

Innovations thérapeutiques dans la prise en charge des IOA complexes

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)

Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Intervenant : Tristan Ferry

Innovations thérapeutiques dans la prise en charge des IOA complexes

L'orateur ne souhaite pas répondre

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- Conférencier ou auteur/rédacteur rémunéré d'articles ou documents
- Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations
- Investigateur principal d'une recherche ou d'une étude clinique

OUI NON

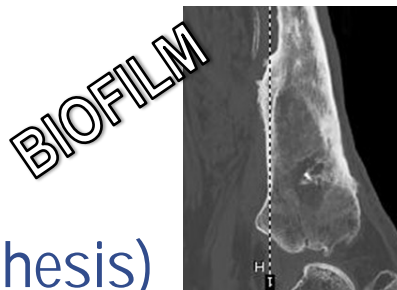
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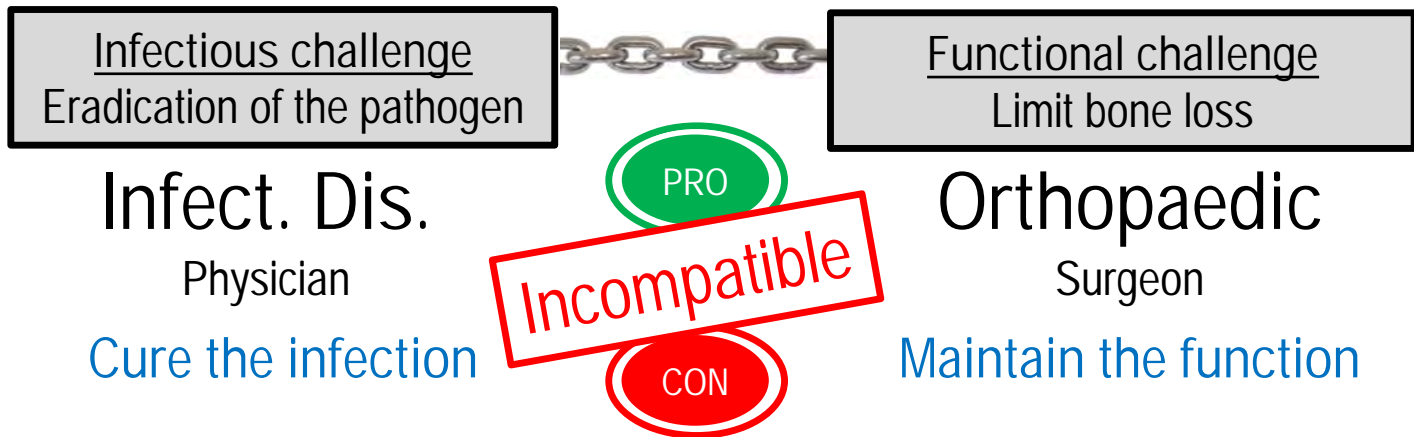
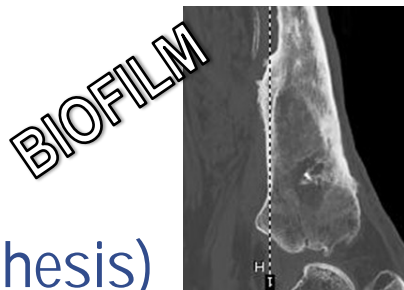
Chronic bone and joint infection

