Medical innovations to maintain the function in patients with PJI

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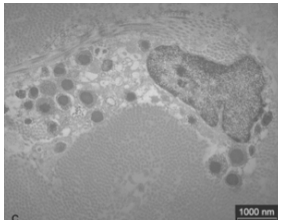
Centre de Référence des IOA complexes de Lyon (CRIOAc Lyon)

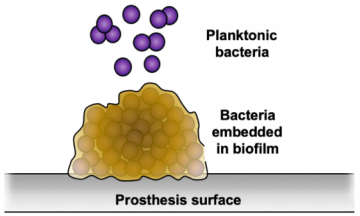
@FerryLyon

Chronic prosthetic joint infection

- One of the **most difficult-to-treat** ID
- Bacterial mechanisms of **persistence**
- **Intracellular survival** (*S. aureus*)
- **Production of biofilm**



Sendi et al.
Clin Infect Dis.
2006



Josse et al.
Front Microb.
2019

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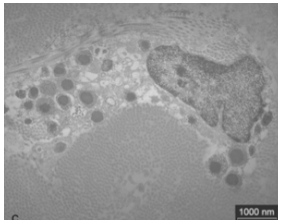

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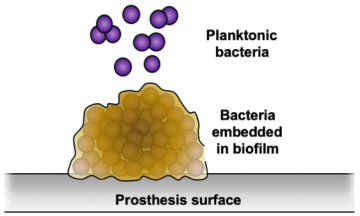


Josse et al.
Front Microb.
2019

Infectious challenge
Eradication of the pathogen

Functional challenge
Limit bone loss

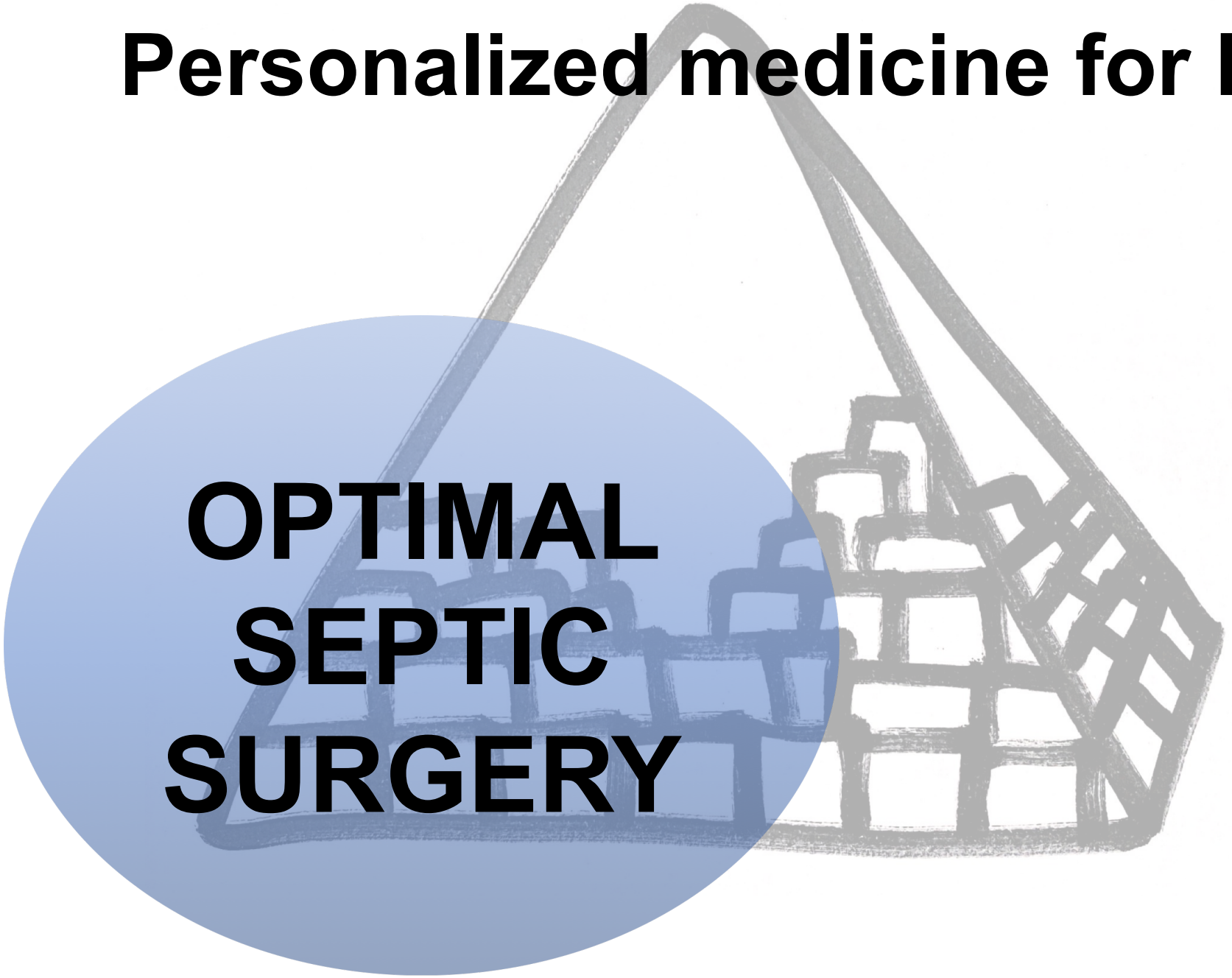
Infect. Dis.
Physician
Cure the infe

PRO
Incompatible
CON

thopaedic
Surgeon
Maintain the function

Personalized medicine for BJI

Personalized medicine for BJI



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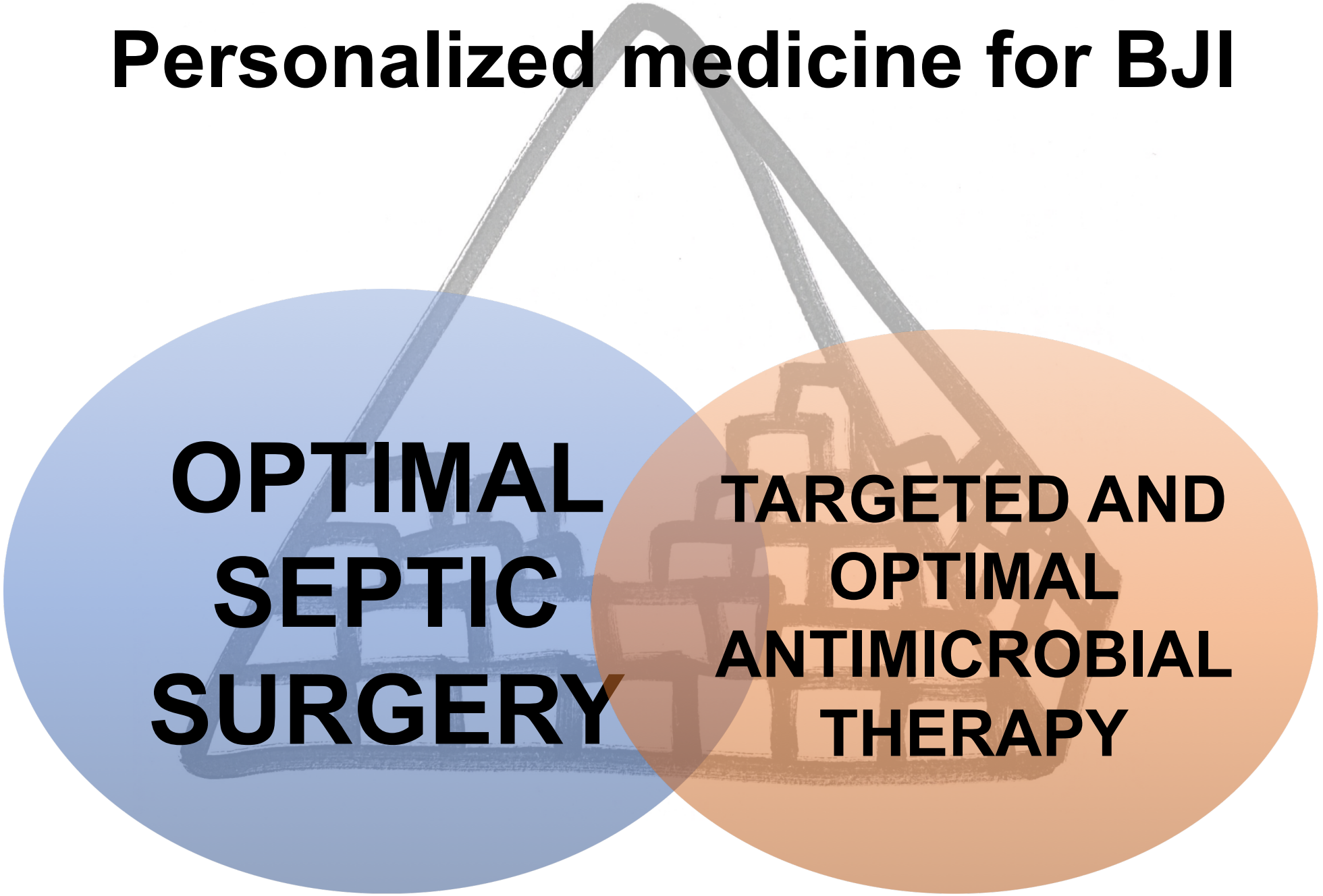

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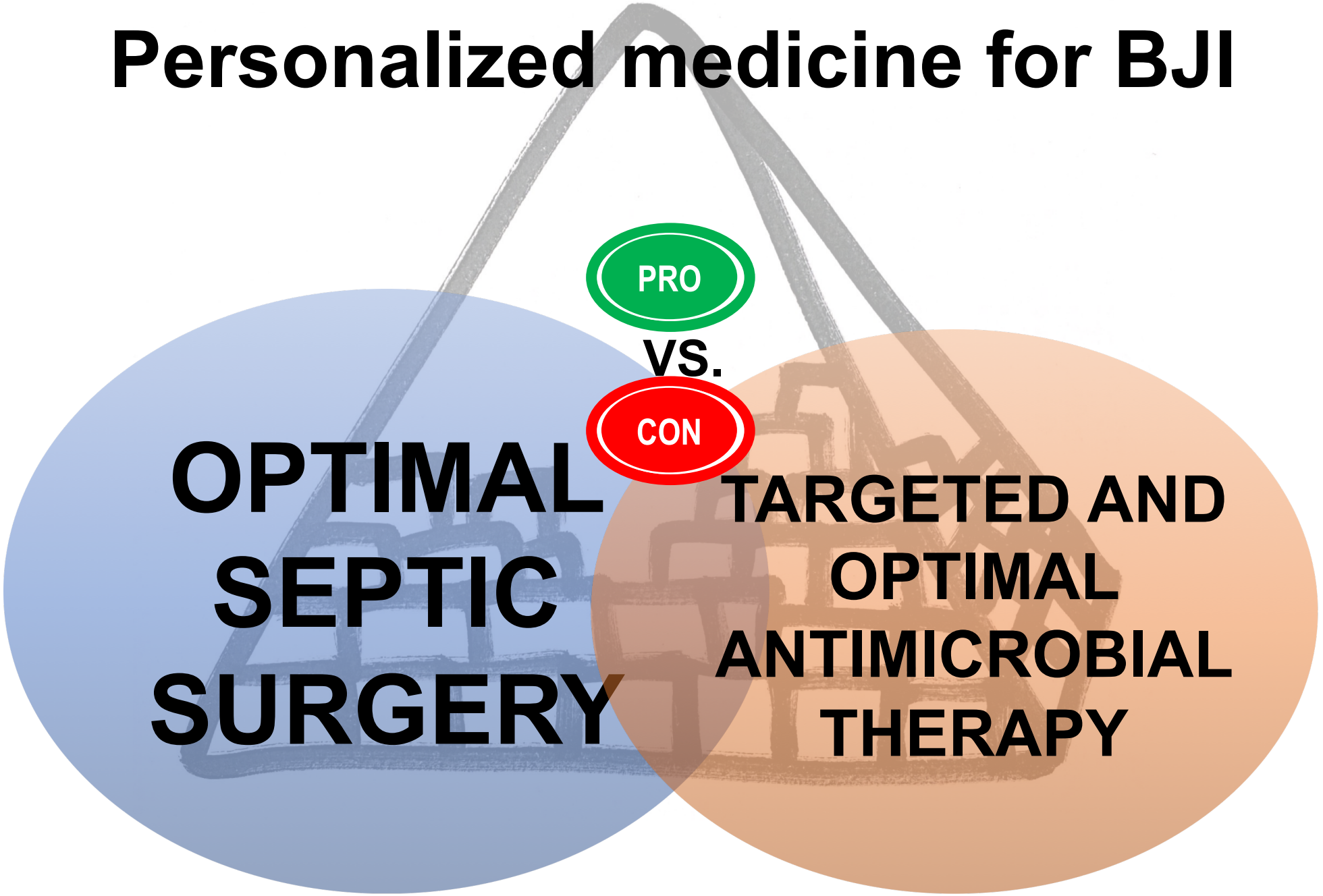

