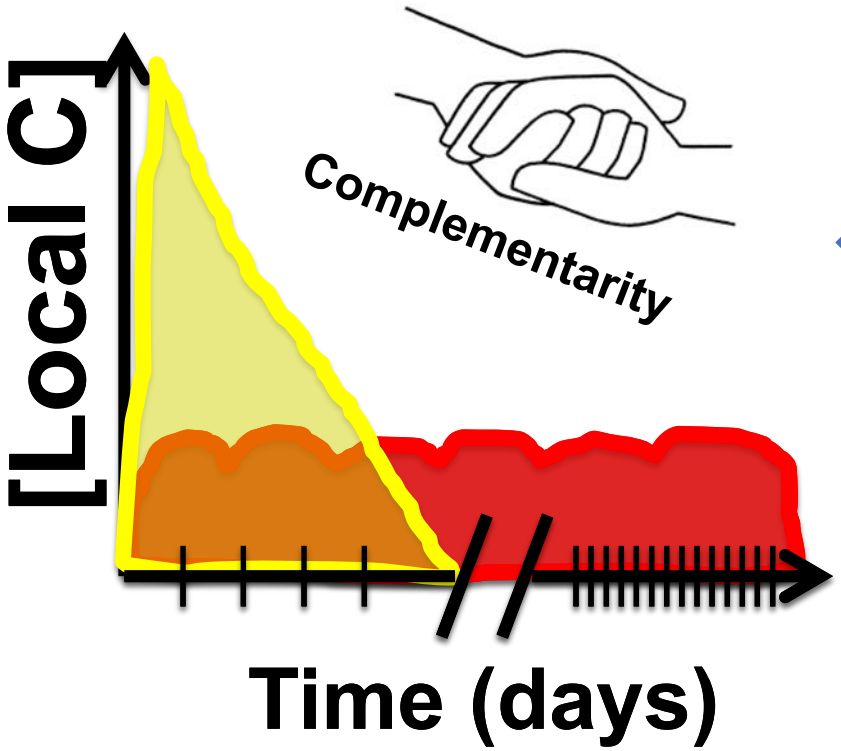
Failure

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 #2

39-year-old man

<u>Relapsing</u> ***P. aeruginosa*** **implant-associated infection** despite 'DAIR', and despite implant removal

<u>Septic nonunion</u> with **<u>persistent</u>** fully susceptible ***<u>P. aeruginosa</u>*** infection

Amputation

PRO

VS.

CON

Bone resection **+ innovative way to <u>treat</u> and <u>rebuild</u> the bone**

Clinical case #2

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

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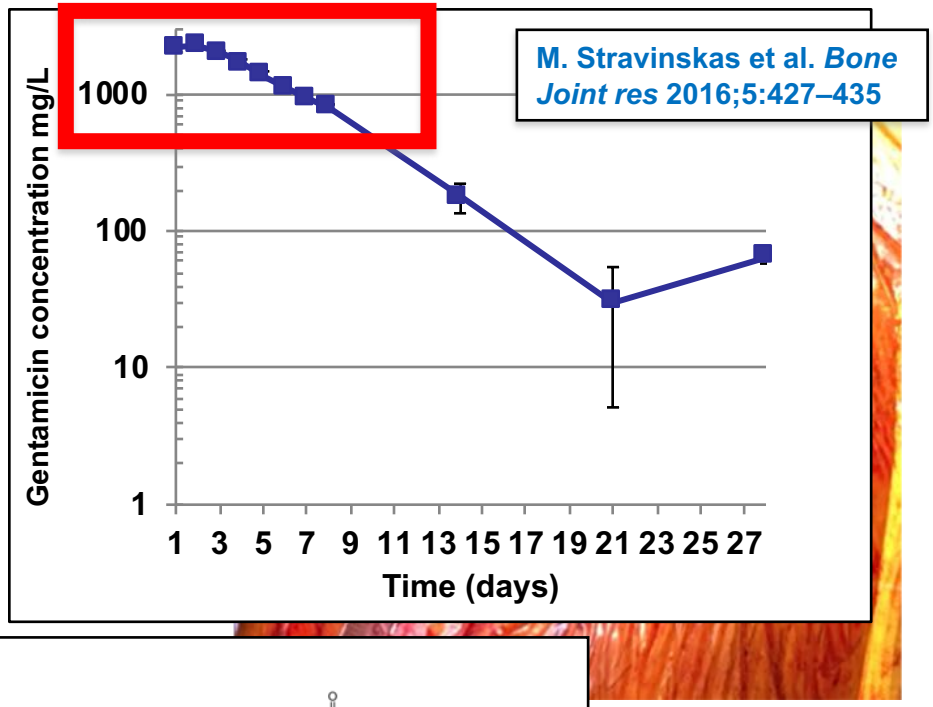

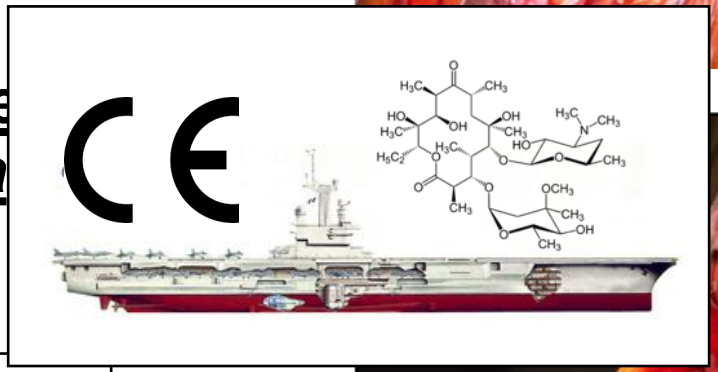

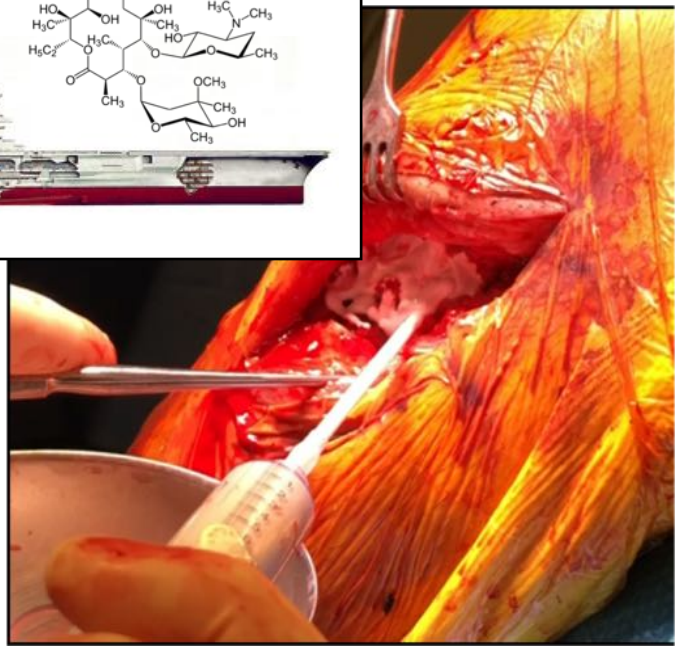

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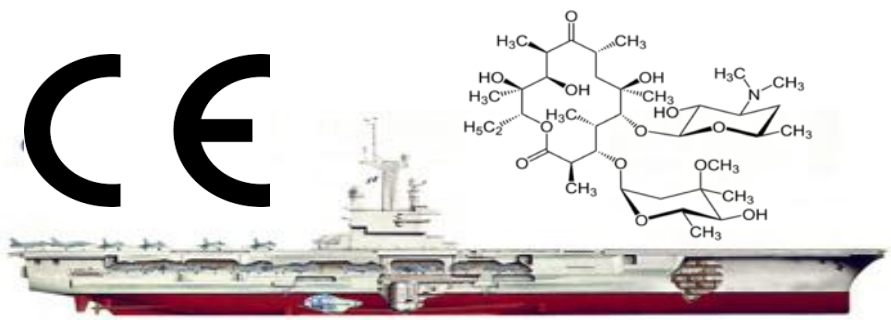
Clinical case #2

CE



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

Favorable outcome at 3 years

Multidisciplinary decision
1st step: Bone resection + spacer
2nd step: Gastrocnemius flap
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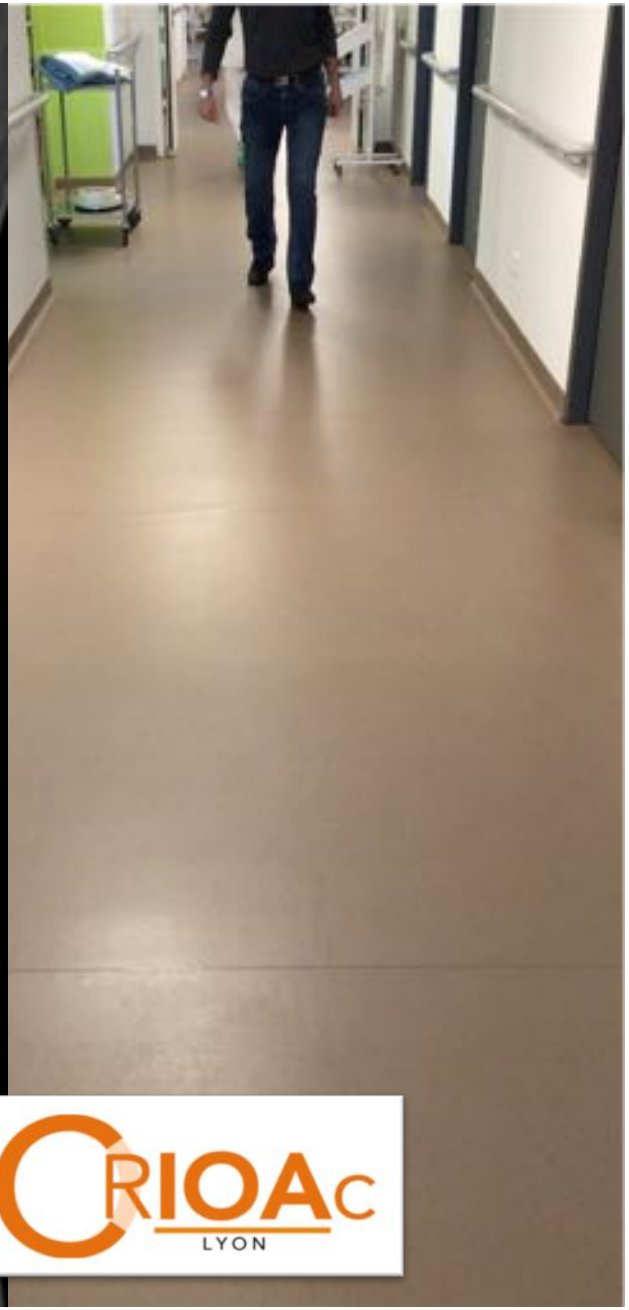