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

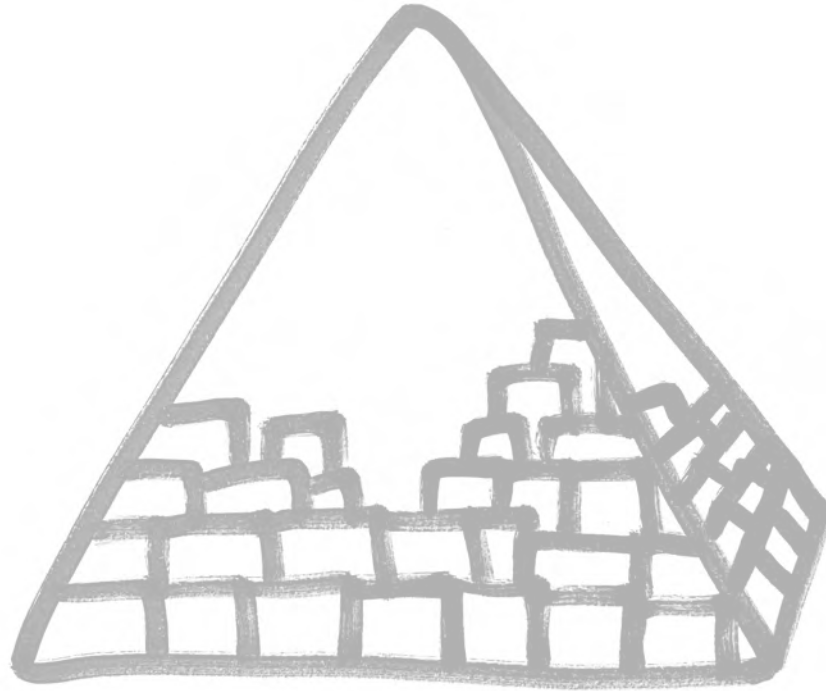


Chronic bone and joint infection

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- Sequestrum in chronic osteomyelitis
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Personalized medicine for BJI