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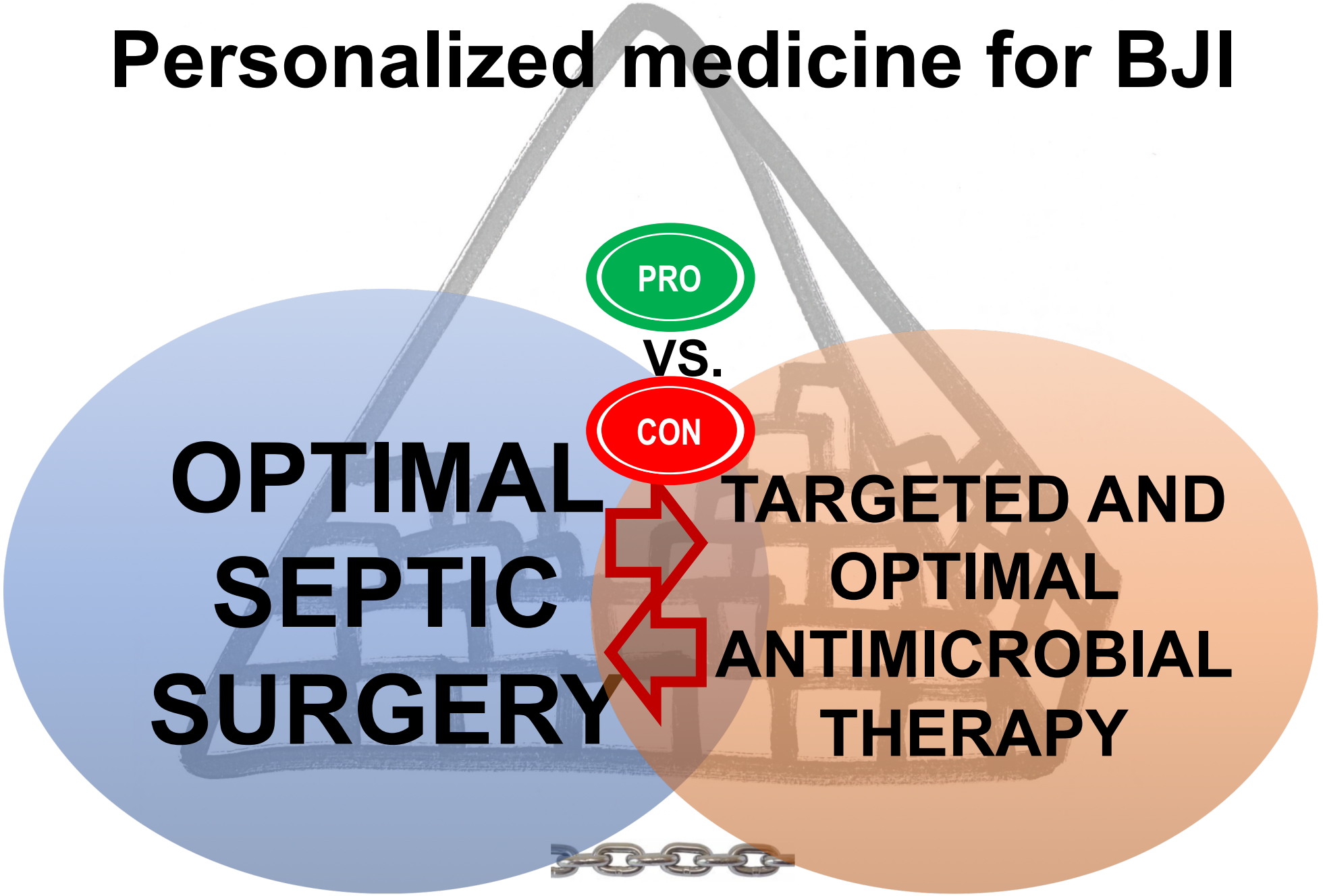

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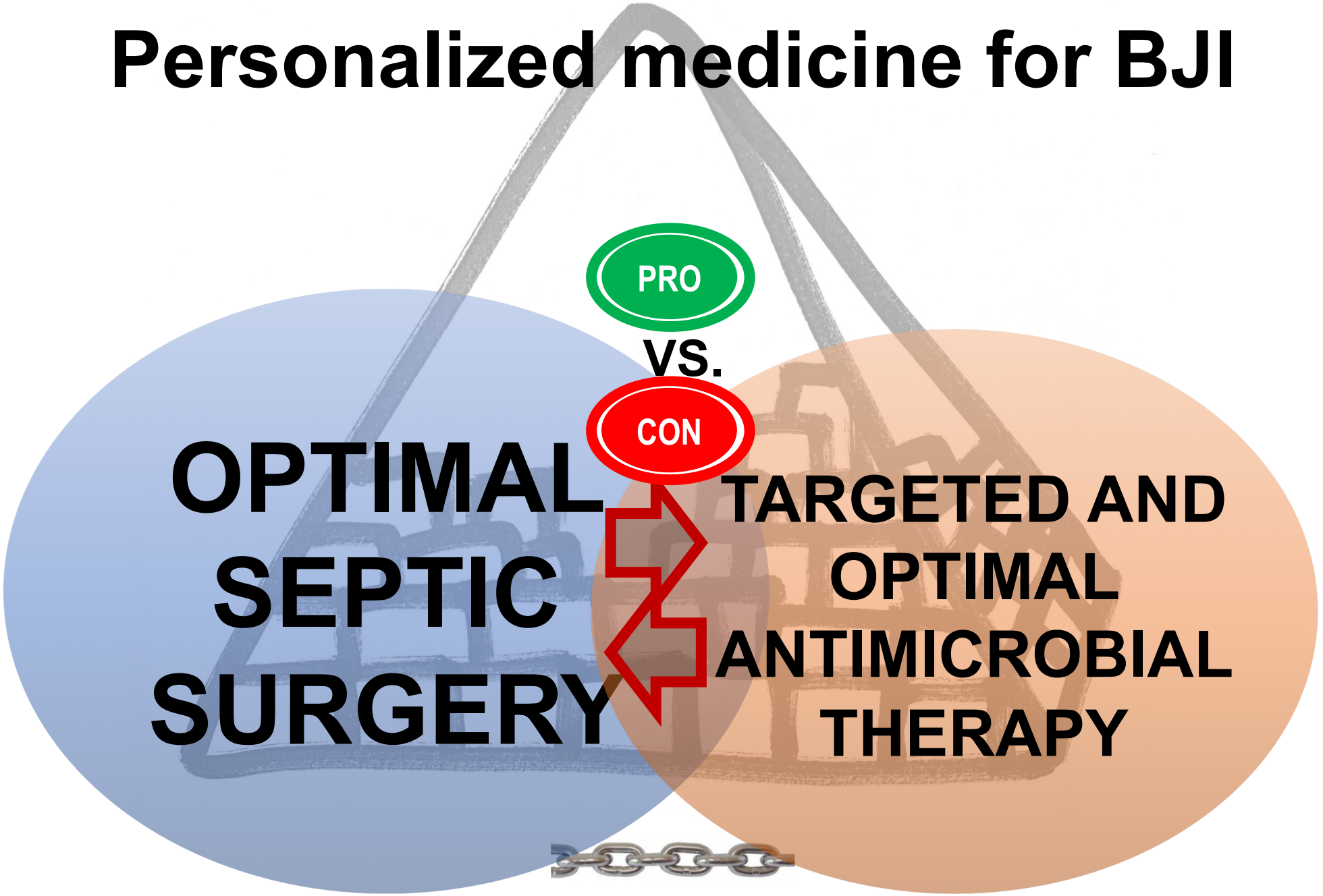
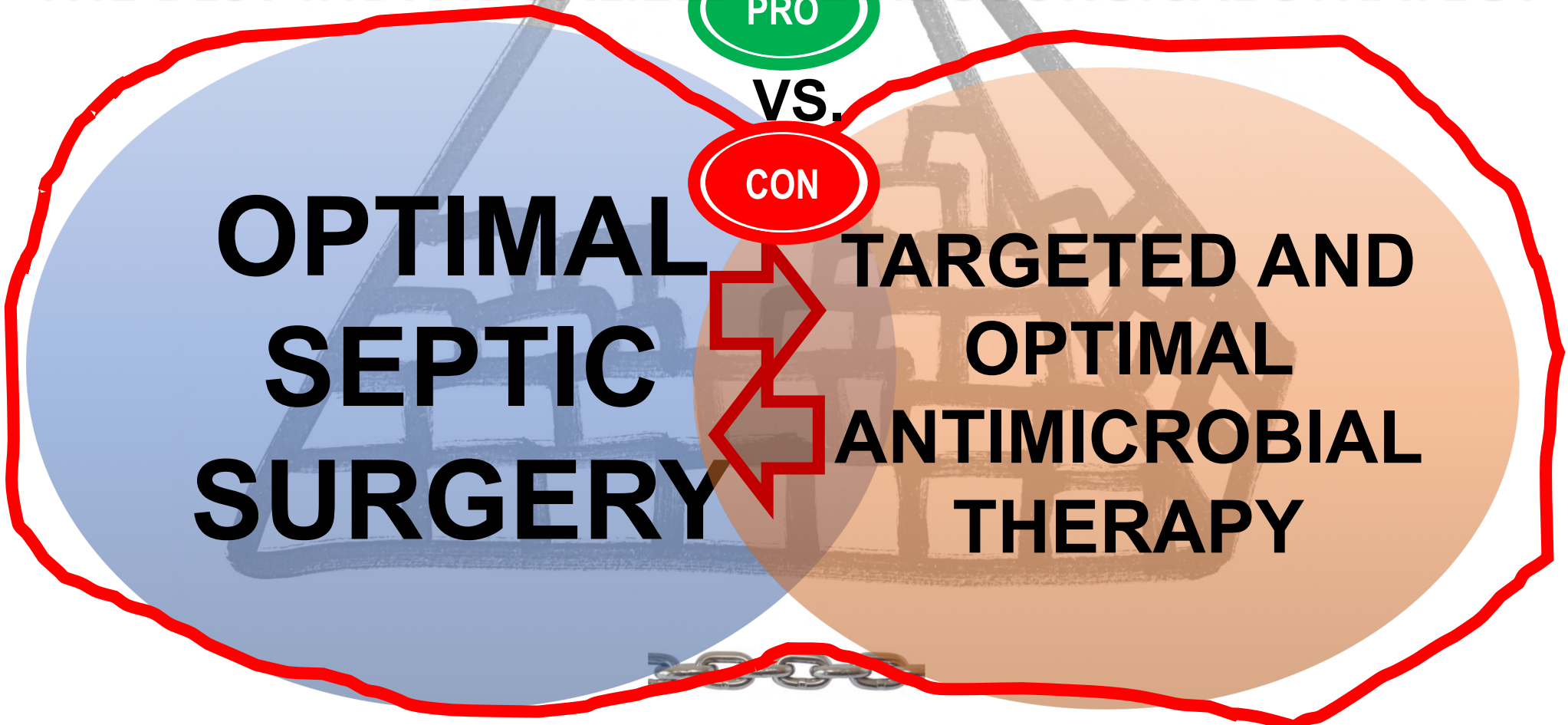


Personalized medicine for BJI

MULTIDISCILINAR MEETING

THE BEST INDIVIDUALIZED MEDICOSURGICAL STRATEGY



Centre de Référence des Infections Ostéo-Articulaires complexes

Antimicrobial suppressive therapy

Consensus document

2017 

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

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).**

Antimicrobial suppressive 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 dox	
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 disease

Chronic relapsing PJI
(resection prosthesis)

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

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
+
Primary ATBx
then
SAT

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

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

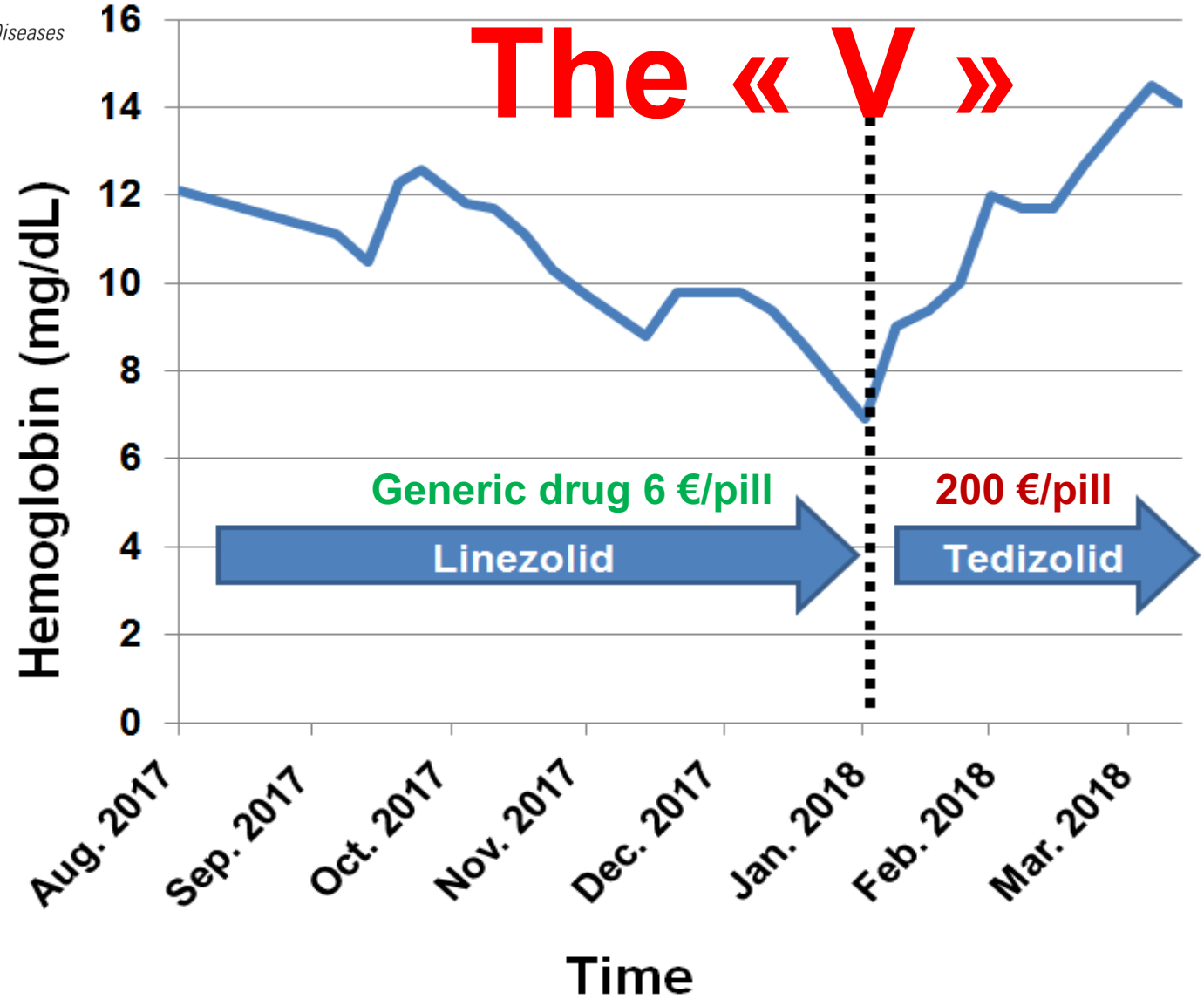


Figure 1. Hemoglobin during time, with continuous decrease under linezolid therapy, followed by a continuous increase after the switch to tedizolid.