HCL HOSPICES CIVILS DE LYON

CRIOAc LYON

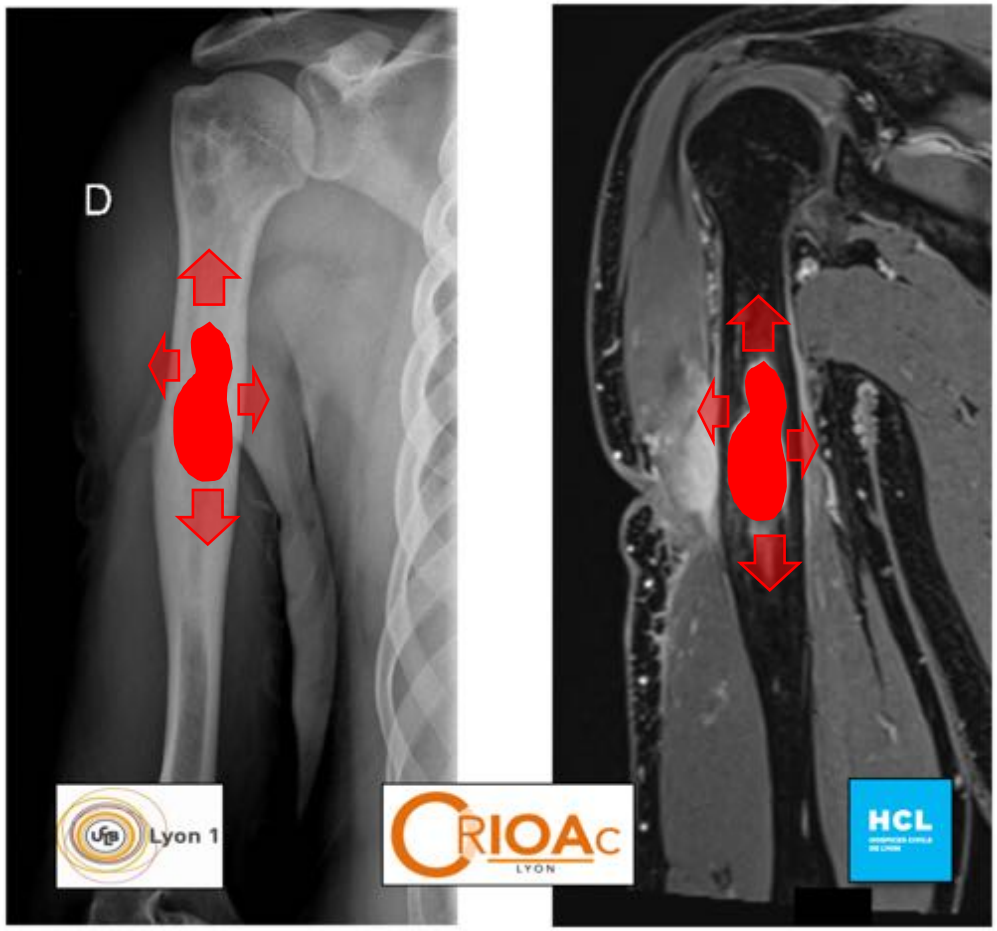
CONVICTION clinical trial

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**

T. Ferry PRME 2019

First inclusion Q2 2021?

CONVICTION clinical trial



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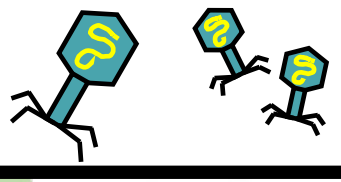
Bacteriophages



Bacteriophage-derived lysins

New antibiotics targeting the biofilm

OPTIMAL SEPTIC SURGERY

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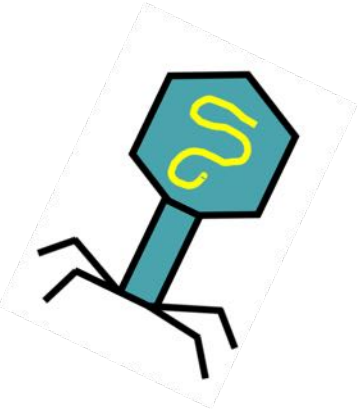
What is a « bacteriophage » ?



- 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*)

10 to 100 fold smaller than a bacteria

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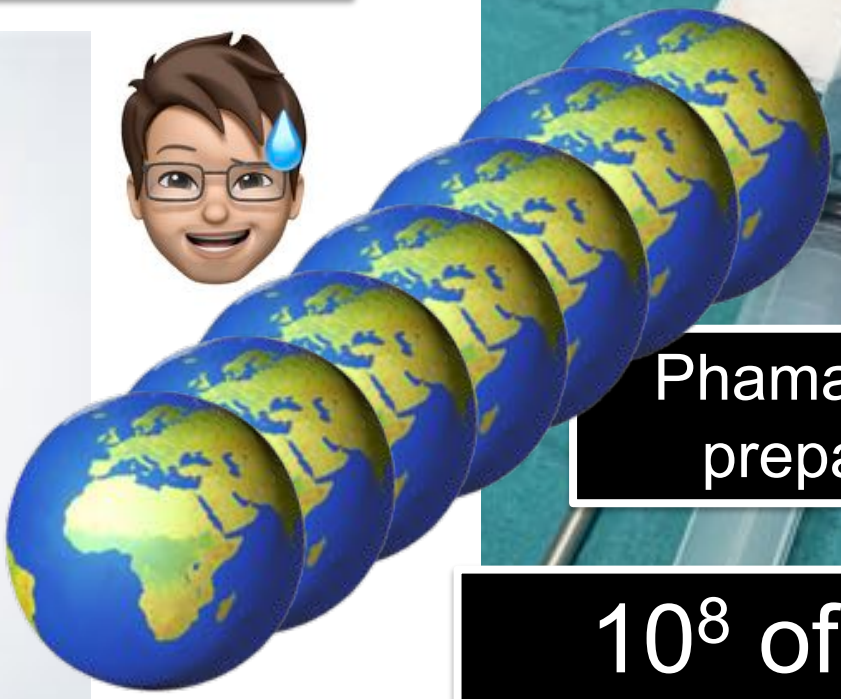

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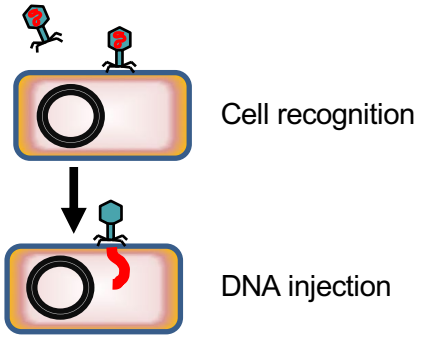
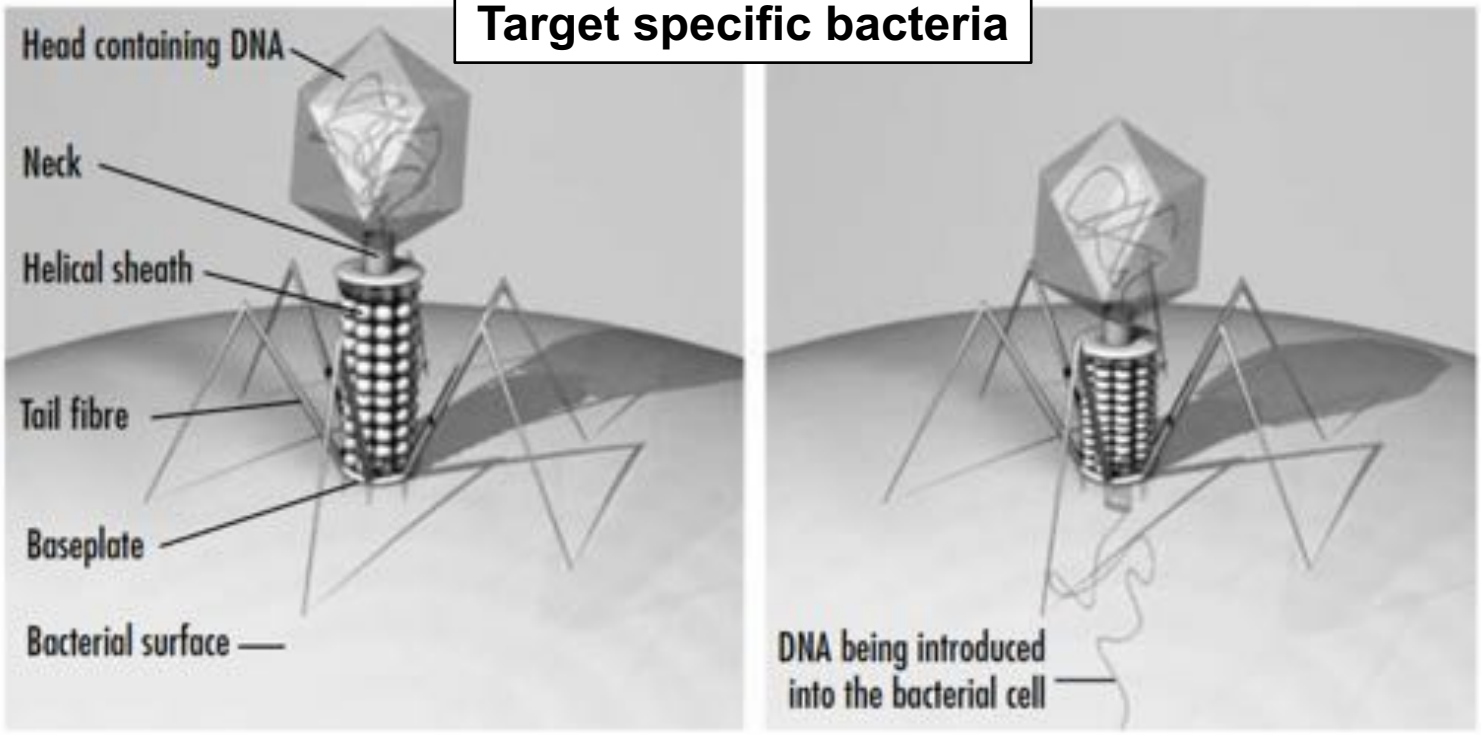
Ferry T. et al.

Virologie

2020;24(1):49-56



Environmental viruses
Target specific bacteria



Ferry T. et al.
Virologie
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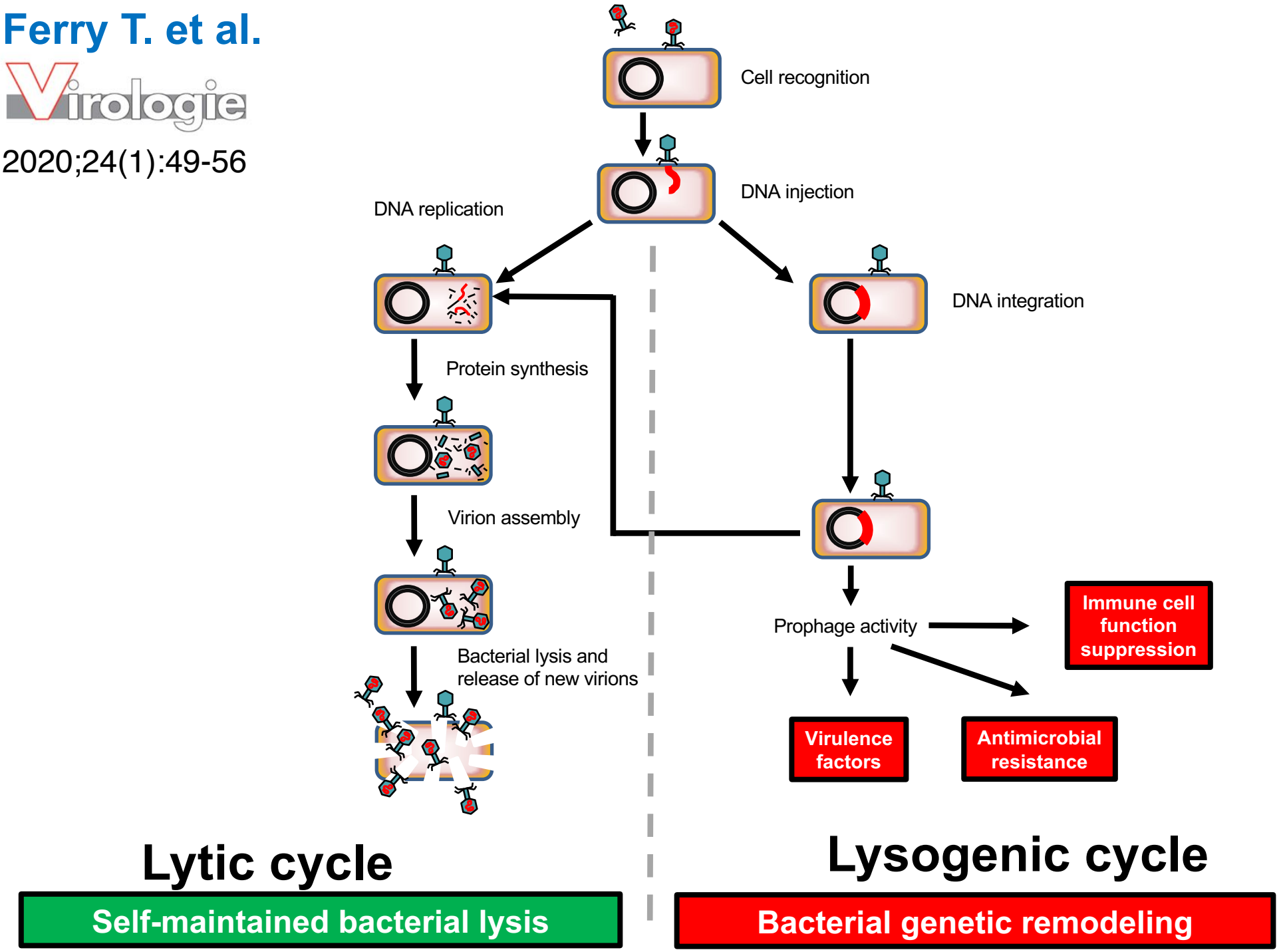