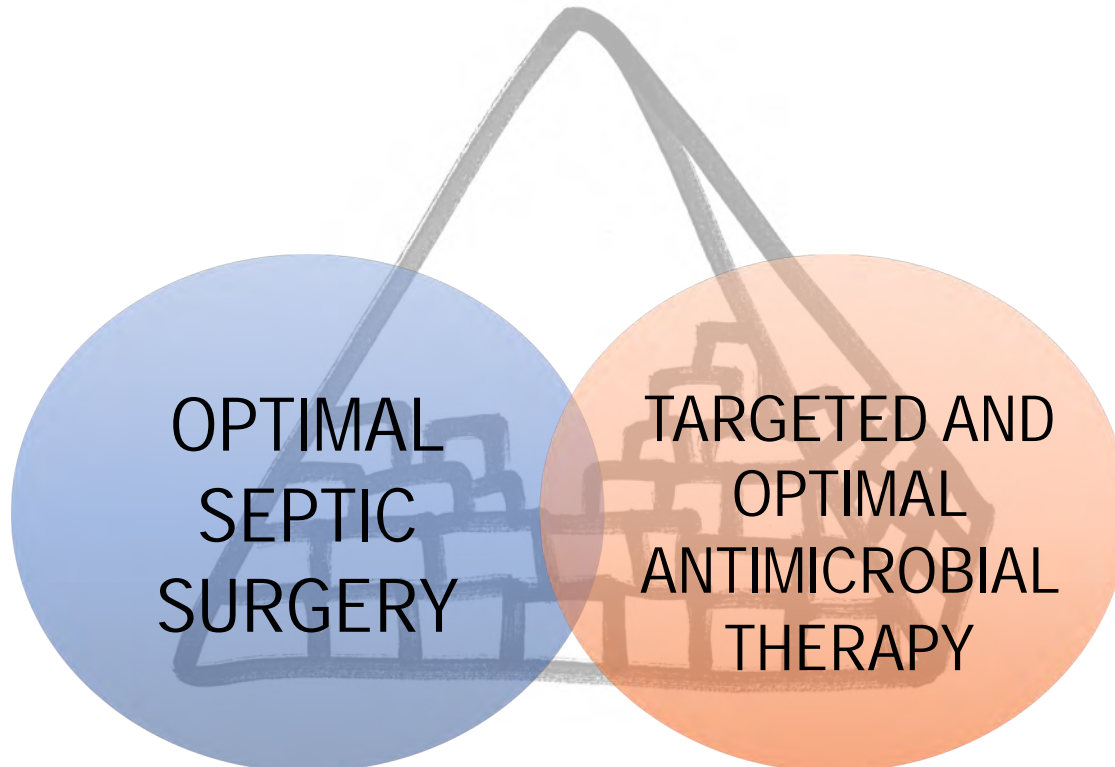


Personalized medicine for BJI

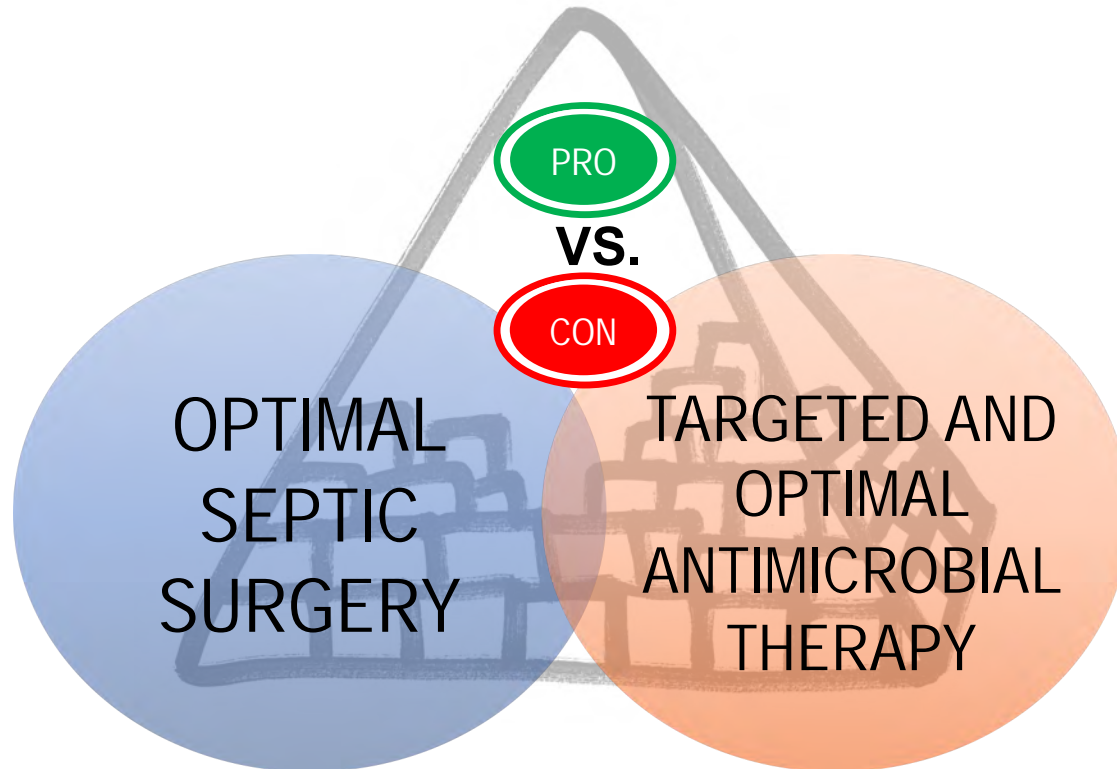


OPTIMAL
SEPTIC
SURGERY

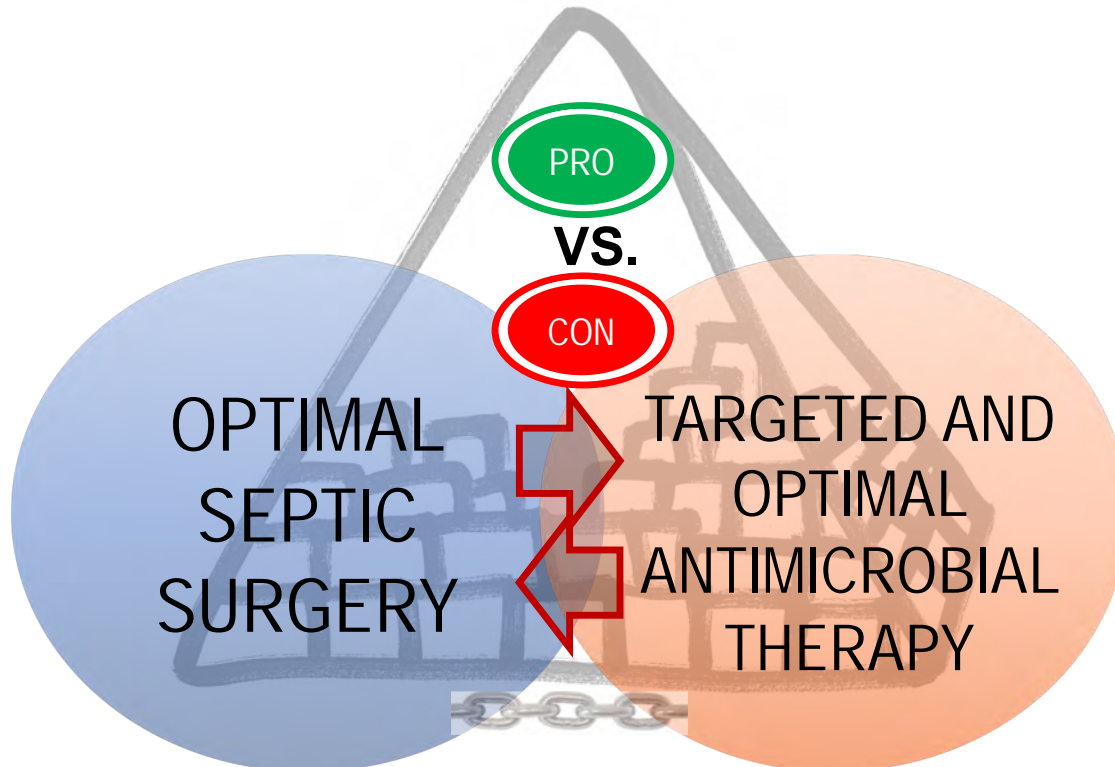
Personalized medicine for BJI



Personalized medicine for BJI

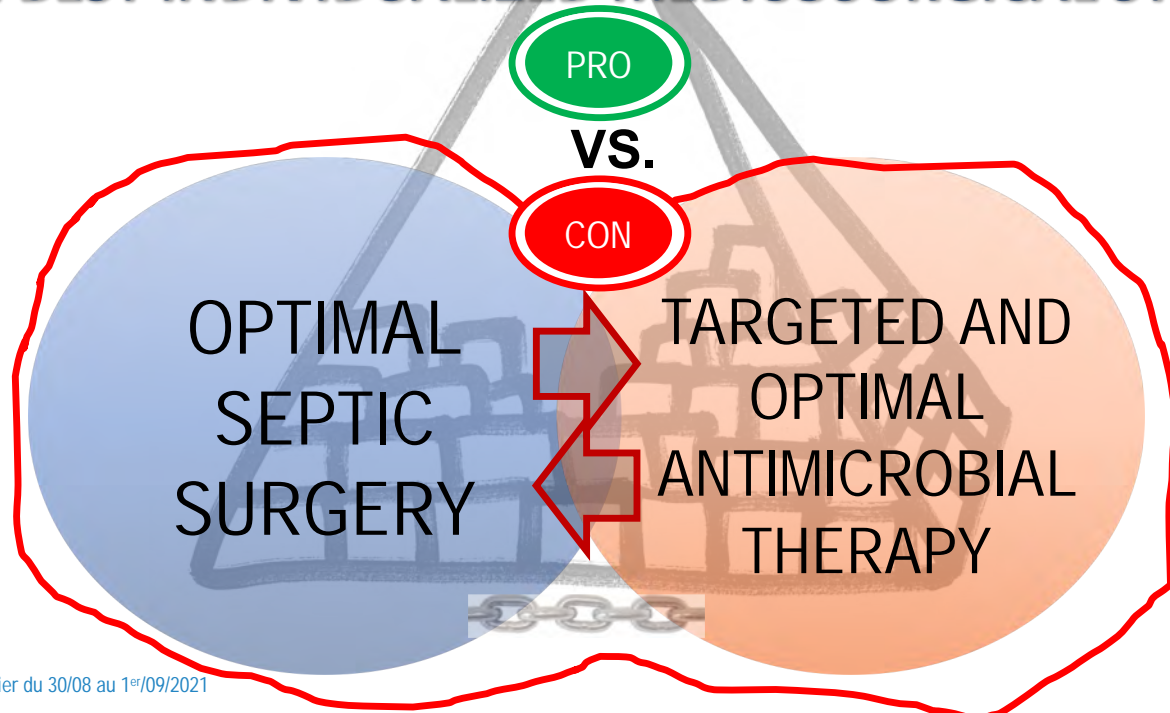