Clinical case #1

71-year-old man
Vitiligo, myocardial disease

Chronic relapsing PJI
(resection prosthesis)

Puncture
only suscept
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Favorable outcome at 3 years

X-ray: asymptomatic partial tibial loosening

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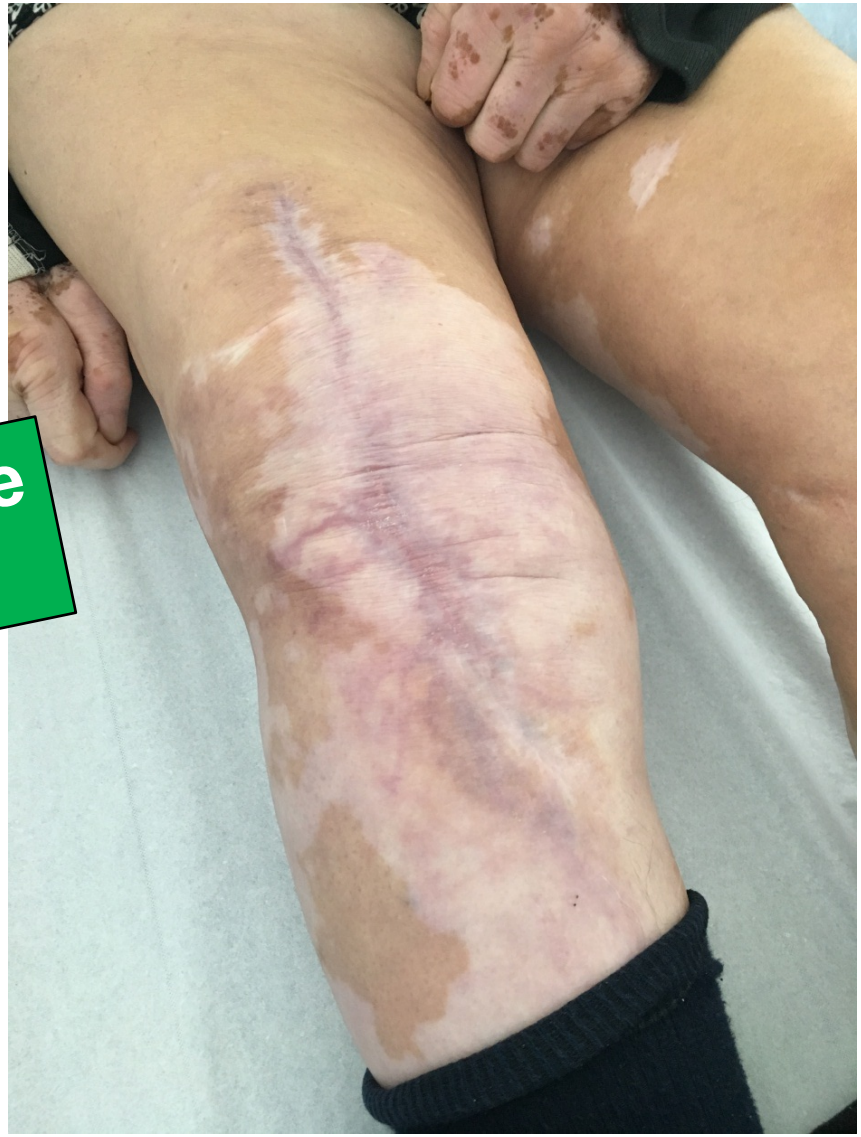

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Ferry T. *et al.*
Open Forum Infectious Diseases 2018

Clinical case #2

82-year-old obese man

Post-operative ***P. aeruginosa*** **PJI** (ciprofloxacin-resistant)

Treated with **iterative 'DAIRs'**, soft-tissue flap and intravenous antibiotics

Worse evolution with necrosis and finally **persistent *P. aeruginosa***

Clinical case #2

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Post-operative ***P. aeruginosa*** **PJI** (ciprofloxacin-resistant)

Treated with **iterative 'DAIRs'**, soft-tissue flap and intravenous antibiotics

Worse evolution with necrosis and finally **persistent *P. aeruginosa***

PRO

Explantation **to cure** but associated with a **considerable loss of function**

VS.

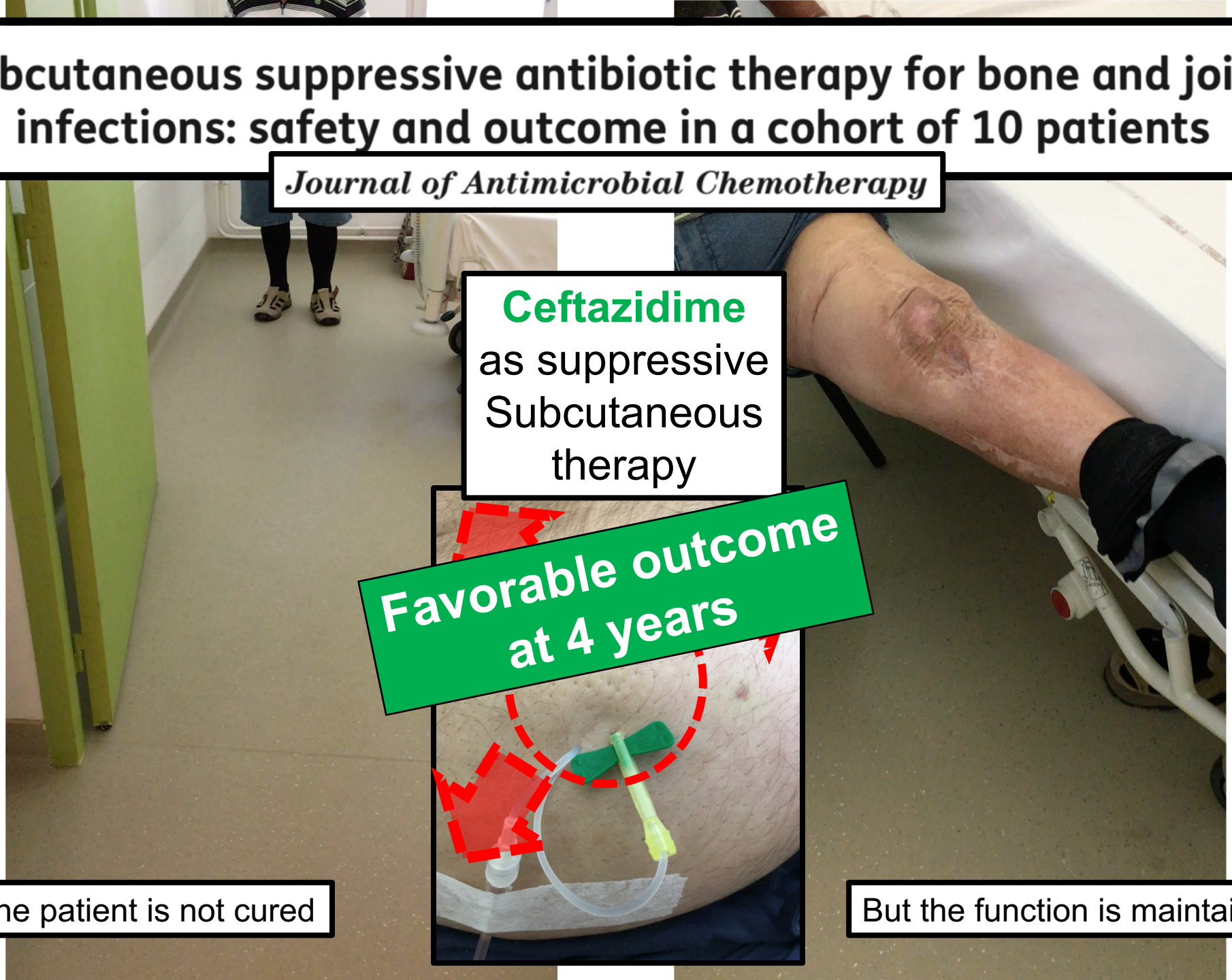
CON

Last DAIR + Necrosis resection + Dermal substitute + Primary ATBx Then

SAT

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

Journal of Antimicrobial Chemotherapy



Ceftazidime as suppressive Subcutaneous therapy

Favorable outcome at 4 years

The patient is not cured

But the function is maintained

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

Journal of Antimicrobial Chemotherapy

Salvage (exceptional) option
Elderly patients
Implant-associated infections
with **resistant pathogens**
Explantation is not reasonable

Ceftazidime (n=1)
Ceftriaxone (n=2)
Ertapenem (n=7)

Median follow-up >12 months

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

Journal of Antimicrobial Chemotherapy

PK-based suppressive therapy SC injection each 48h

Salvage (exceptional) option
Elderly patients
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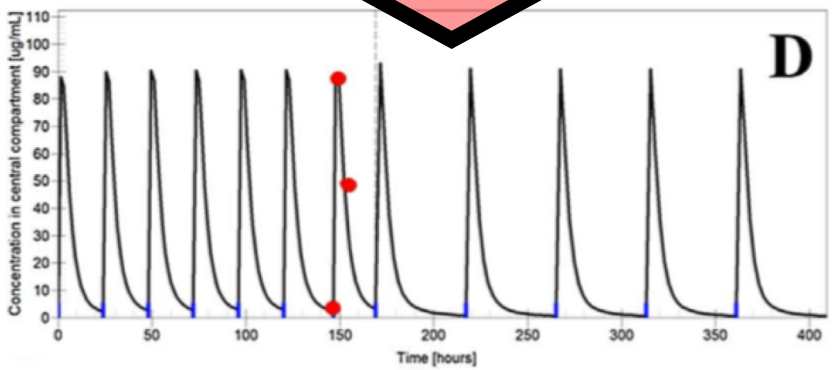
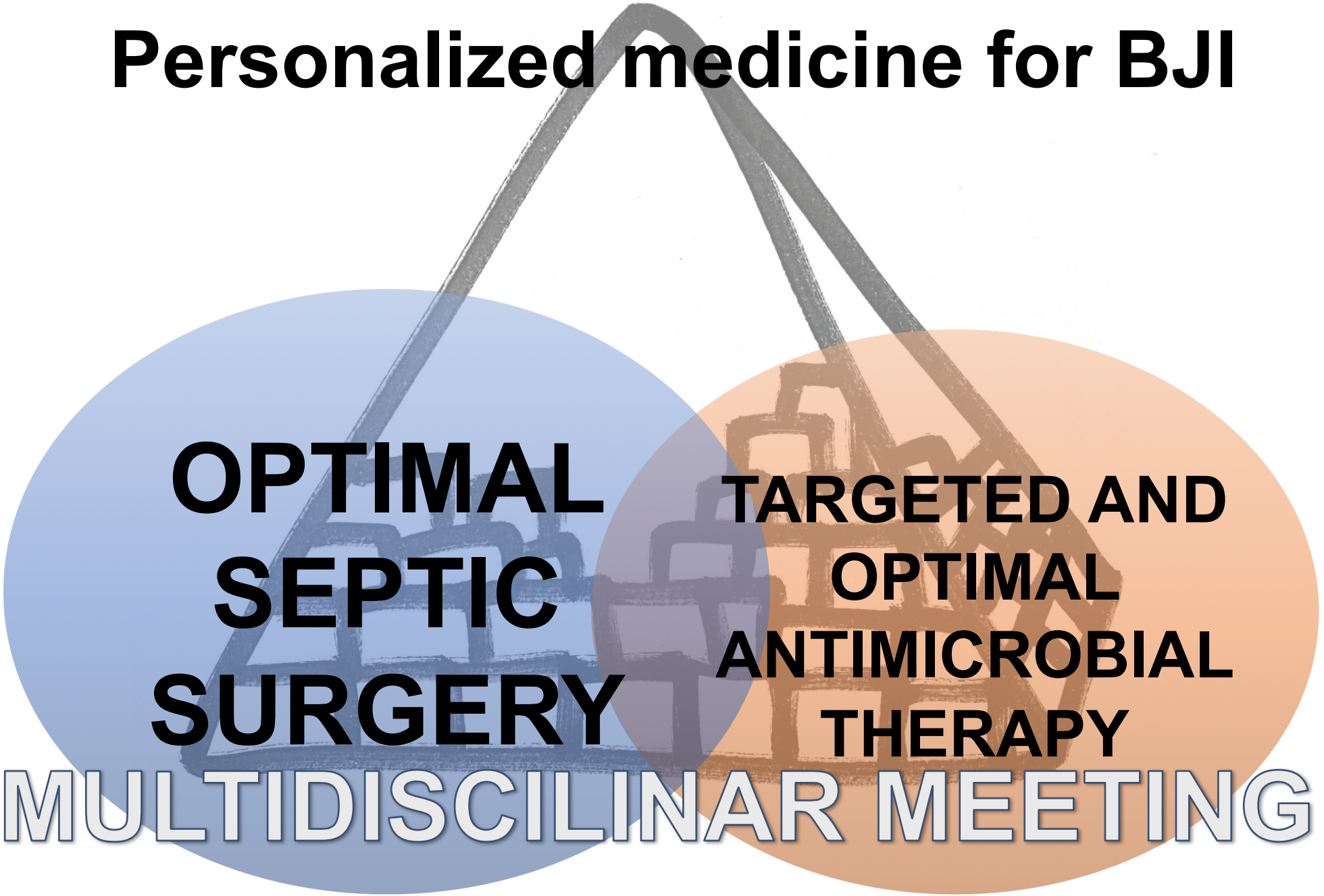


Lyon BJI Study group 2020

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

Personalized medicine for BJI



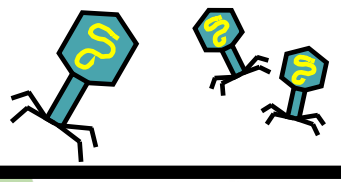
Personalized medicin

AntibioticS-loaded PMMA cements

Antibiotic-loaded bone substitutes

ADJUVANT INNOVATIVE ANTI-INFECTIVE AGENTS

Bacteriophages



Bacteriophage-derived lysins

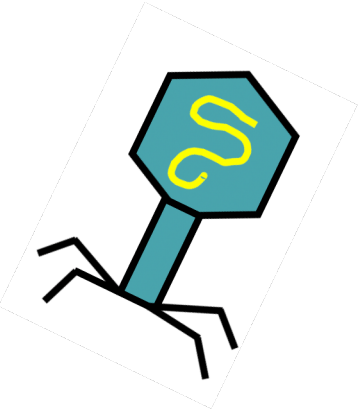
New antibiotics targeting the biofilm

OPTIMAL SEPTIC SURGERY

TARGETED AND OPTIMAL ANTIMICROBIAL THERAPY

MULTIDISCILINAR MEETING

What is a « bacteriophage » ?