Ferry T. et al.
Virologie
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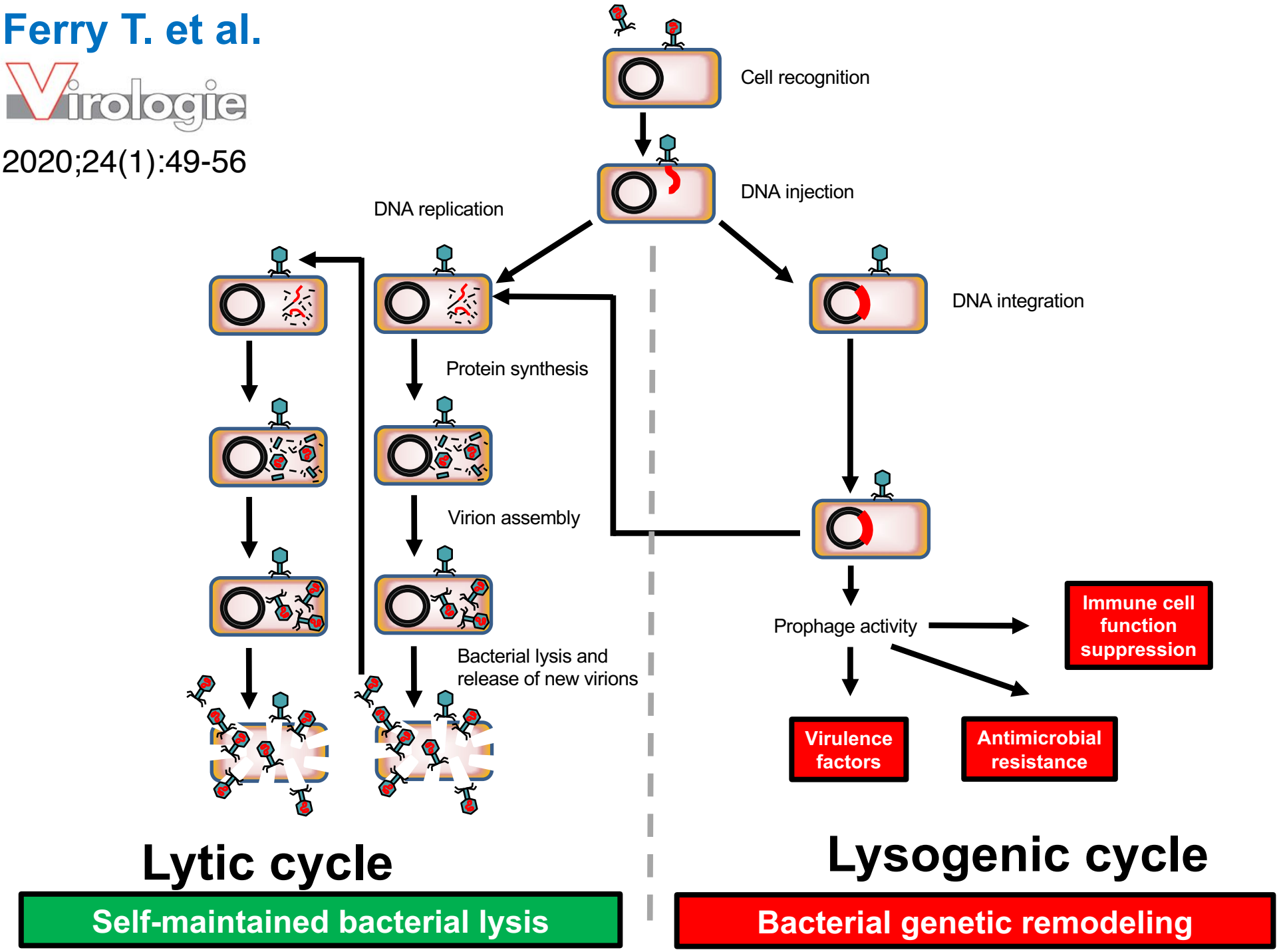

Ferry T. et al.
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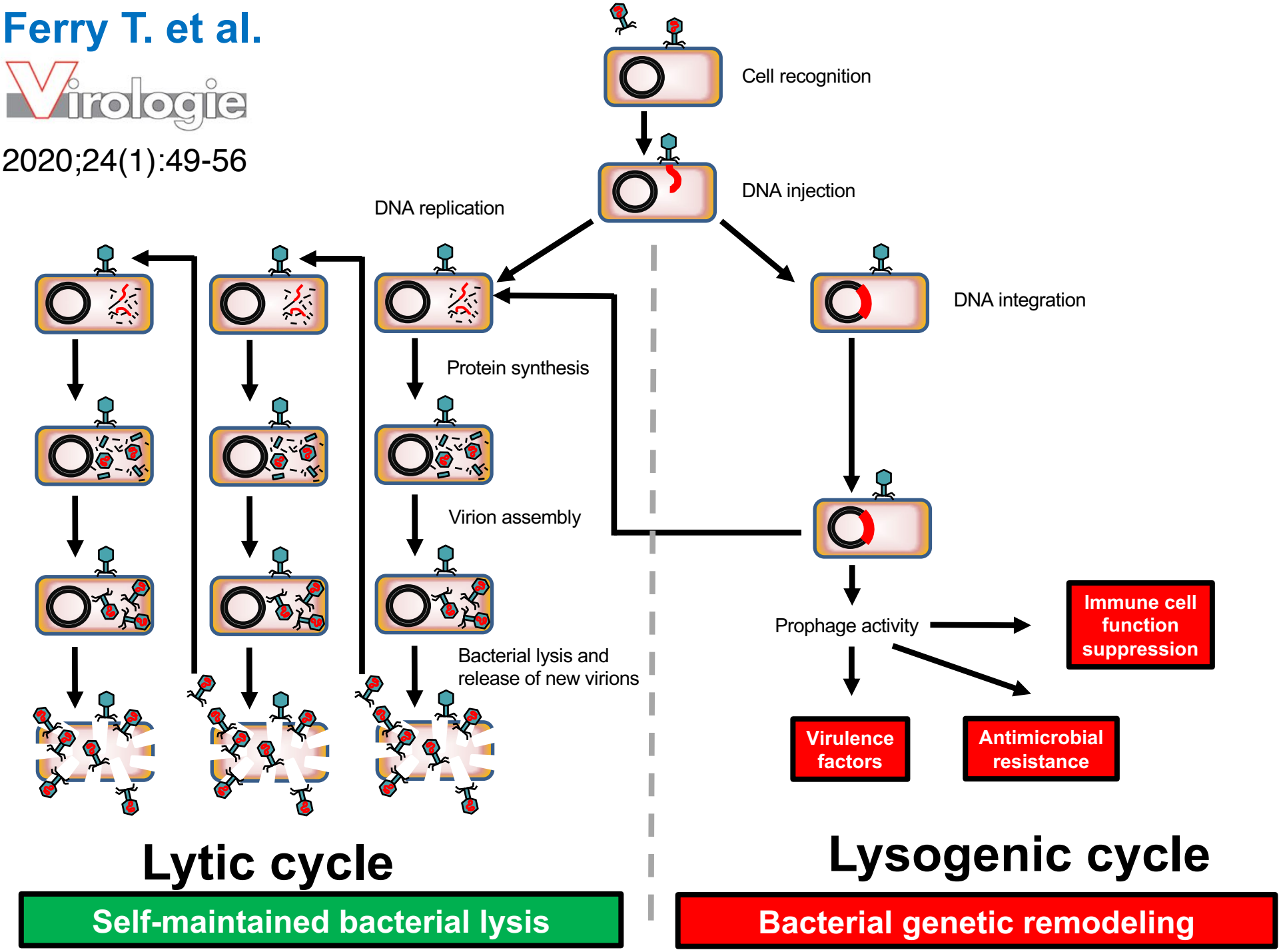
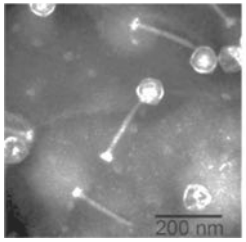
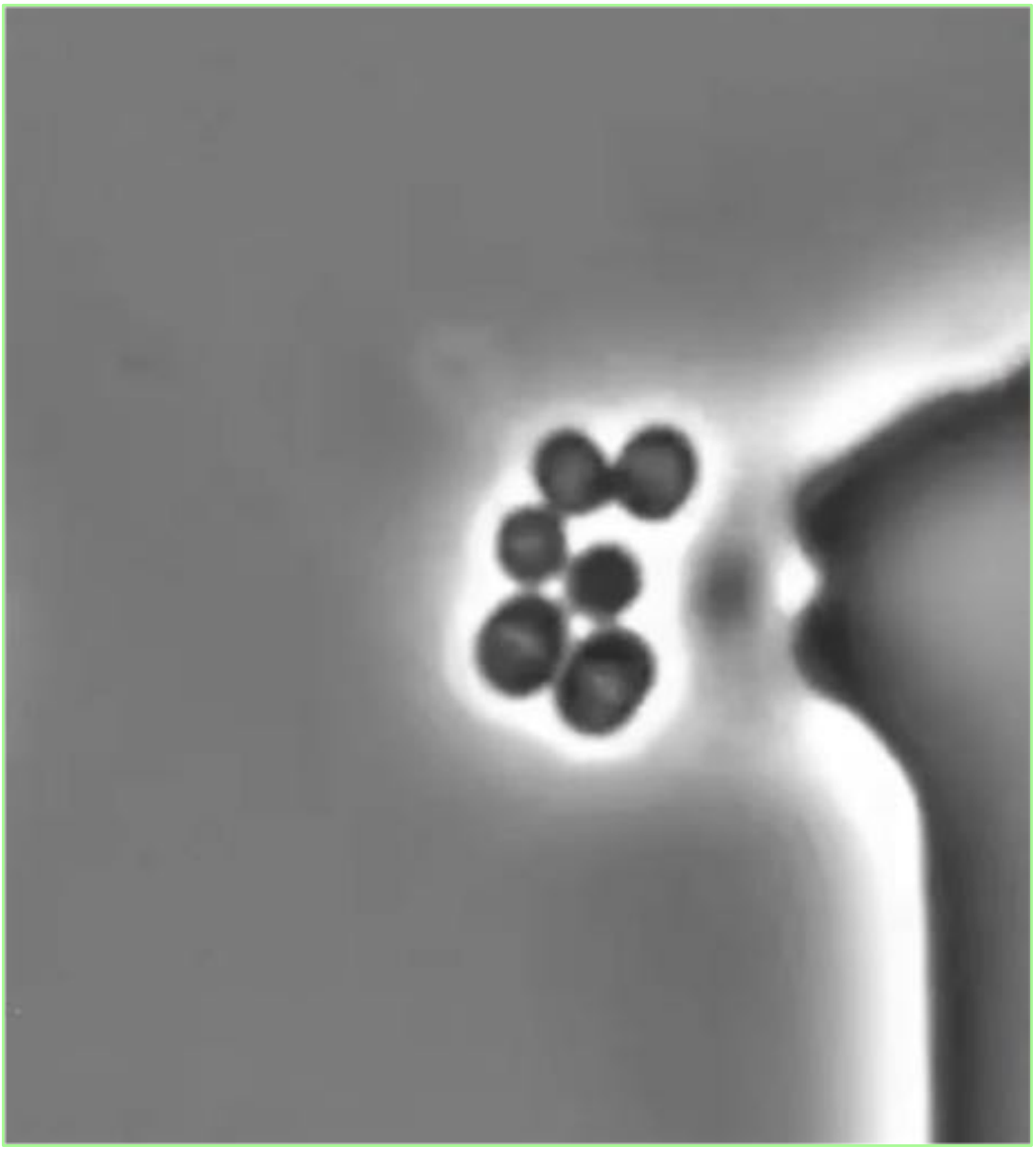


A clear antibacterial activity!