Personalized medicine for BJI

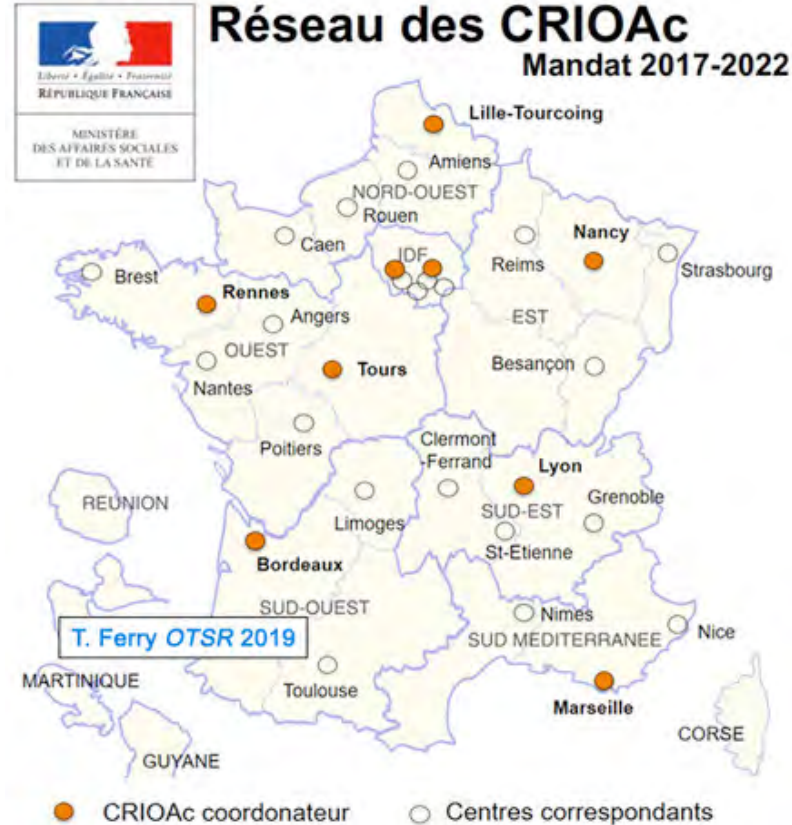


Personalized medicine for BJI

MULTIDISCIPLINAR MEETING THE BEST INDIVIDUALIZED MEDICOSURGICAL STRATEGY



Centre de Référence des Infections Ostéo-Articulaires complexes CRIOAc