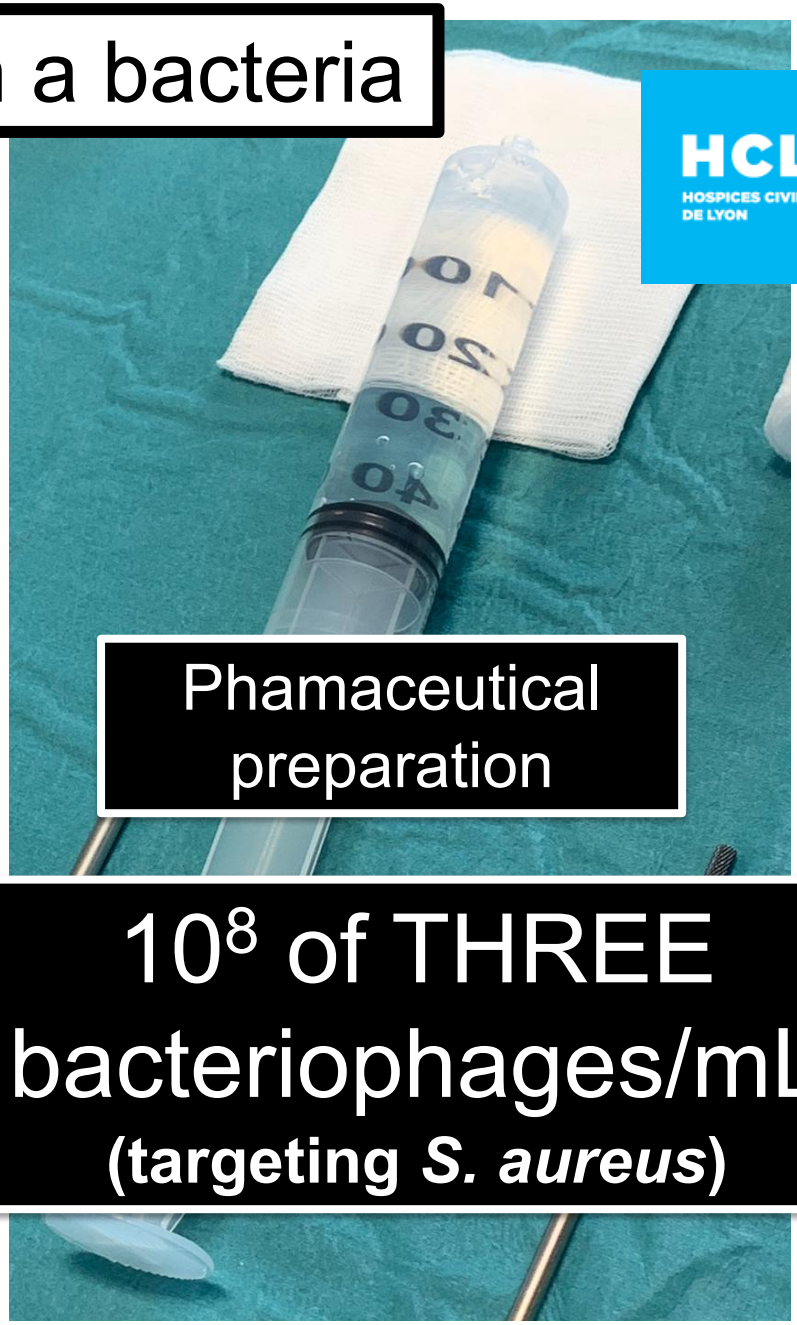


- Suffix –phage, *phagos* φαγεῖν (*phagein*), "to eat", “to devour"
- **Viruses that infect ONLY bacteria**
- Classification (*myoviridae, podoviridae, etc…)*
- **A phage is specific to A TYPE of bacteria**
- **Largely abundant in the biosphere: 10^{31} bacteriophages on the planet, more than every other 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

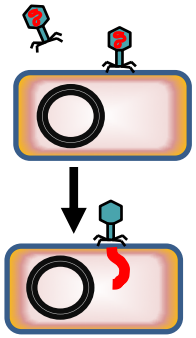
X million of ≠ Bactériophage**S** !!!
(targeting environmental bacteria)



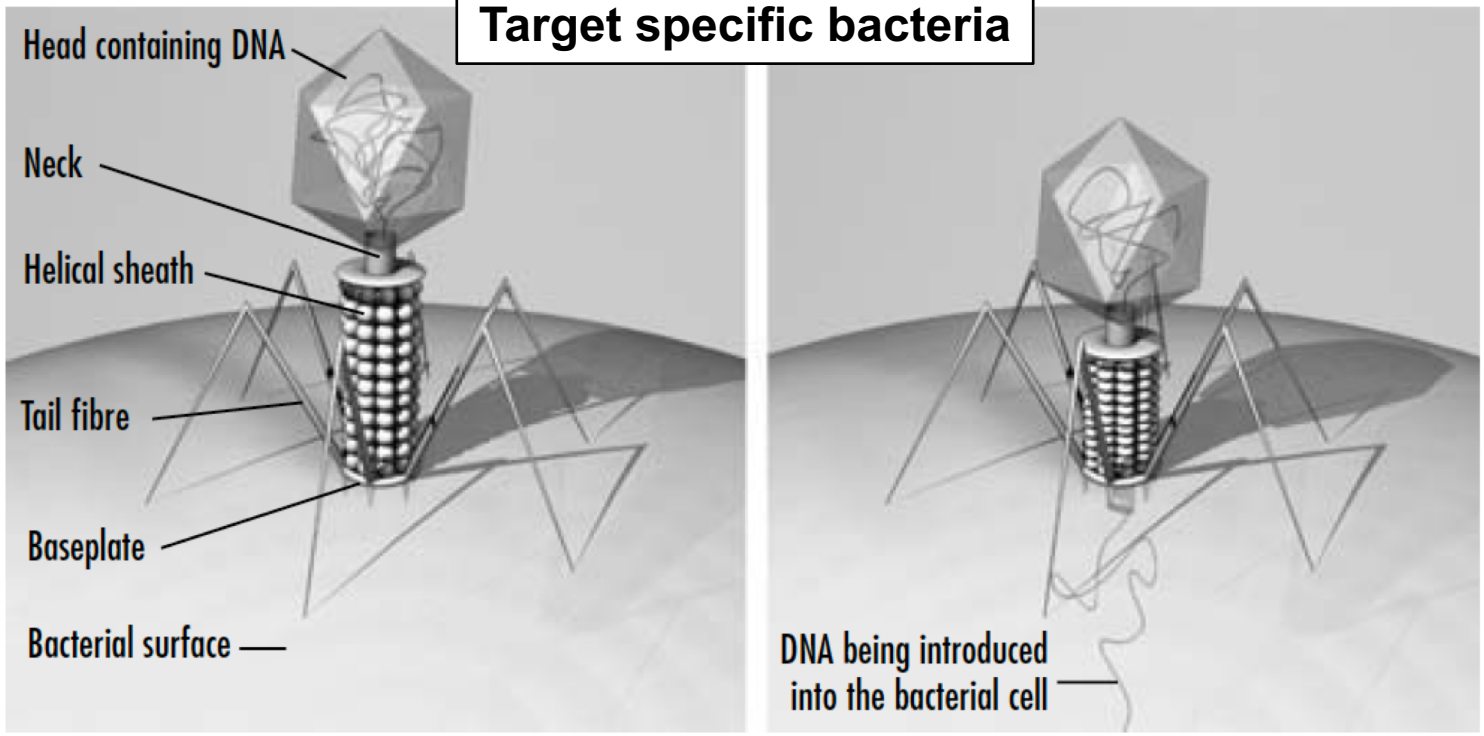
Phamaceutical preparation

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

Ferry T.



Environmental viruses
Target specific bacteria



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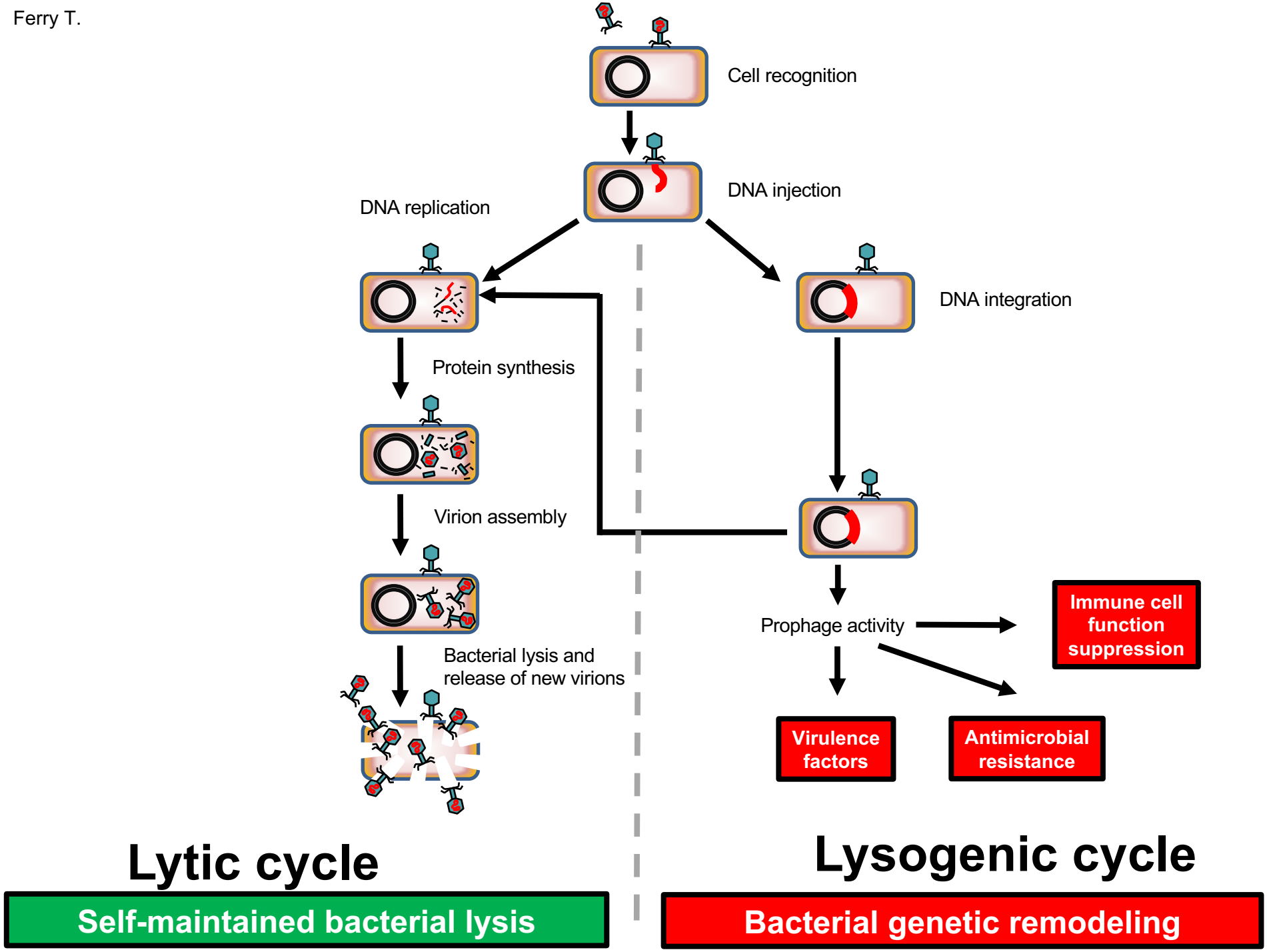
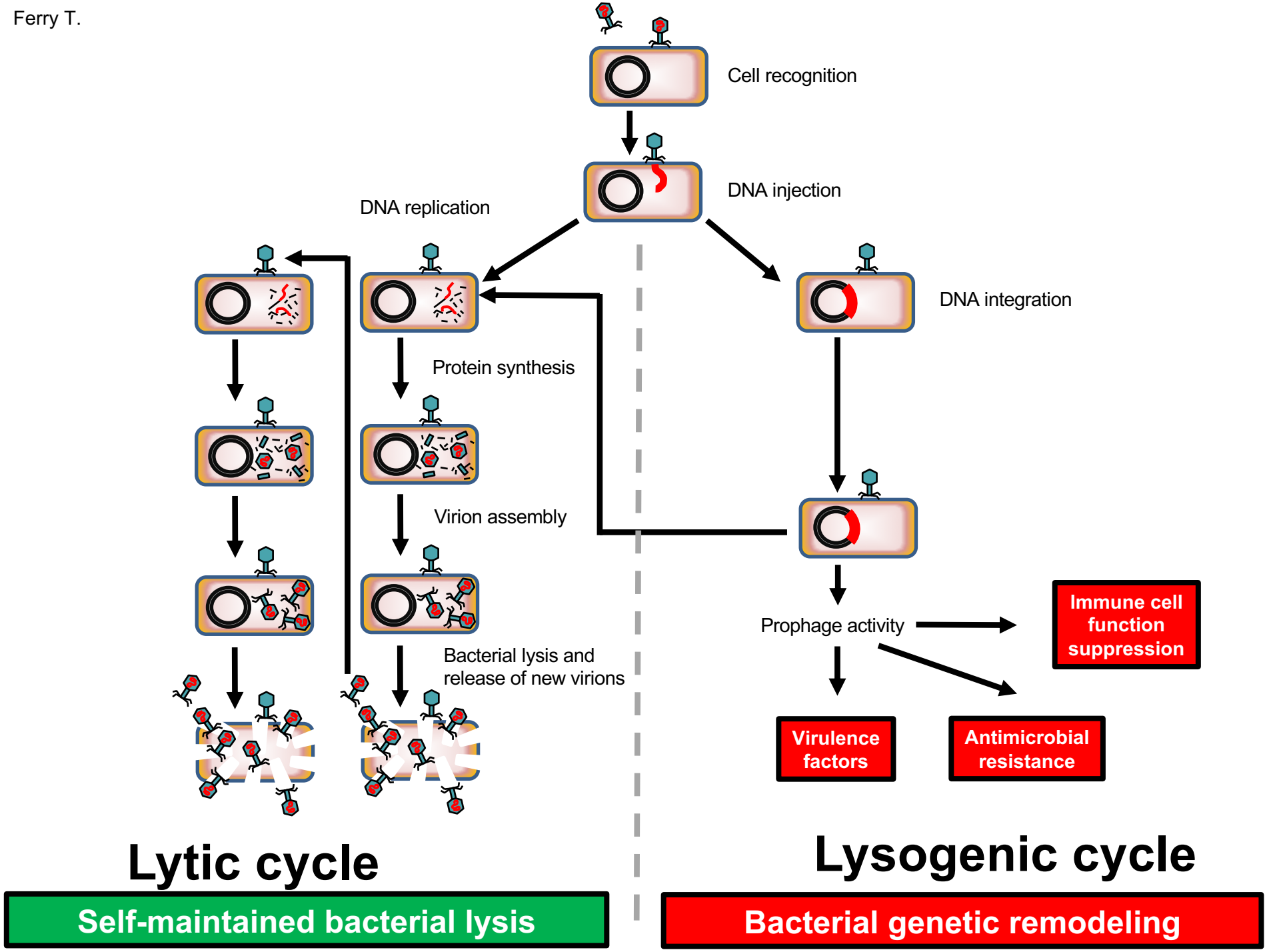