S. aureus being lysed by the Sa2 phage



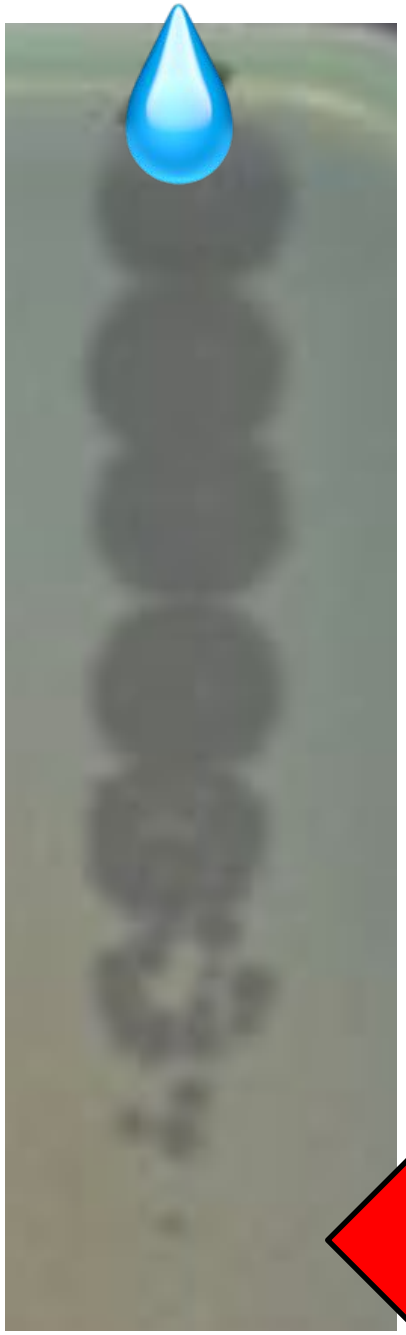
Bacterial DNA appeared in green



Courtesy Pascal Maguin
Luciano Marraffini Lab
THE ROCKEFELLER UNIVERSITY

A clear antibacterial activity!

Phagogram



Phage

10^{10}

10^{9}

10^{8}

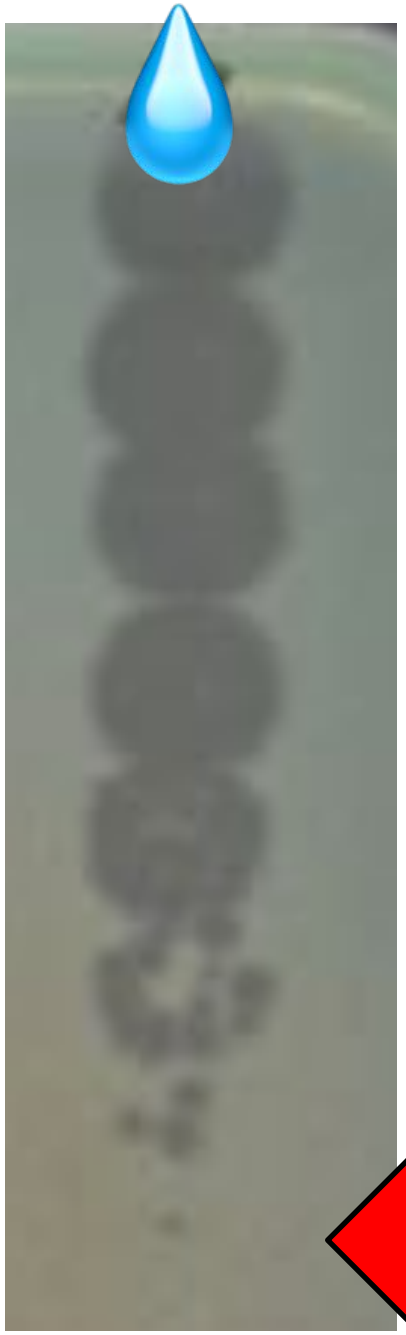
10^{7}

10^{6}

10^{5}

PFU/mL

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



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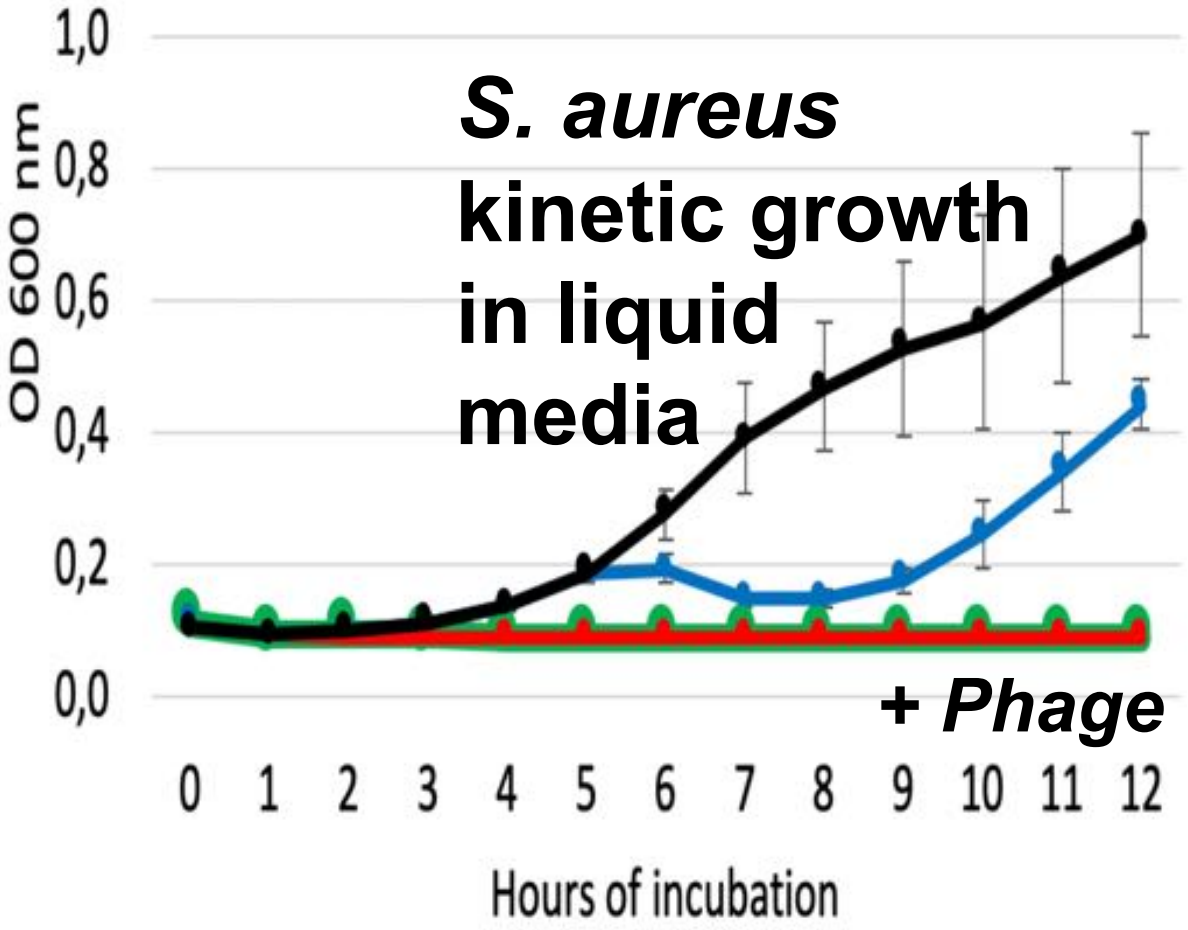
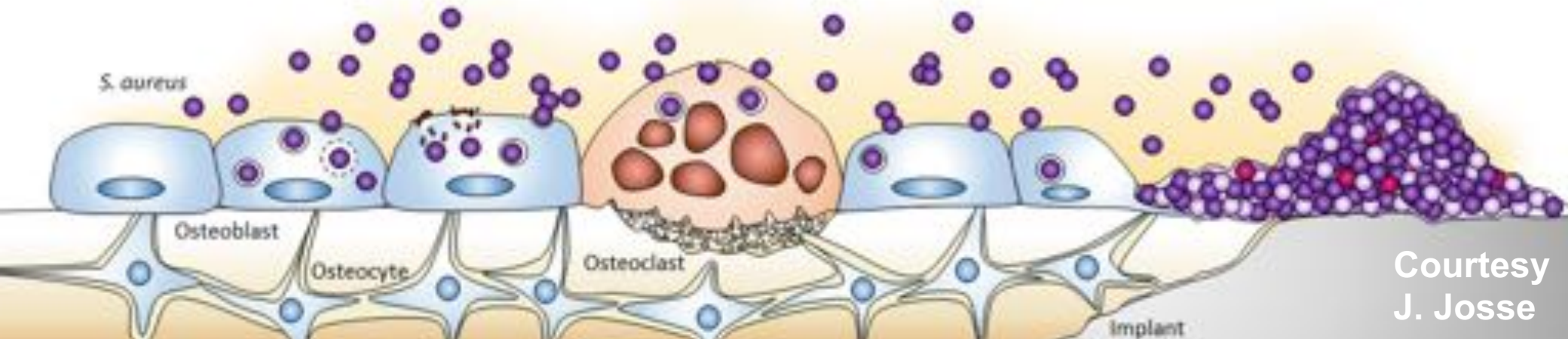