Centre de Référence des Infections Ostéo-Articulaires complexes CRIOAc



Réseau des CRIOAc Mandat 2017-2022



STAPHYLOCOQUES
Centre National de Référence

Pr. Tristan Ferry
MD, PhD
Infectiologist

Pr. Sébastien Lustig
MD, PhD
Orthopaedic surgeon

Pr. Frédéric Laurent
PharmD, PhD
Microbiologist

UfB Lyon

IAI EBPN

Inserm

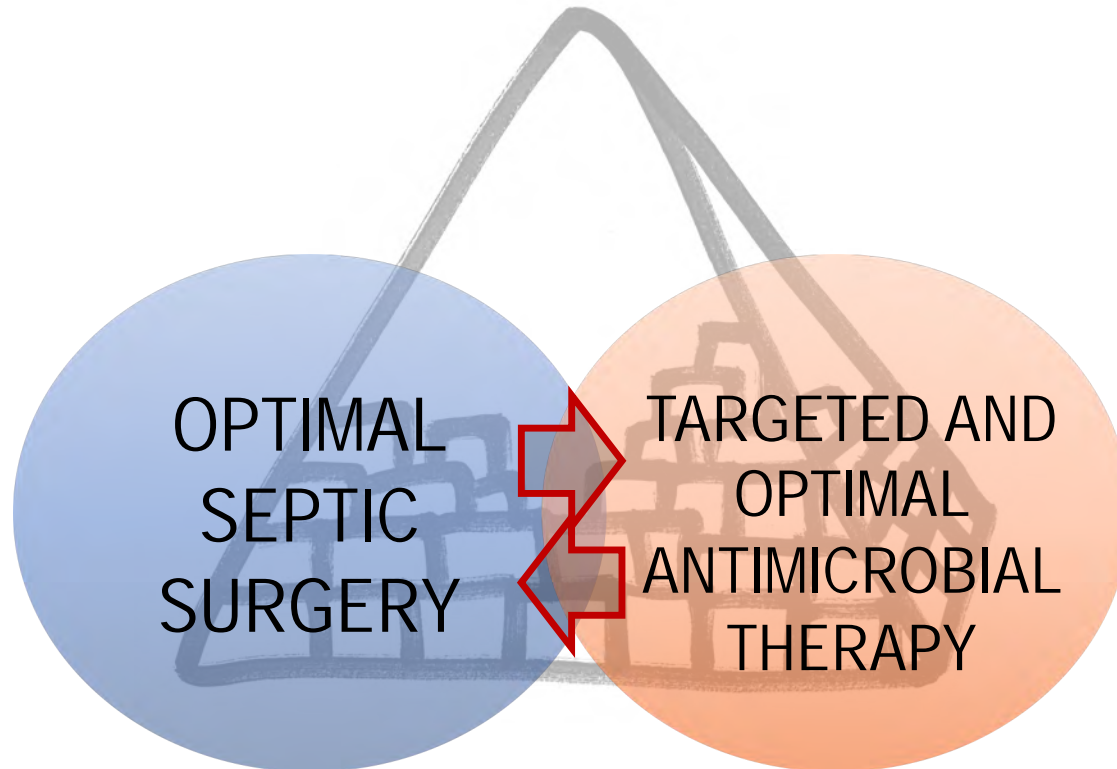
CRB
Centre de Ressources Biologiques

HCL
HOSPICES CIVILS DE LYON

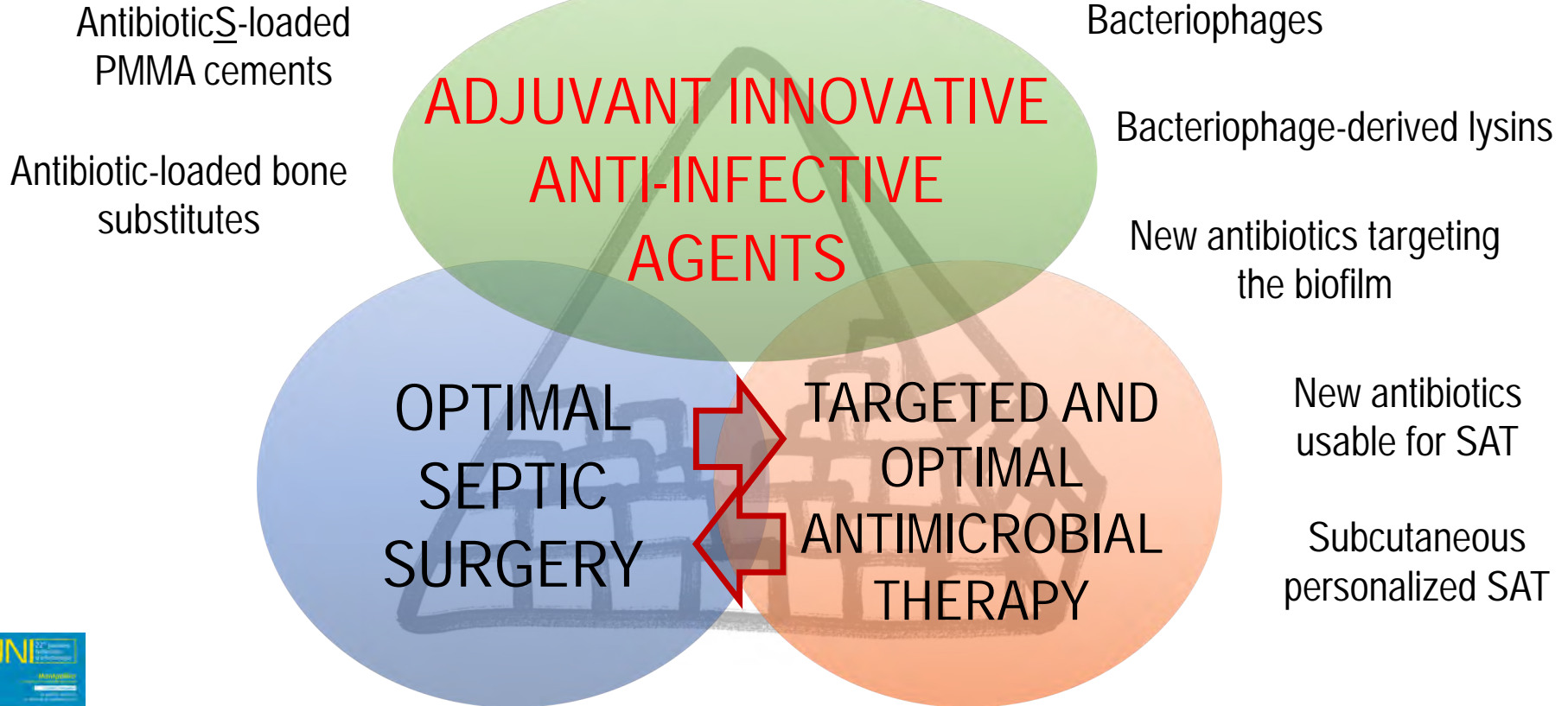
ciri
Centre International de Recherche en Infectiologie