Cell recognition
DNA injection
DNA replication
DNA integration
Protein synthesis
Virion assembly
Bacterial lysis and release of new virions
Prophage activity
Immune cell function suppression
Virulence factors
Antimicrobial resistance
Lytic cycle
Lysogenic cycle
Self-maintained bacterial lysis
Bacterial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

Ferry T.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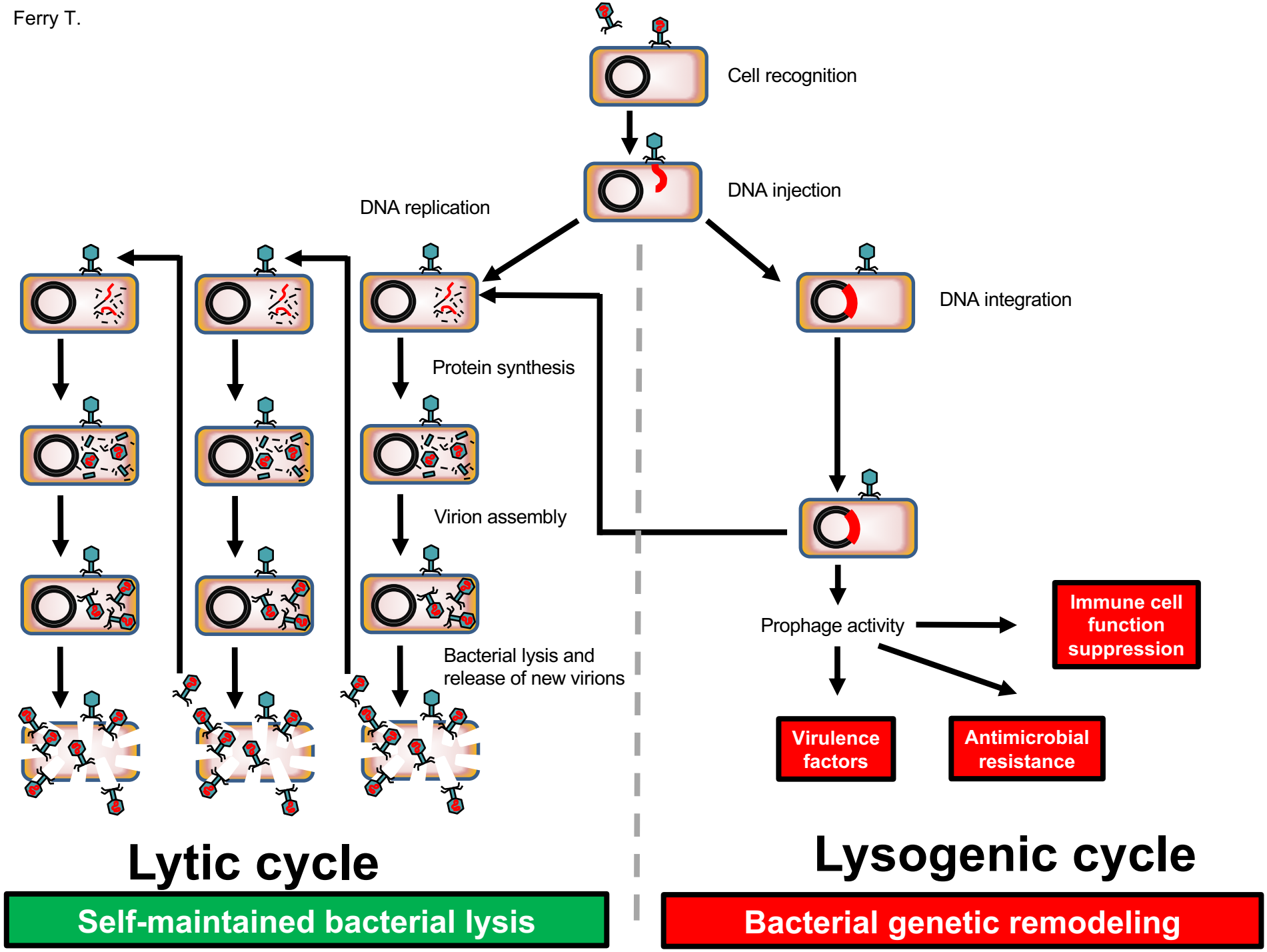
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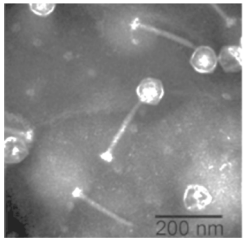
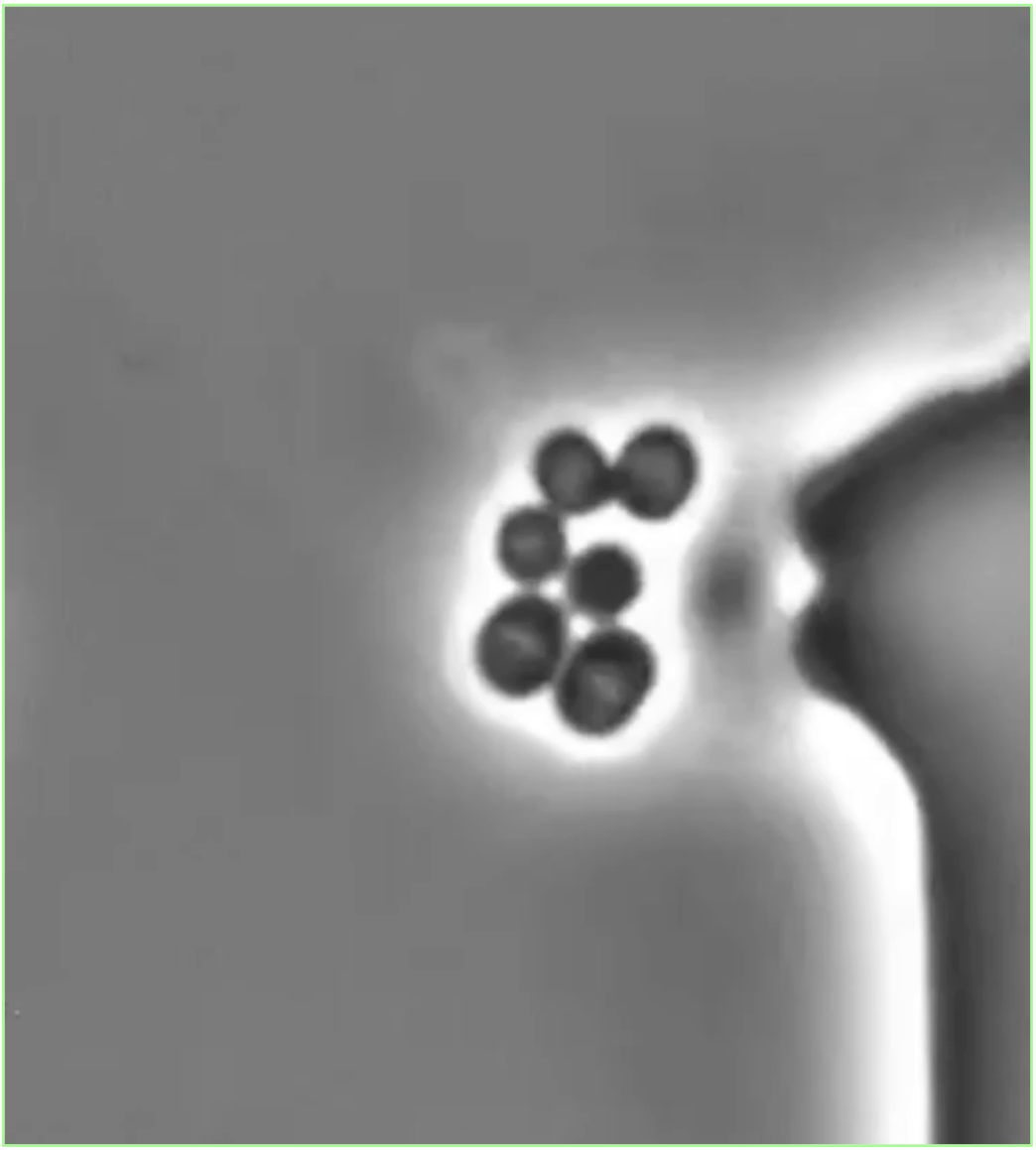
Lysogenic cycle
Self-maintained bacterial lysis
Bacterial genetic remodeling

A clear antibacterial activity!

S. aureus being lysed by the Sa2 phage



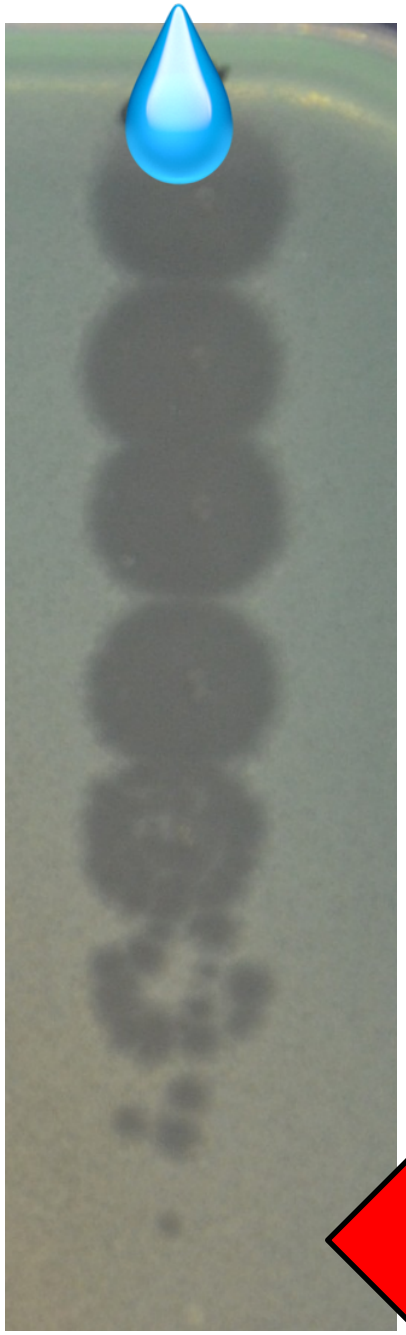
Bacterial DNA appeared in green



Courtesy Pascal Maguin
Luciano Marraffini Lab
THE ROCKEFELLER UNIVERSITY

A clear antibacterial activity!