***S. aureus* culture on a gelosis**

Persisters in chronic BJI

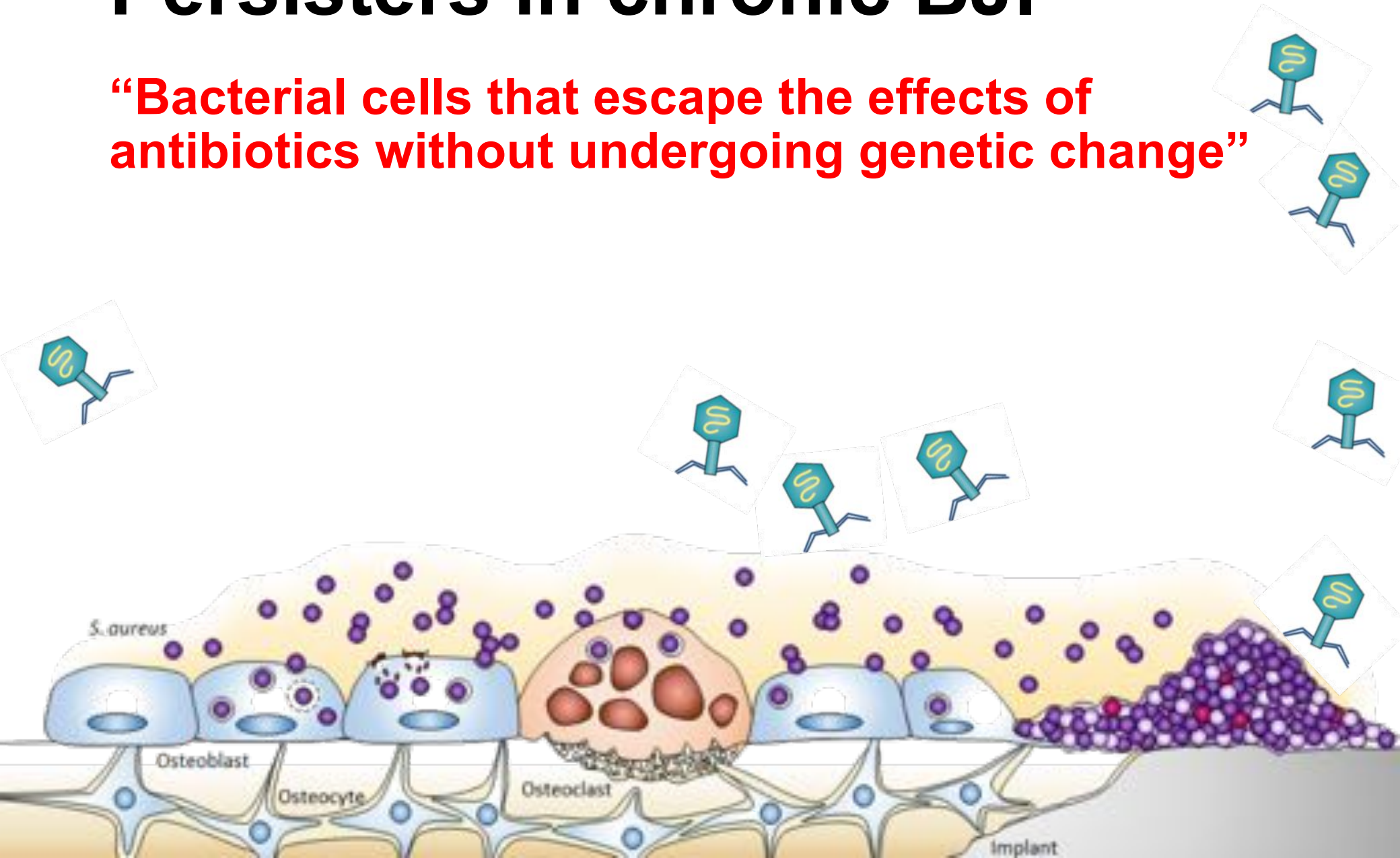
"Bacterial cells that escape the effects of antibiotics without undergoing genetic change"



Courtesy
J. Josse

Persisters in chronic BJI

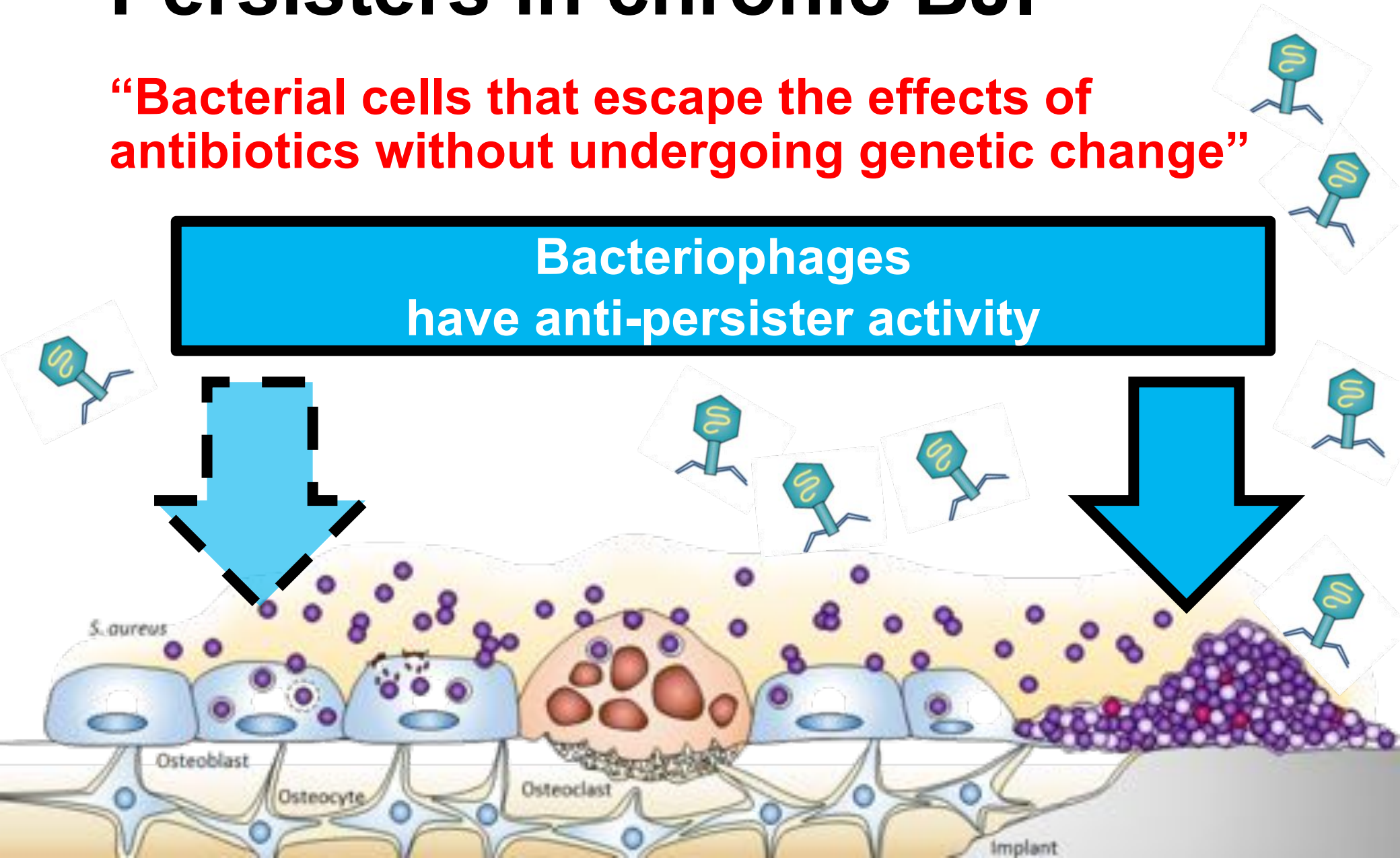
"Bacterial cells that escape the effects of antibiotics without undergoing genetic change"



Persisters in chronic BJI

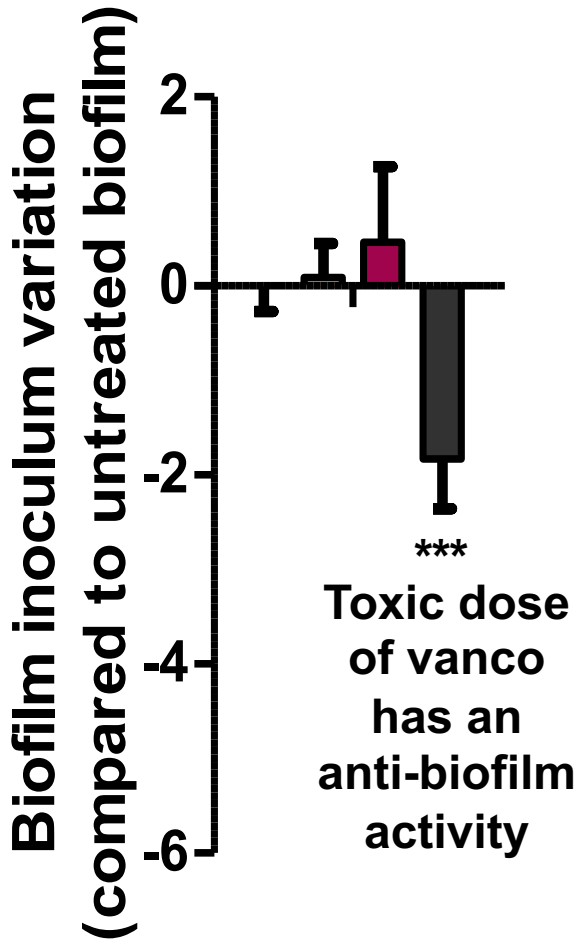
"Bacterial cells that escape the effects of antibiotics without undergoing genetic change"

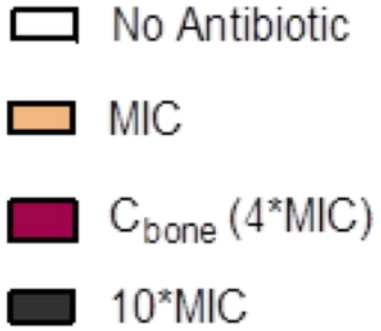
Bacteriophages have anti-persister activity



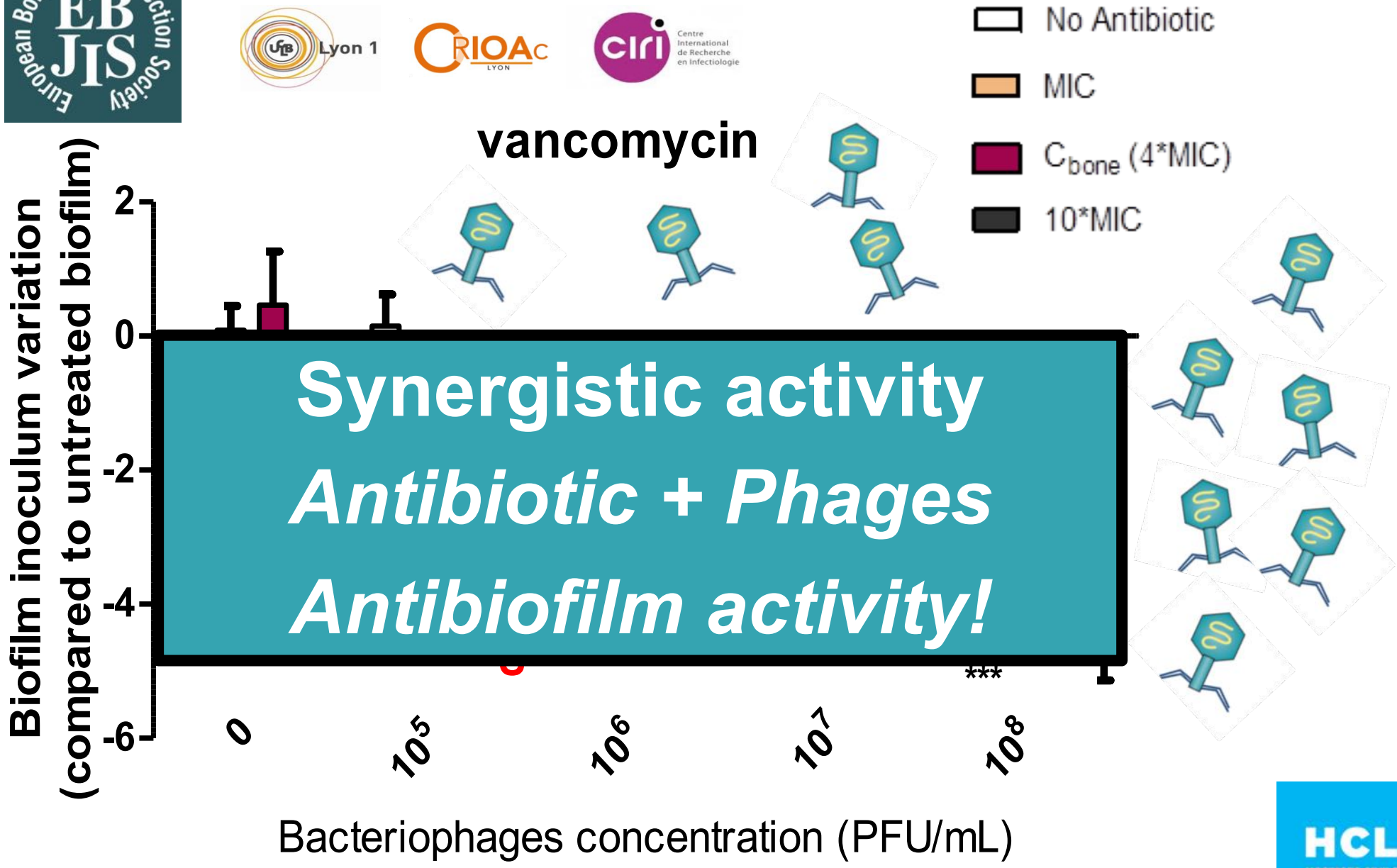
C. Kolenda et al. Antimicrob Agents Chemother 2019