Phagogram



Phage

10^{10}

10^{9}

10^{8}

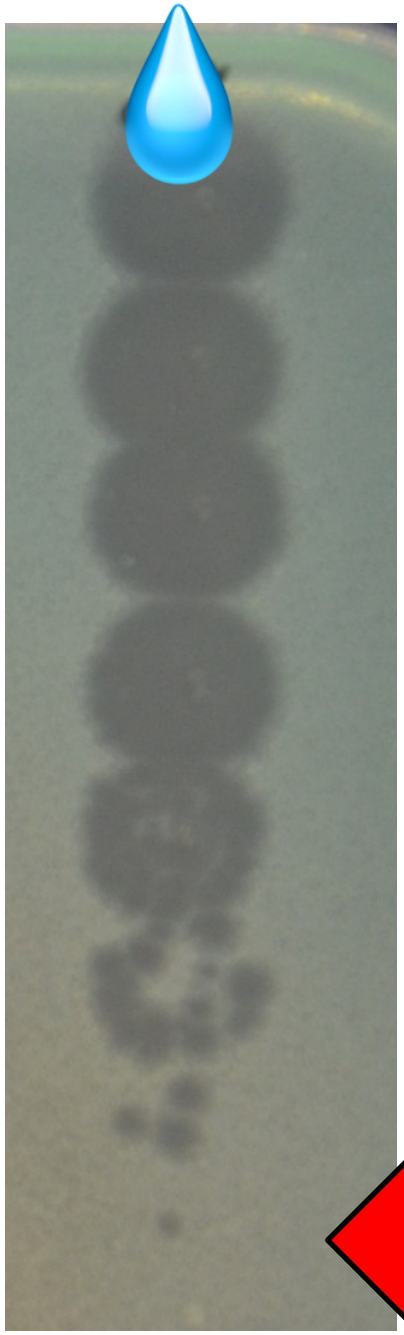
10^{7}

10^{6}

10^{5}

PFU/mL

S. aureus culture on a gelosis



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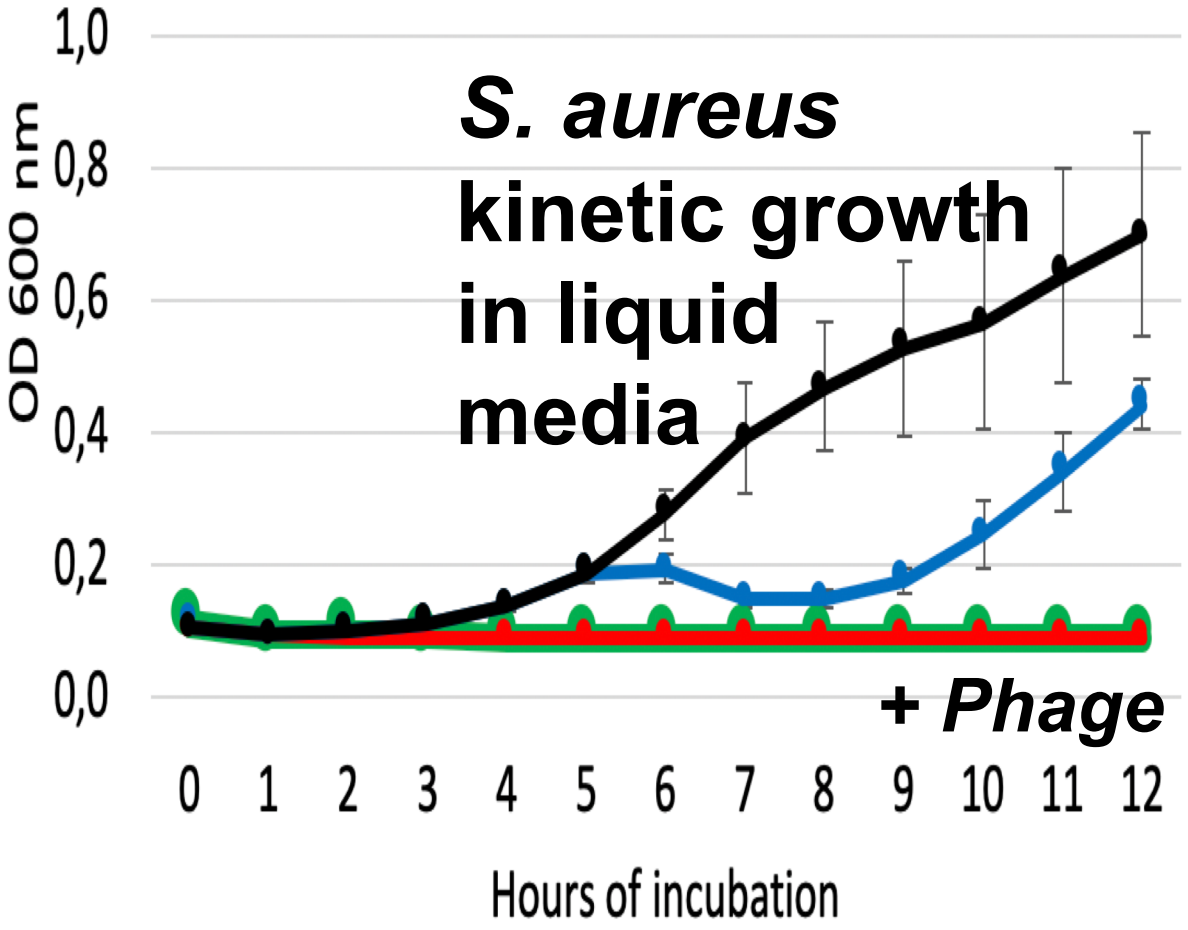
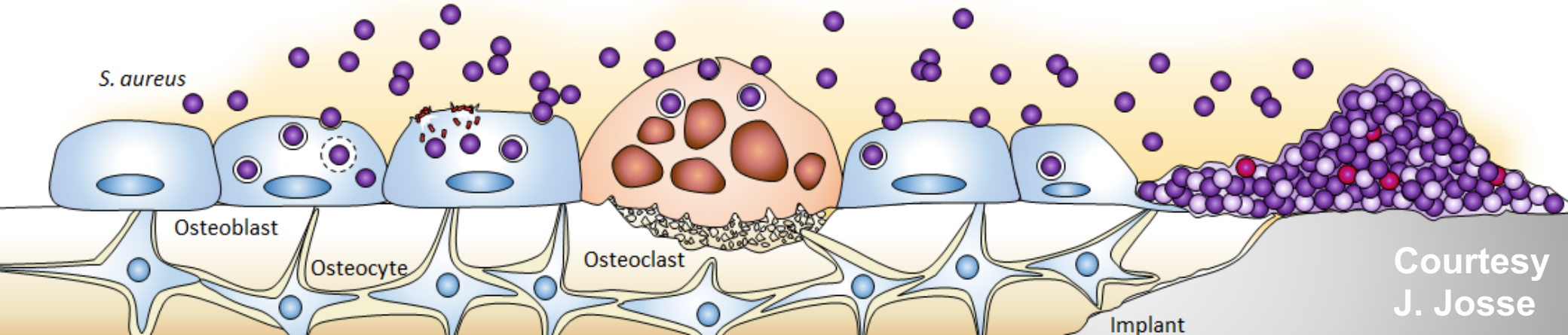


S. aureus culture on a gelosis

Persisters in chronic BJI

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



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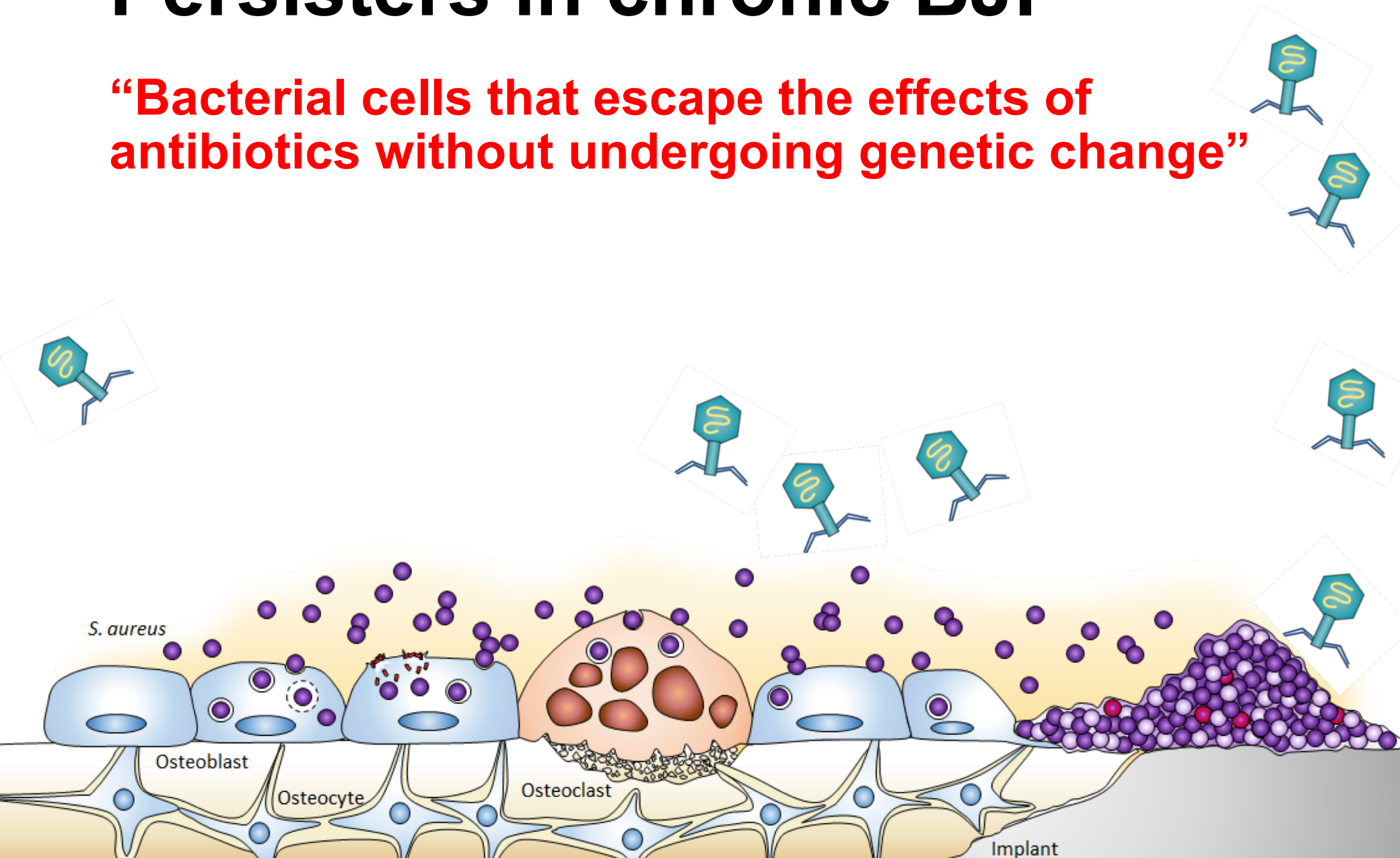
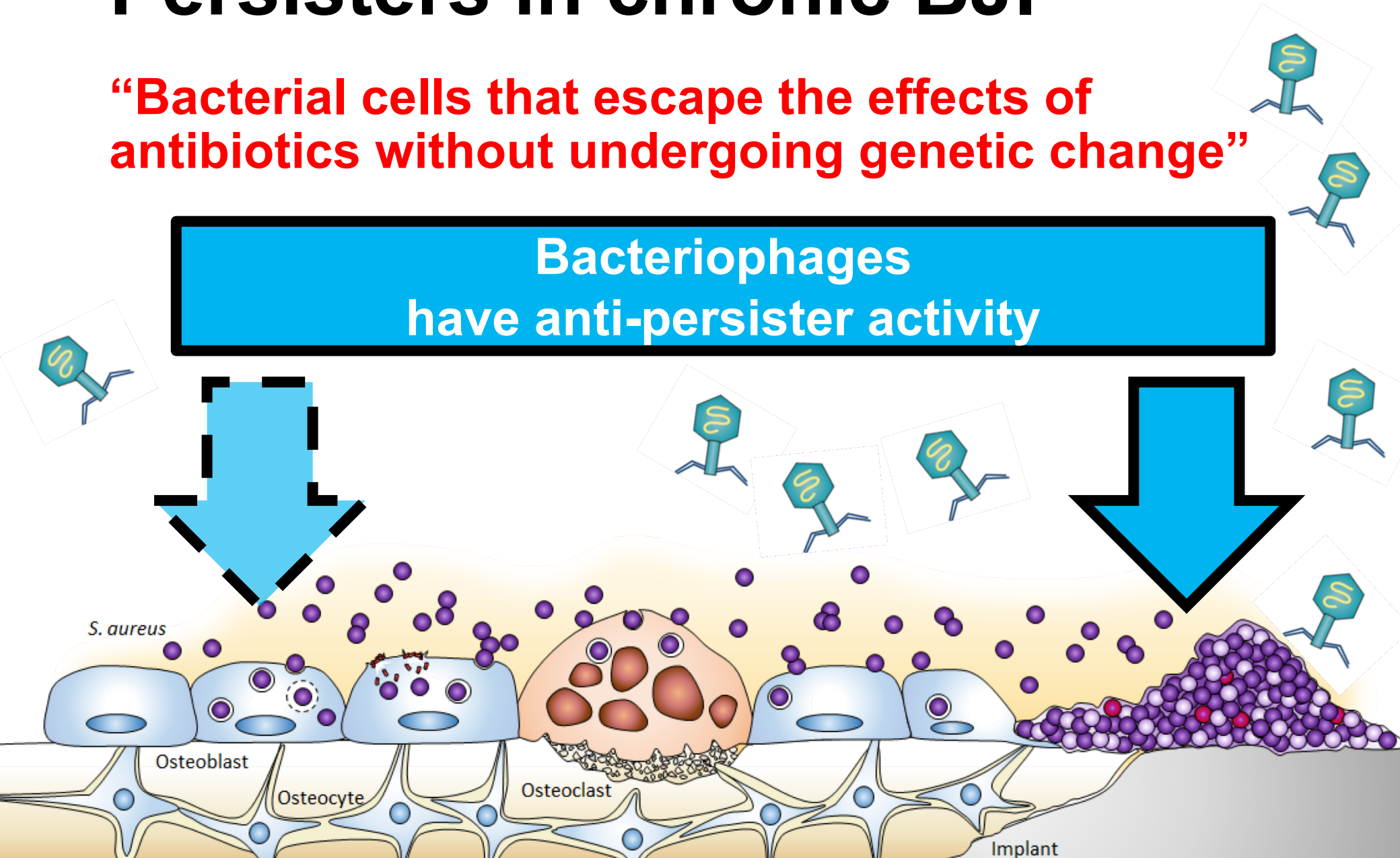


Persisters in chronic BJI

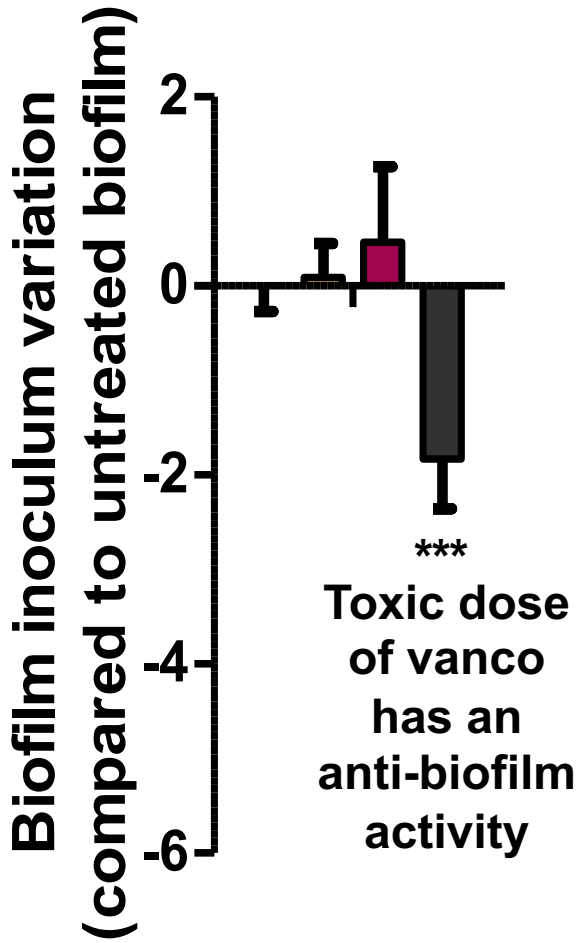
"Bacterial cells that escape the effects of antibiotics without undergoing genetic change"