vancomycin





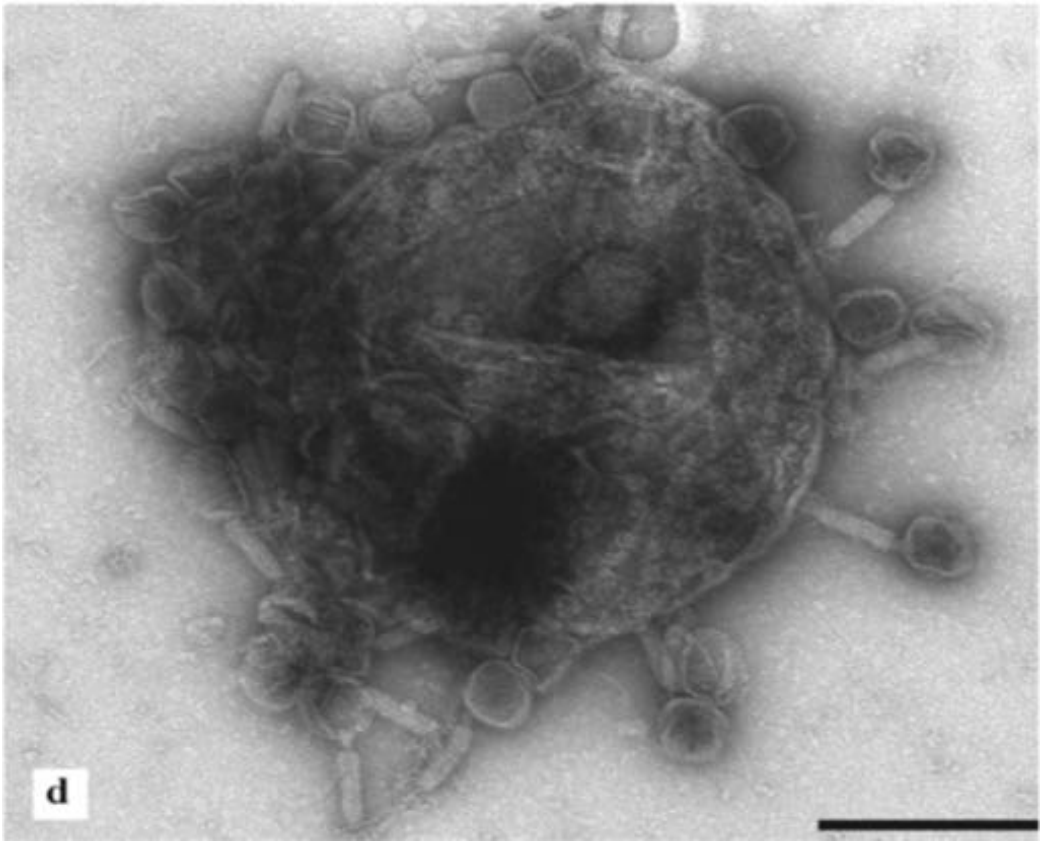
C. Kolenda et al. Antimicrob Agents Chemother 2019



Cocktails produced in 2020 by the Eliava Institute

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

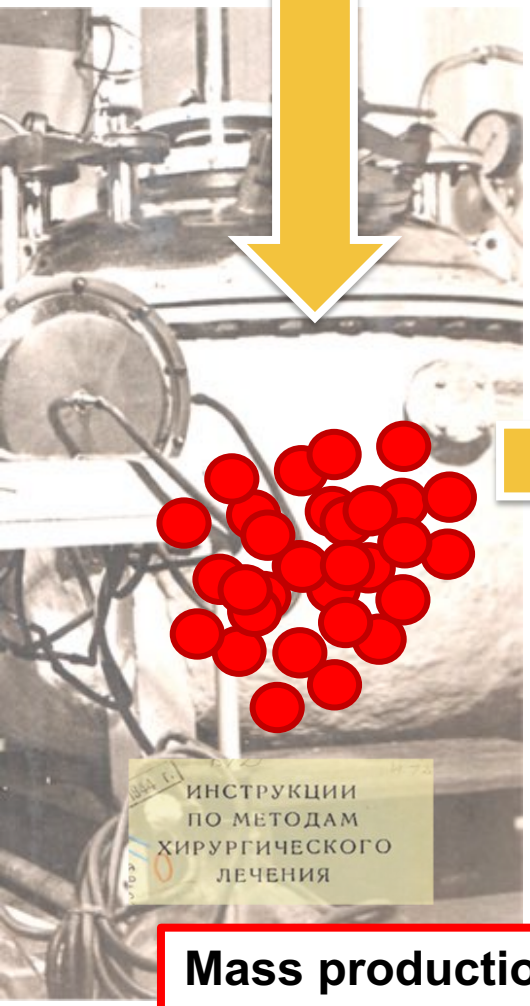
Bacteriophage ISP (*Myoviridae*)

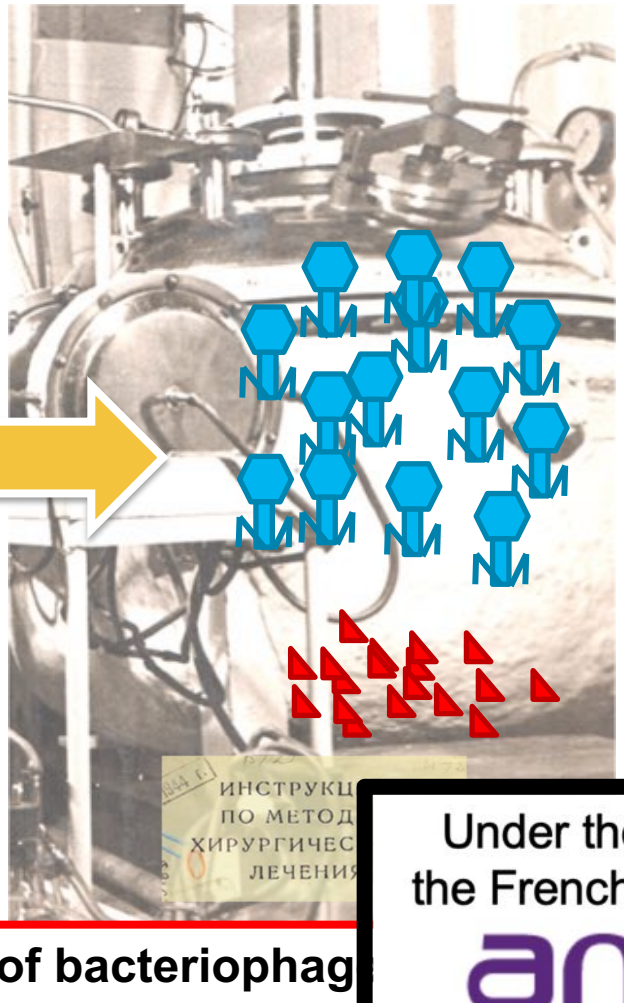


Merabishvili et al. PloS ONE 2009

T. Ferry. *The story of Phage therapy*

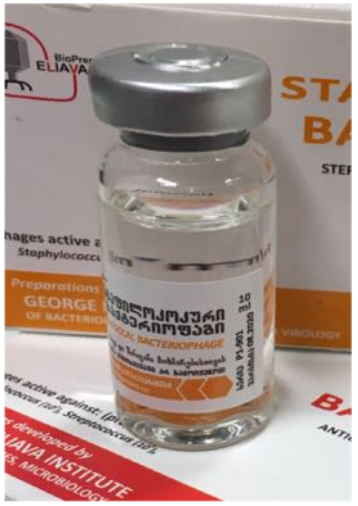
Not meeting Good Manufacturing Practices (GMP)





Mass production of bacteriophag
in Soviet Union during WWII

Pyrogenic
Bacterial
remnant?



10^6 phages/mL

AMPLIPHI BIOSCIENCES CORPORATION
ARMATA PHARMACEUTICALS
PHERECYDES PHARMA

GMP

Purified and
oduced as
a drug

0 phages/mL

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

T. Ferry. *The story of Phage therapy*

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?

Ferry T. 2018 *Open Forum Infectious Diseases*

Lyon 1

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CRIOAc LYON

ciri Centre International de Recherche en Infectiologie

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,

frontiers in Medicine

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

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 #3

80-year-old man

<u>Relapsing MSSA</u> prosthetic left knee infection (past revision)

<u>Failure</u> under <u>suppressive antimicrobial therapy</u>

Complex orthopaedic situation with past femoral fracture

Impossible to walk (painful knee)


Septic arthritis


Fistula and purulent discharge

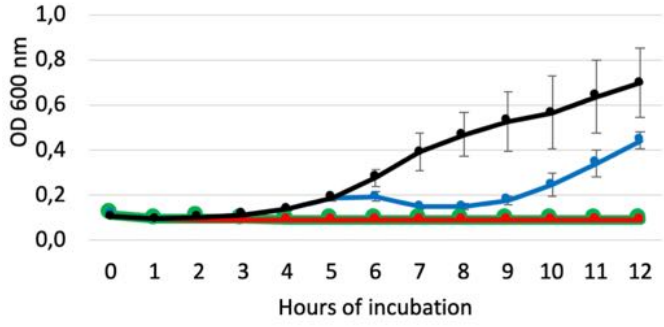
Clinical case #3

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



Phagogram
Selection of active bacteriophages

ID Clinic

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ADJUVANT INNOVATIVE ANTI-INFECTIVE AGENTS
OPTIMAL SEPTIC SURGERY
TARGETED AND OPTIMAL ANTIMICROBIAL THERAPY
MULTIDISCILINAR MEETING

Surgery

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Lab

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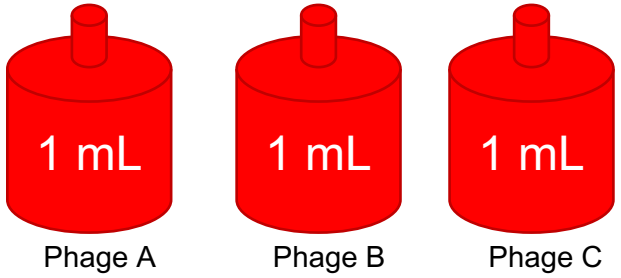
Active GMP