Bacteriophages have anti-persister activity



C. Kolenda et al. Antimicrob Agents Chemother 2019

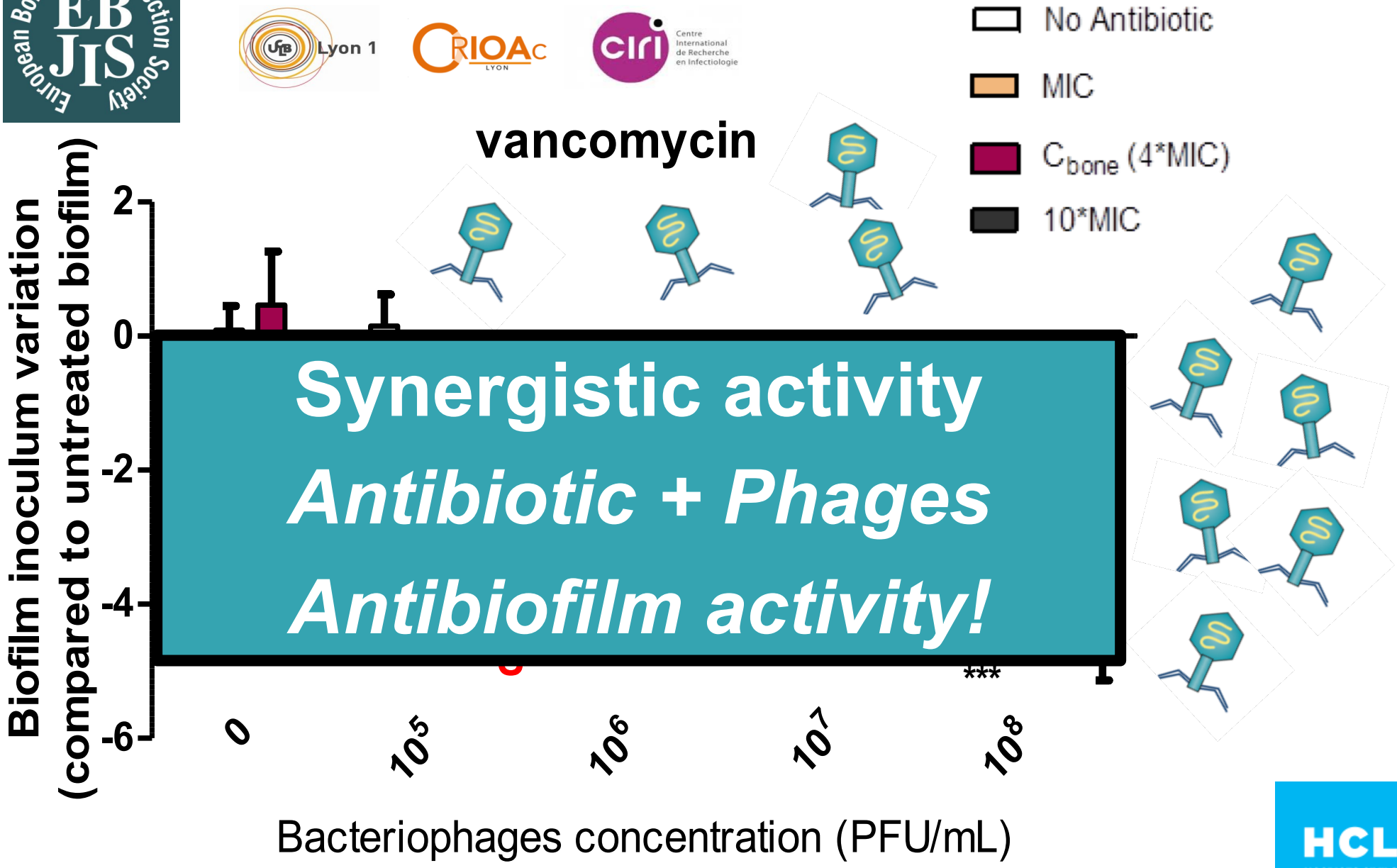
vancomycin



Toxic dose of vanco has an anti-biofilm activity

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

C. Kolenda et al. Antimicrob Agents Chemother 2019

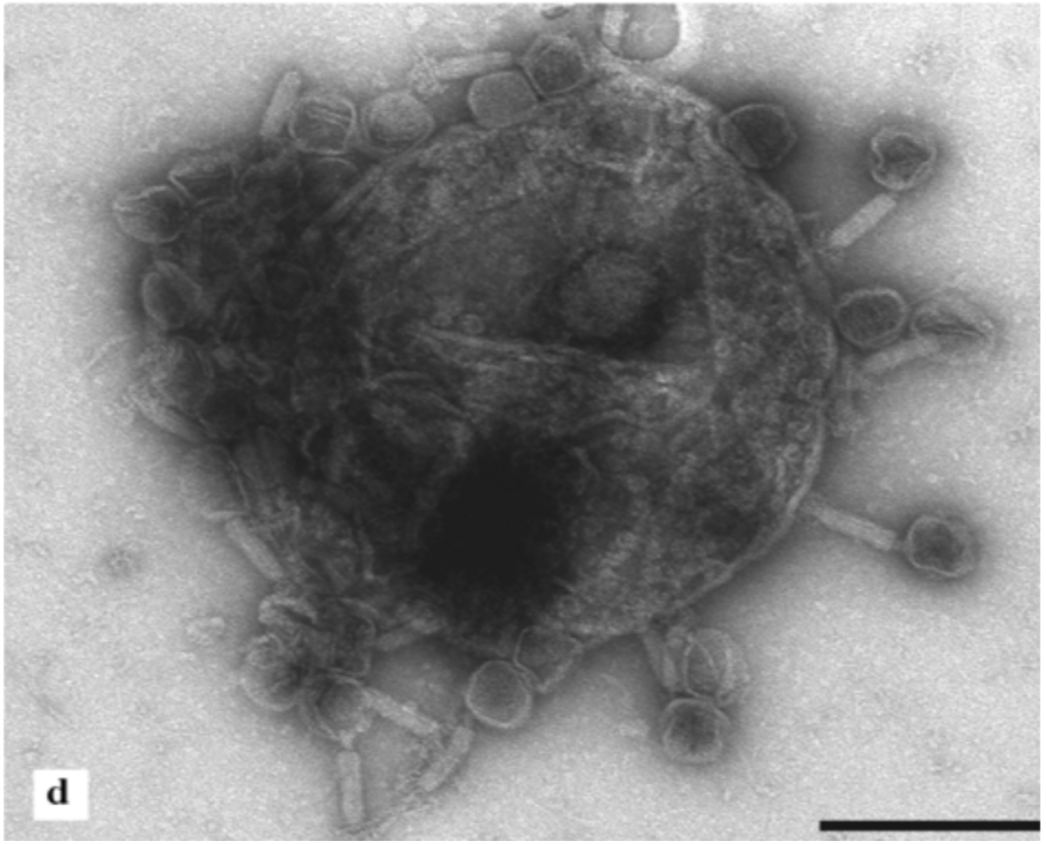


Cocktails produced in 2020 by the Eliava Institute

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

T. Ferry

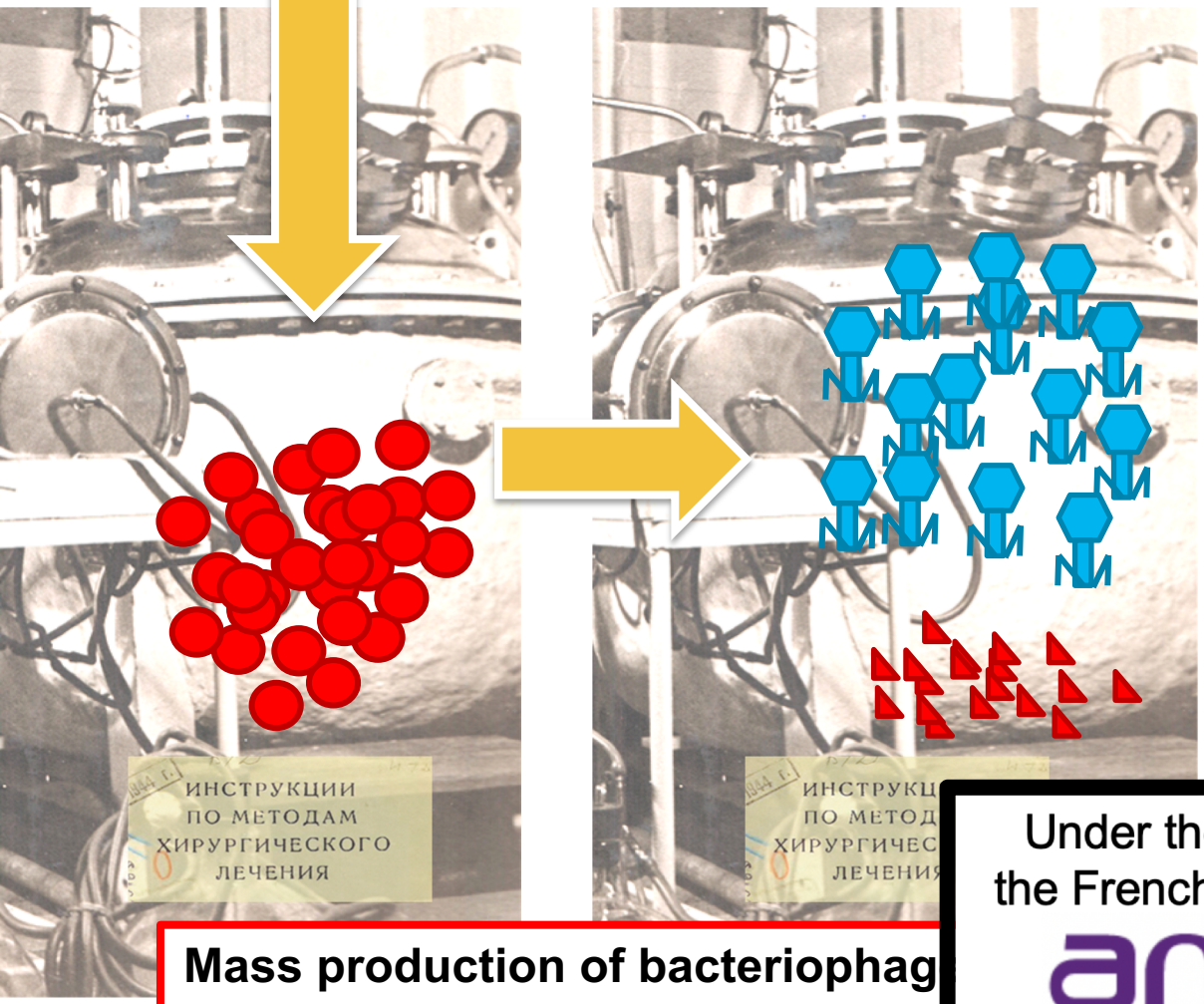
Bacteriophage ISP (*Myoviridae*)



Merabishvili et al. PloS ONE 2009

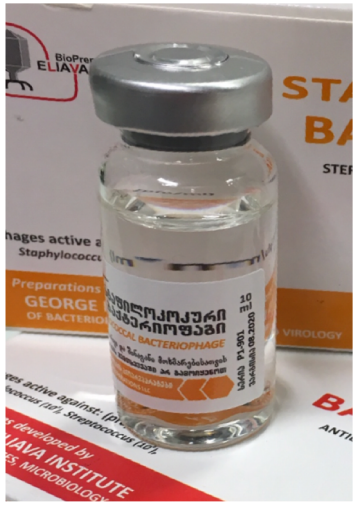
T. Ferry. *The story of Phage therapy*

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*

Clinical case #3

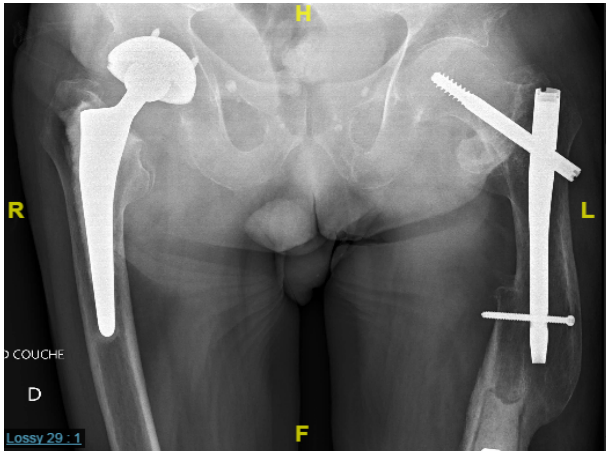
80-year-old man

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

<u>Failure</u> under <u>SAT</u>

Complex orthopaedic situation with past femoral fracture

Impossible to walk (painful knee)




Septic arthritis


Fistula and purulent discharge

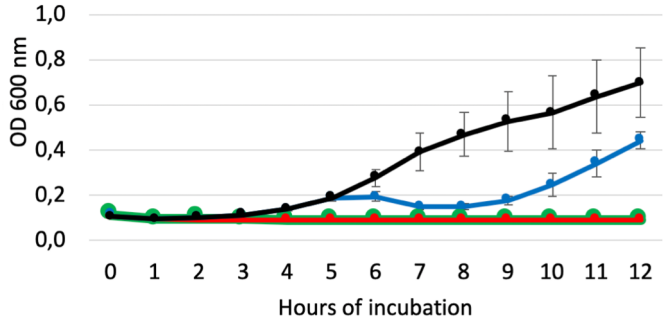
Clinical case #3

Amputation
(but not feasible !) ?

<u>Doing nothing</u>, but poor clinical situation with **<u>risk of complication and death</u>**

<u>Conservative surgery</u>
"Debridement And Implant Retention" (DAIR) +
<u>innovative approach to disrupt biofilm</u>
+
<u>SAT</u>

Lyon Phage team



Phagogram
Selection of active bacteriophages

ID Clinic

HCL HOSPICES CIVILS DE LYON

CRIOAc LYON

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

Surgery

HCL HOSPICES CIVILS DE LYON

Lab

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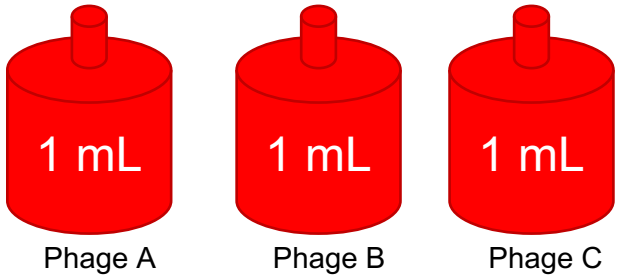
Active GMP

***S. aureus* Bactériophages**



Under the supervision of

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Agence nationale de sécurité du médicament et des produits de santé

French Health Authority

Pharmacy

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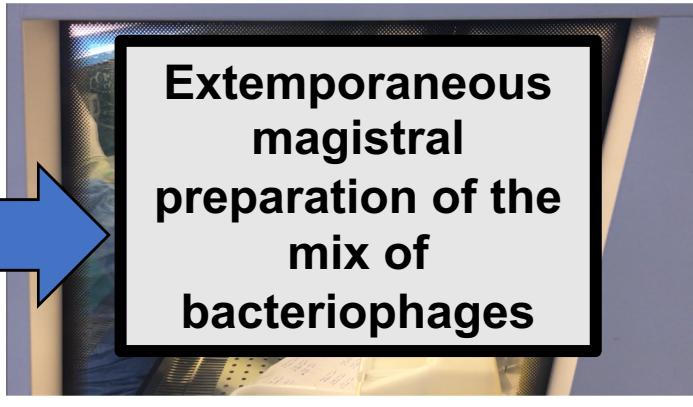
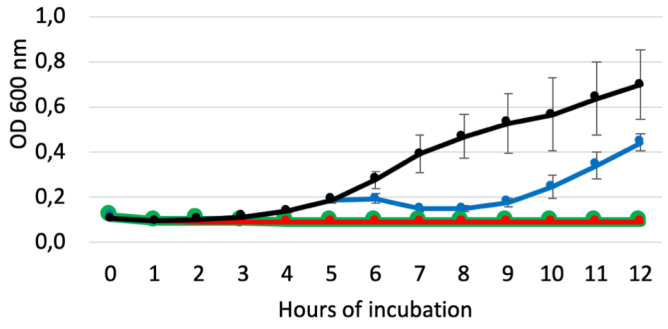


Extemporaneous magistral preparation of the mix of bacteriophages

Lyon Phage team



Phagogram
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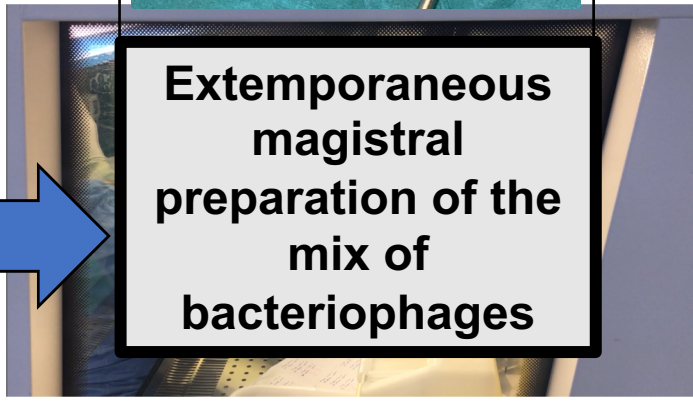
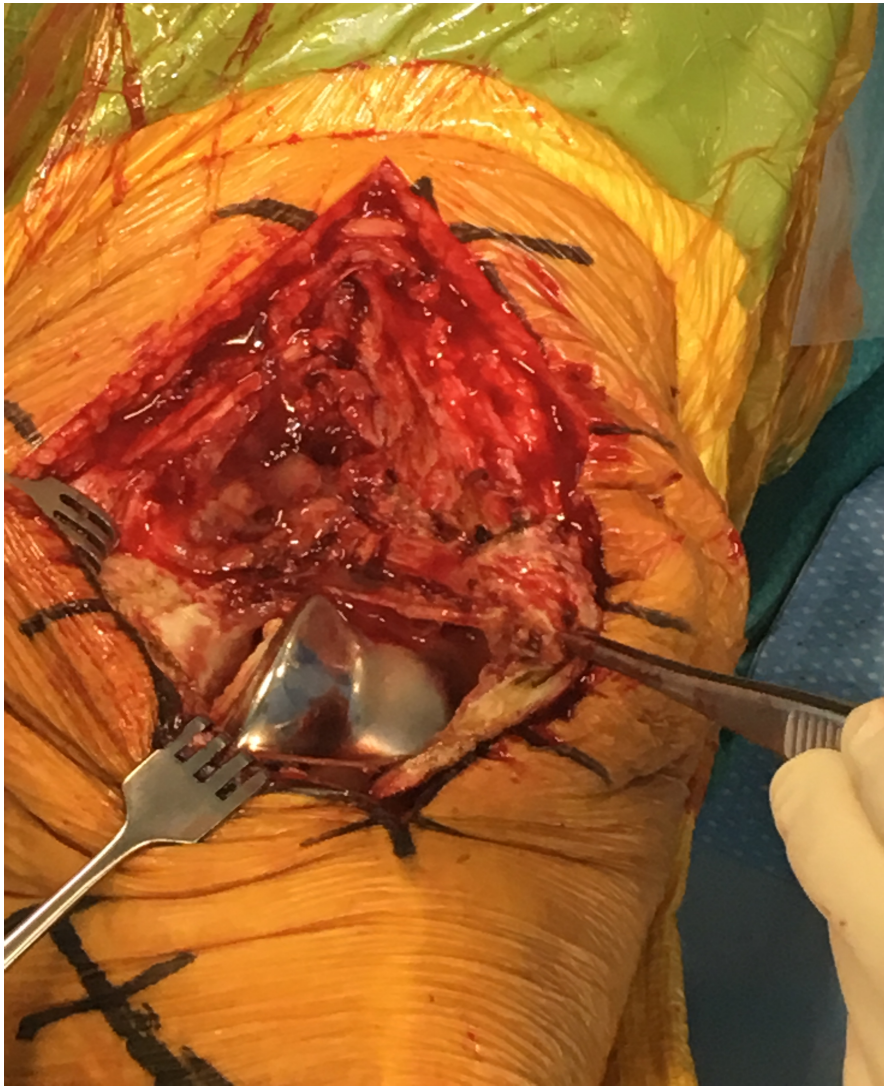


Extemporaneous magistral preparation of the mix of bacteriophages



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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.

‘Debridement And Implant Retention’ (DAIR) with local administration of personalized cocktail of bacteriophages (PhagoDAIR) followed by suppressive antibiotherapy as salvage therapy in four patients with relapsing prosthetic knee infection

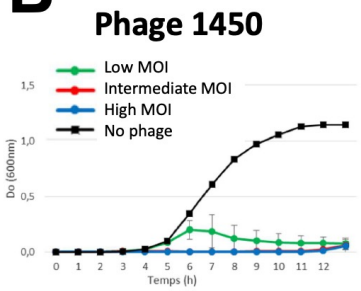
Phago DAIR

CRIOAc LYON

A

Left PKI with purulent joint effusion

B



Phagogram (Killing assay)

D

Favorable outcome at 1 year

Submitted
30th ECCMID
Paris, France
18 –21 April 2020

PHERECYDES PHARMA

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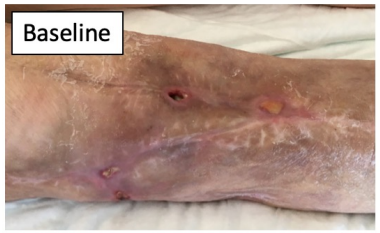
Conclusions: Personalized bacteriophage therapy has the potential to be used as salvage therapy during DAIR in patients with relapsing *S. aureus* and *P. aeruginosa* prosthetic knee infection, **to improve the efficacy of suppressive antibiotics, and to avoid considerable loss of function.**

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

A

B

C



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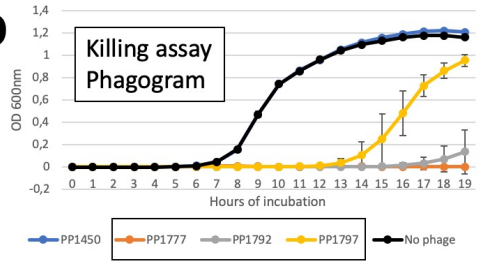
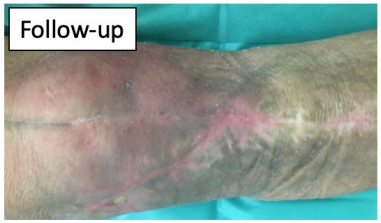


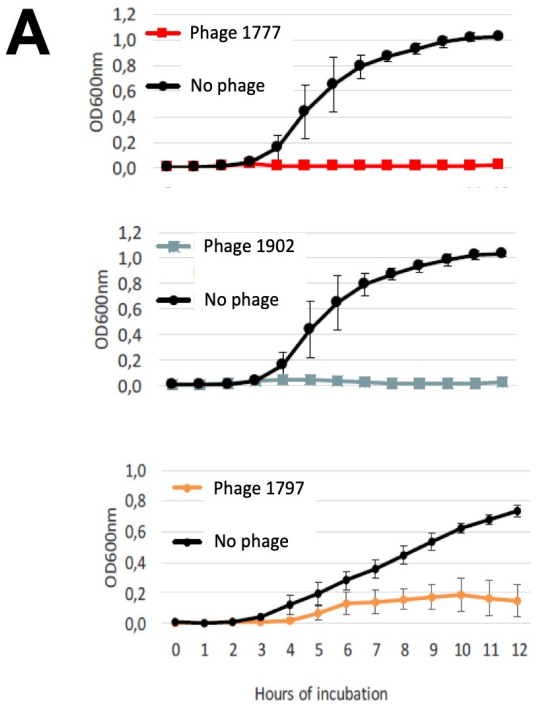
E

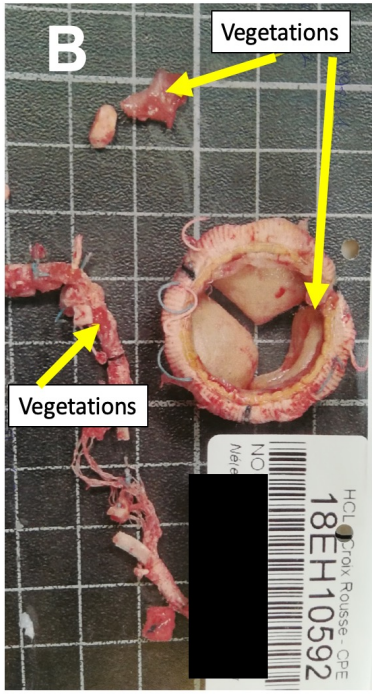


Submitted
30th ECCMID
Paris, France
18 –21 April 2020

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 <u>two</u> cases





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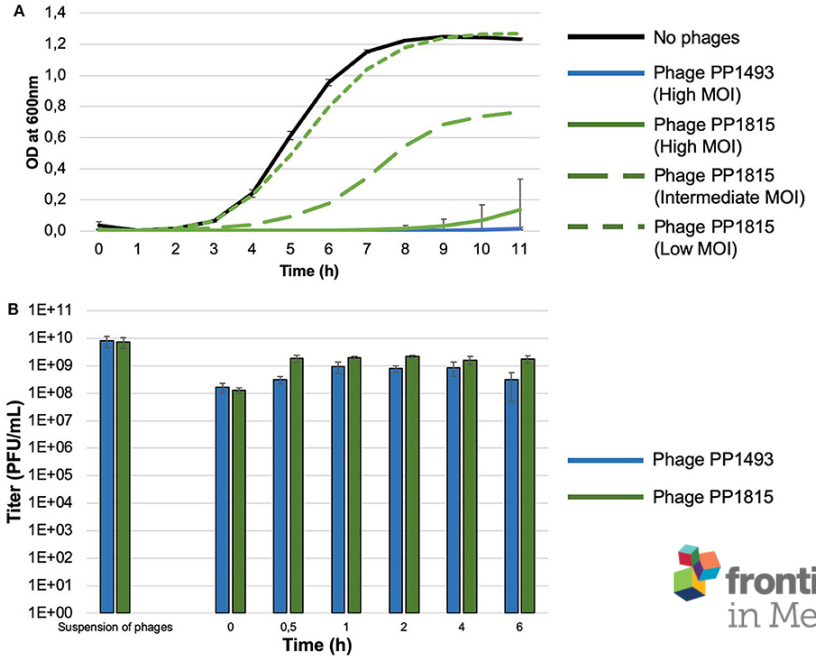
Conclusions: **The type of filter used for the magistral preparation and the duration of the perfusion influenced the phage titer, as the titer in the patient's blood.** Personalized GMP bacteriophage therapy has the potential to be used as salvage therapy of *P. aeruginosa* intravascular implant infections.

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*



frontiers in Medicine

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

Tristan Ferry ✉, Fabien Boucher, Cindy Fevre, Th
Jérôme Josse, Christian Chidiac, Guillaume L'hos

Journal of Antimicrobial Chemotherapy, Volume

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

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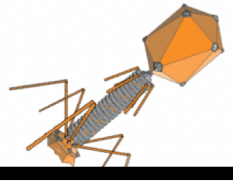
Open Forum Infectious Diseases

BRIEF REPORT



Salvage Debridement
Implant Retention ("
Local Injection of a S
of Bacteriophages: Is
an Elderly Patient Wi
Staphylococcus *aureu*
Infection?

Ferry T. 2018

Phage therapy as adjuvant to conservative surgery and antibiotics to salvage patients with relapsing S. aureus prosthetic knee infection

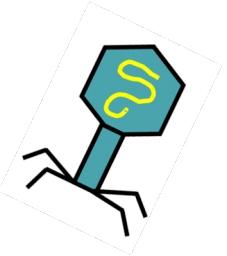
frontiers

Tristan Ferry[1*], Camille Kolenda[1], Cécile Batailler[1], Claude-Alexandre Gustave[1], Sebastien Lustig[1], Matthieu Malatray[1], Cindy Fevre[2], Jérôme JOSSE[1], Charlotte Petitjean[1], Christian Chidiac[1], Gilles Leboucher[1], Frederic Laurent[1]

Conclusion

- **Suppressive antimicrobial therapy (SAT)**
  - **May help to keep the function** in patients with PJI
  - But limited number of conventional drugs are available
  - **Major role of ID physician** and **multidisciplinary approach**
  - New oral (tedizolid) or intravenous (long acting ATBx) drugs are promising
  - Subcutaneous SAT is also an (exceptional) option

- **Phage therapy seems to be relevant for PJI**
  - **"PhagoDAIR" procedure** implemented in CRIOAc Lyon
  - Relapsing patients, for whom phages facilitated the efficiency of SAT
  - **12 patients with PJI (among 16 treated with phages)**
  - At this time only *S. aureus* and *P. aeruginosa* could be targeted
  - **Need for national phage center** (in each country?)
  - Crucial need for academic and private collaborations with national health authorities
  - **Clinical trials have to be performed to demonstrate a potential benefit of phage therapy in less severe patients**



Lyon BJI Study group

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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

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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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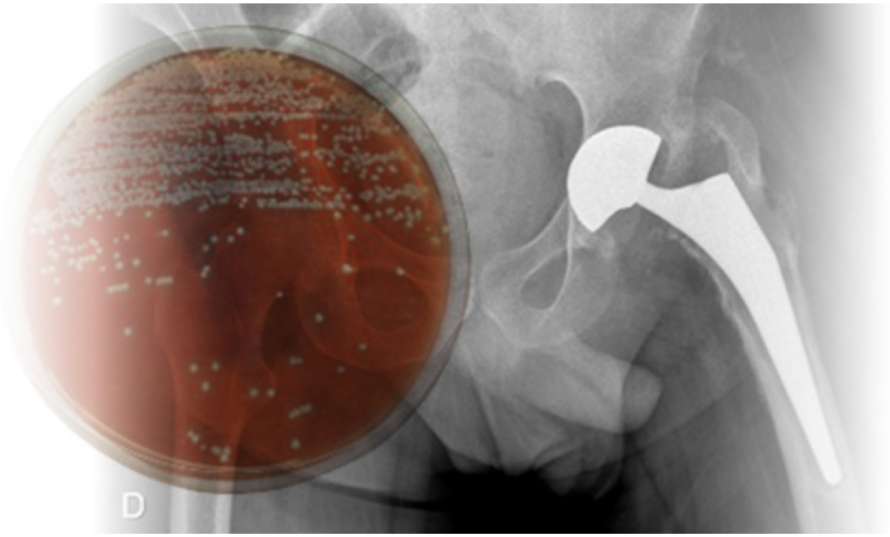
http://www.crioac-lyon.fr



- Published cases
- Open acces studies in pdf
- All thesis in pdf
- All recommendations
- **Newsletter**

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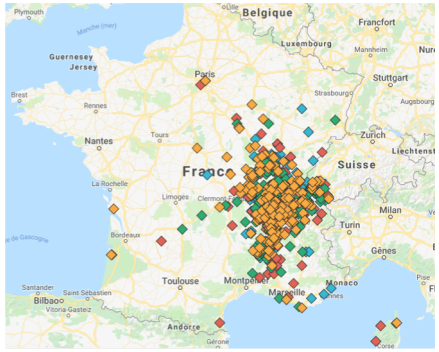

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