***S. aureus* Bactériophages**



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French Health Authority

Pharmacy

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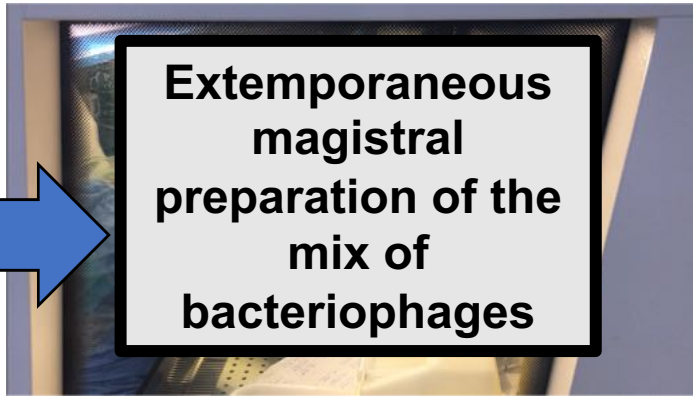
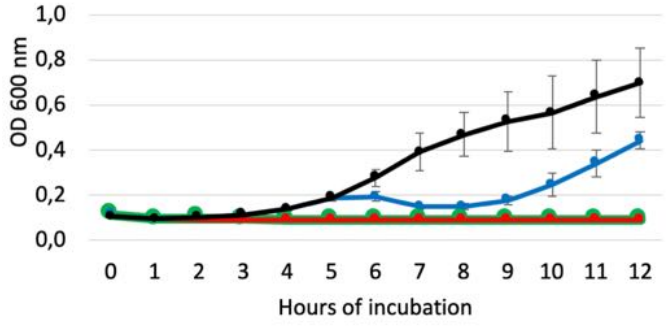


Extemporaneous magistral preparation of the mix of bacteriophages

Lyon Phage team



Phagogram
Selection of active bacteriophages

ID Clinic

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ADJUVANT INNOVATIVE ANTI-INFECTIVE AGENTS
OPTIMAL SEPTIC SURGERY
TARGETED AND OPTIMAL ANTIMICROBIAL THERAPY
MULTIDISCILINAR MEETING

Surgery

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Lab

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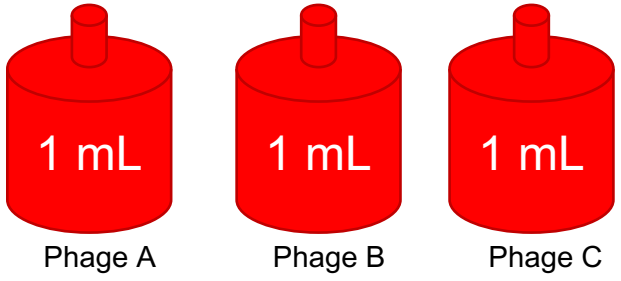
Active GMP

***S. aureus* Bactériophages**



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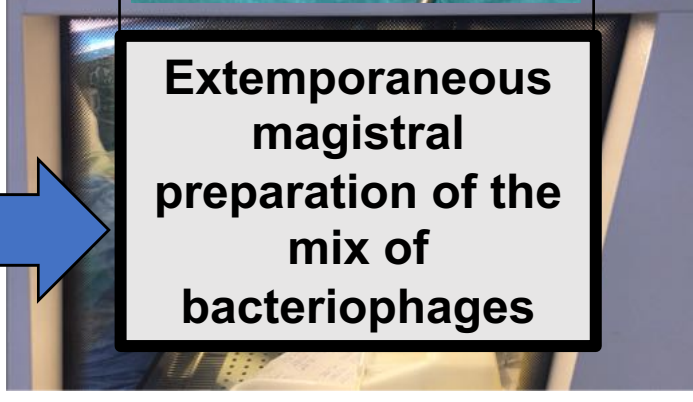

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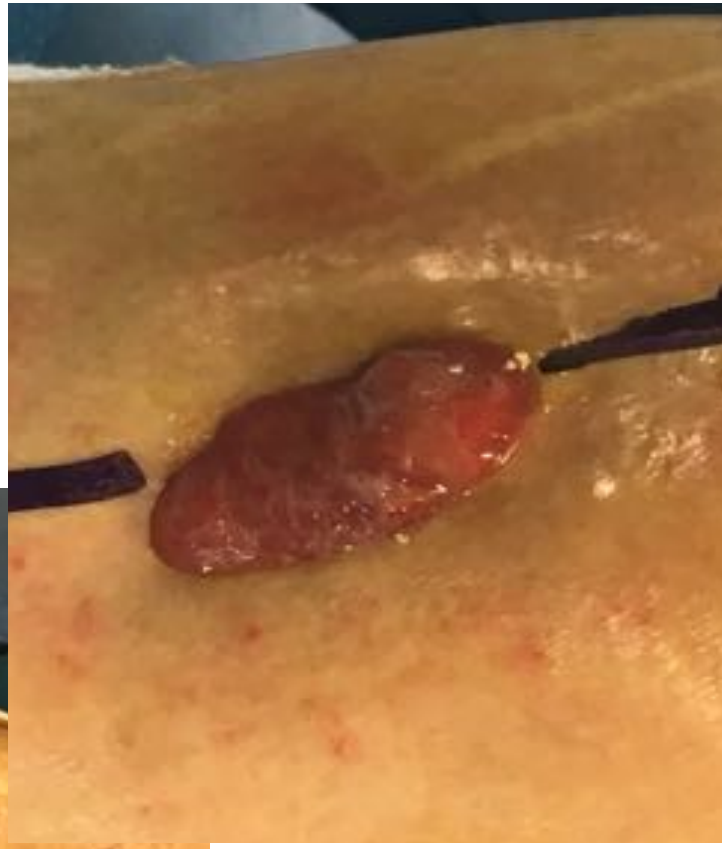

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“Debridement And Implant Retention” (DAIR)

“PhagoDAIR”

<u>One shot</u> peroperative phage application after “DAIR”

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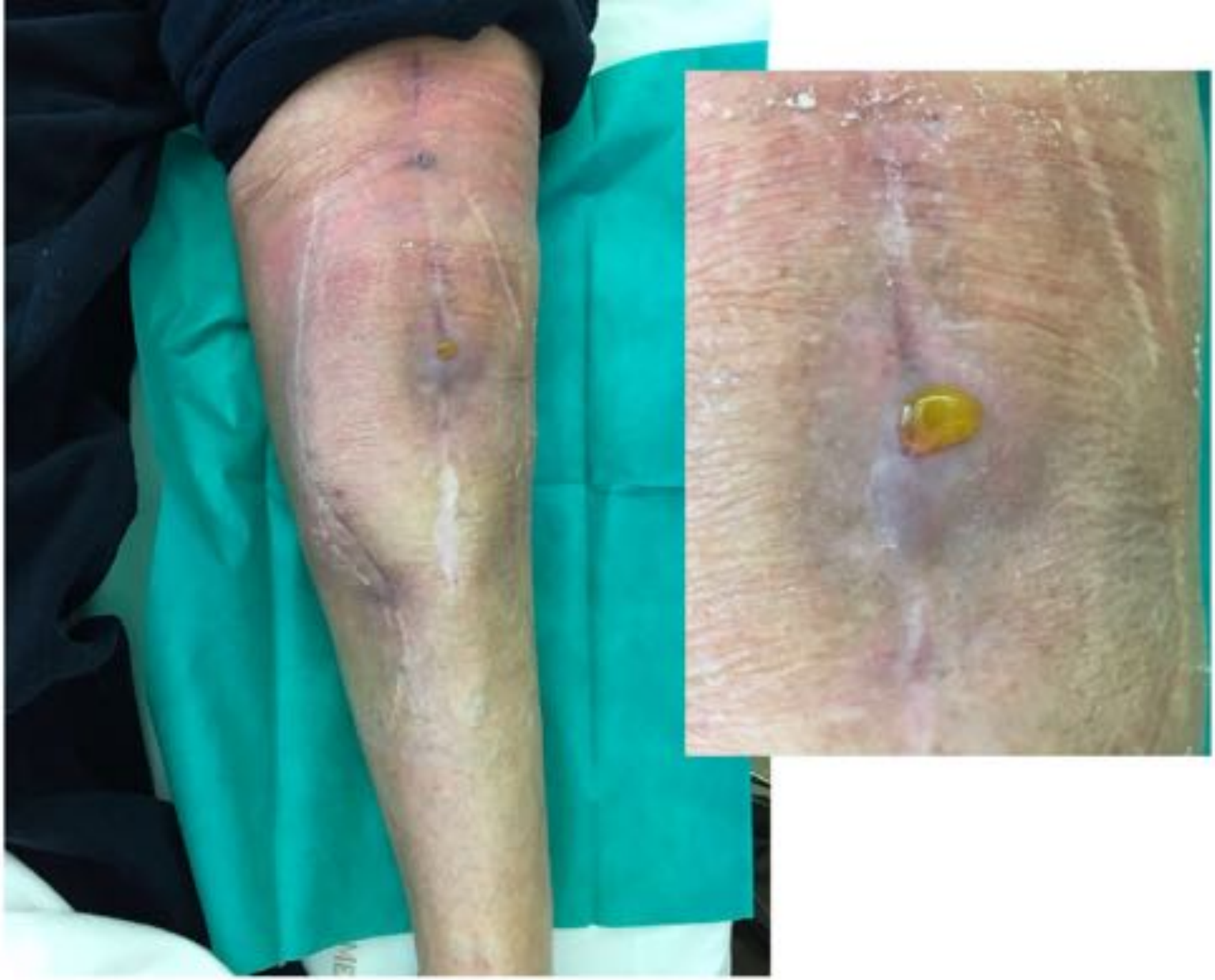


Clinical case #3

<u>Post-operative</u> antibiotics:

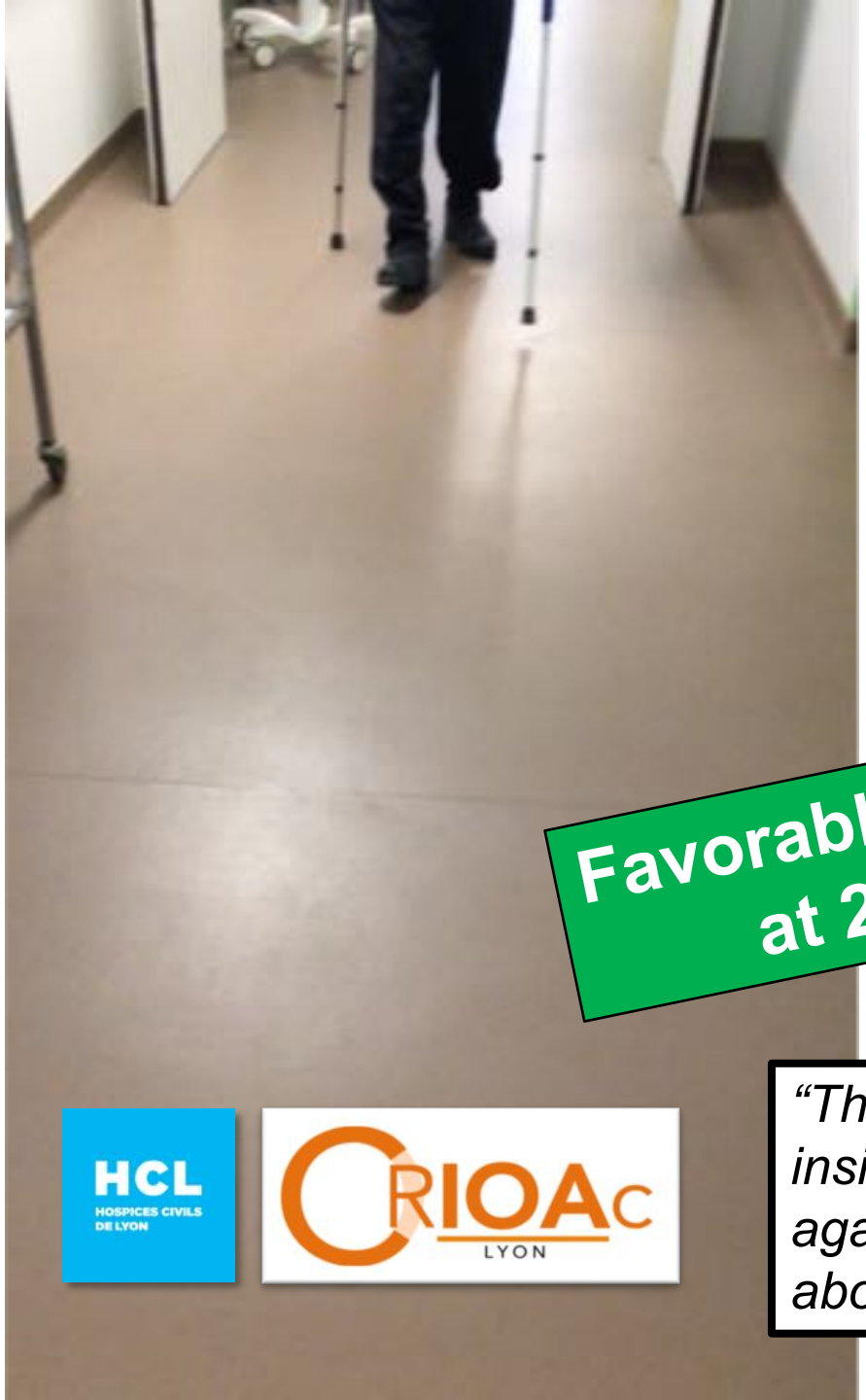
Daptomycin + Rifampin

<u>At day 4</u> (only MSSA in all intraoperative samples):

Levofloxacin + Rifampin

<u>Then:</u>

Cefalexin as suppressive antimicrobial therapy



Favorable outcome at 2 years

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

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T. Ferry et al.

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frontiers in Medicine

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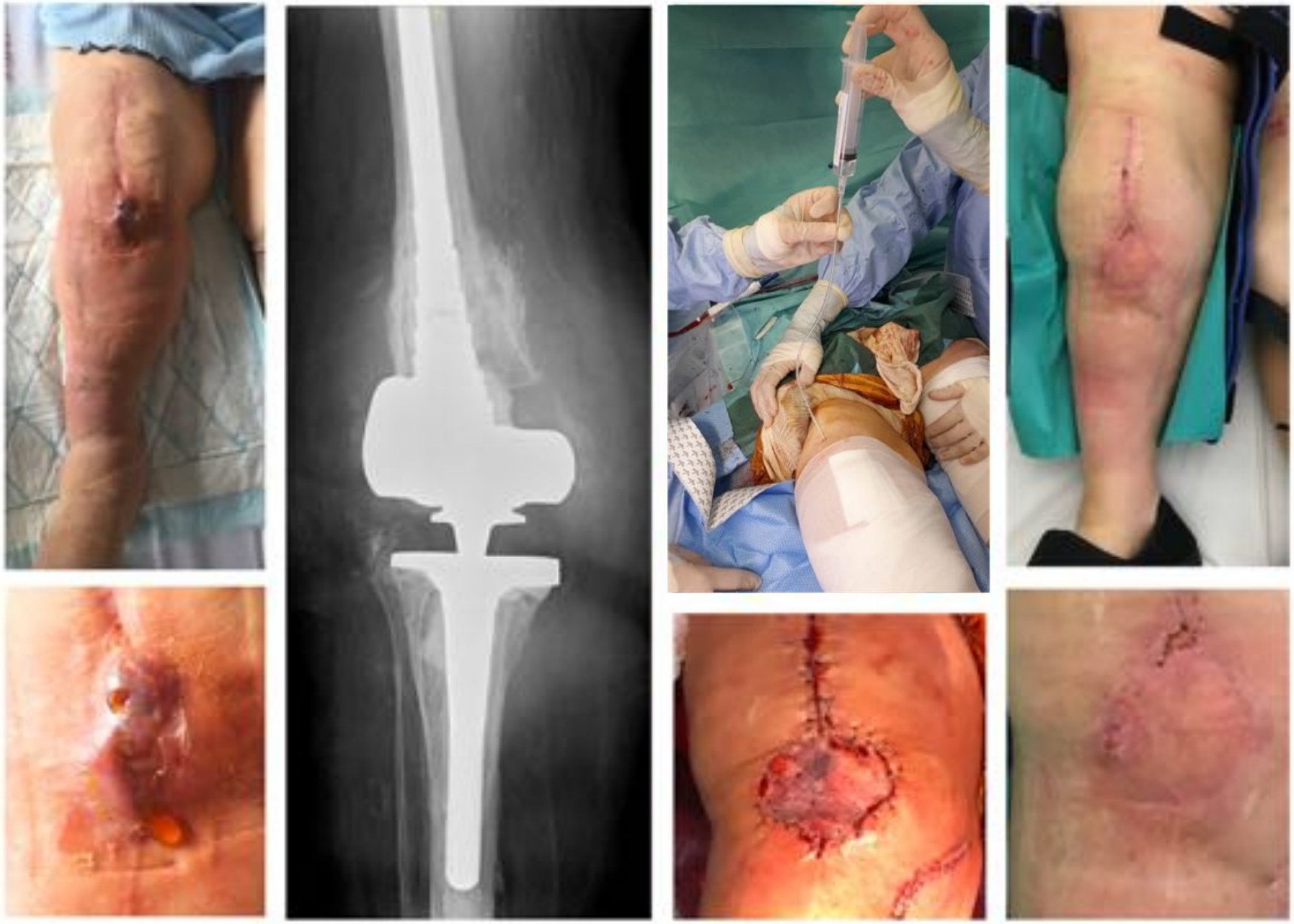

frontiers in Medicine

T. Ferry et al.

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

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

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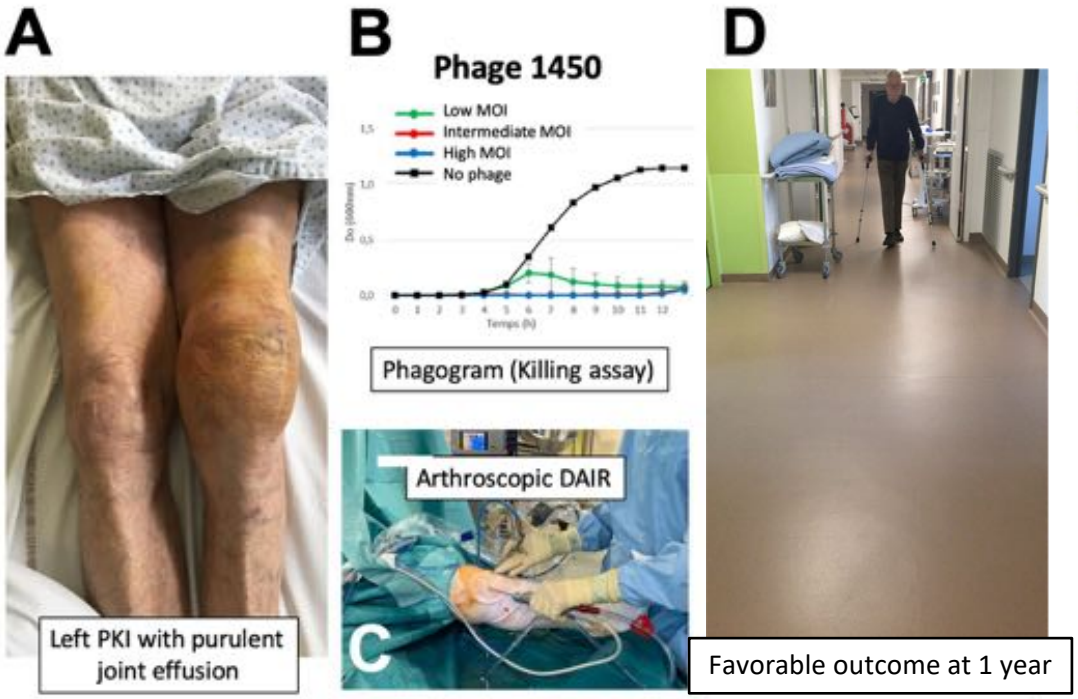
Phago DAIR

CRIOAc LYON



Submitted

30th ECCMID

Paris, France
18 –21 April 2020

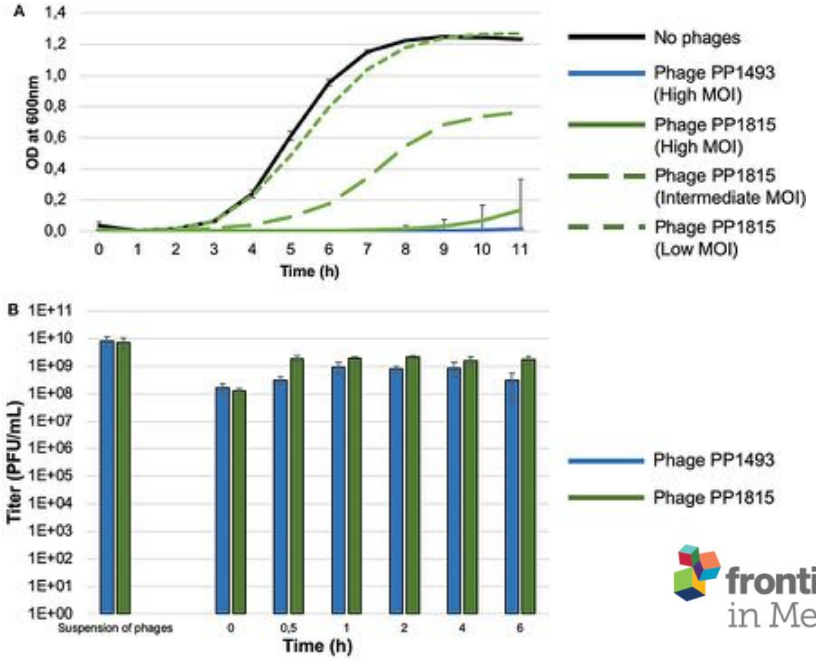
PHERECYDES PHARMA

HCL HOSPICES CIVILS DE LYON

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 Petitjean[6], Joseph Chateau[7], Cindy Fevre[6], Emmanuel Forestier[8], Sophie Brosset[7], Gilles Leboucher[9], 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*



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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 multidisciplinar 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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5ème Congrès national des CRIOAc

À Lyon

Les 20-21-22 octobre 2021 !

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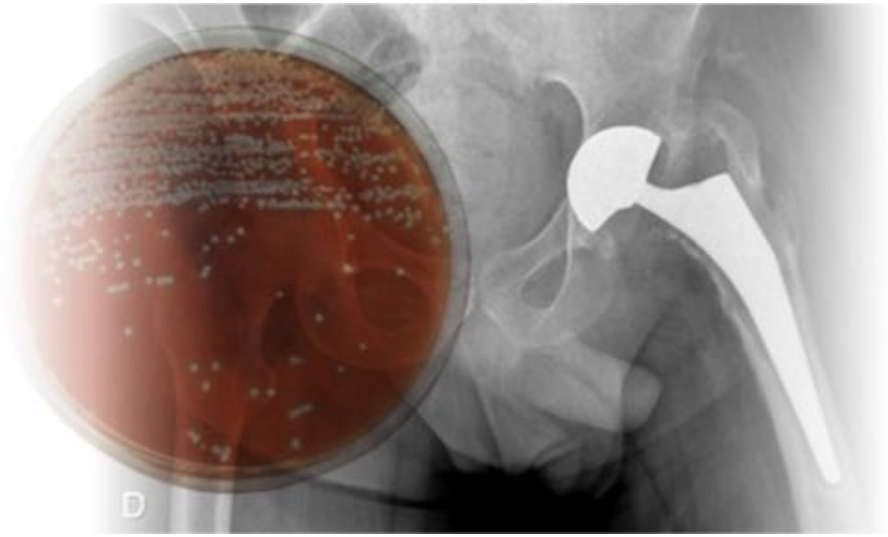

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- All thesis in pdf
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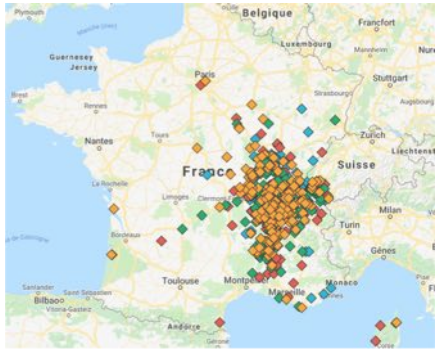

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