Personalized medicine for BJI



Personalized medicine for BJI



Personalized medicine for BJI

Antibiotic-loaded PMMA cements

Antibiotic-loaded bone substitutes

ADJUVANT INNOVATIVE
ANTI-INFECTIVE
AGENTS

OPTIMAL
SEPTIC
SURGERY

TARGETED AND
OPTIMAL
ANTIMICROBIAL
THERAPY

Bacteriophages

Bacteriophage-derived lysins

New antibiotics targeting
the biofilm

New antibiotics
usable for SAT

Subcutaneous
personalized SAT

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



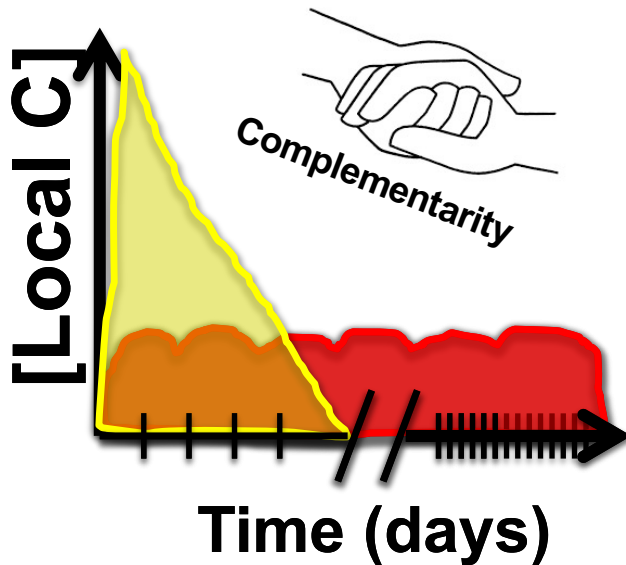
Failure



Acquisition
of resistance and/or
small colony variants

Innovation = local therapy

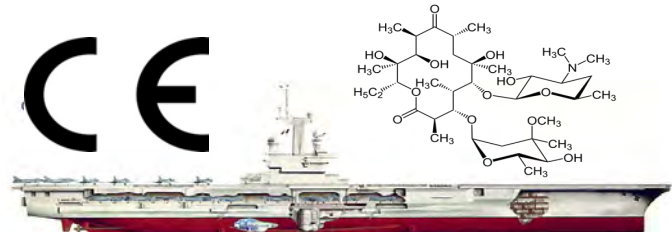
- Antibiotics administered **systemically**
- Antibiotics administered **locally** with particular **carriers** (ex. bone substitute)



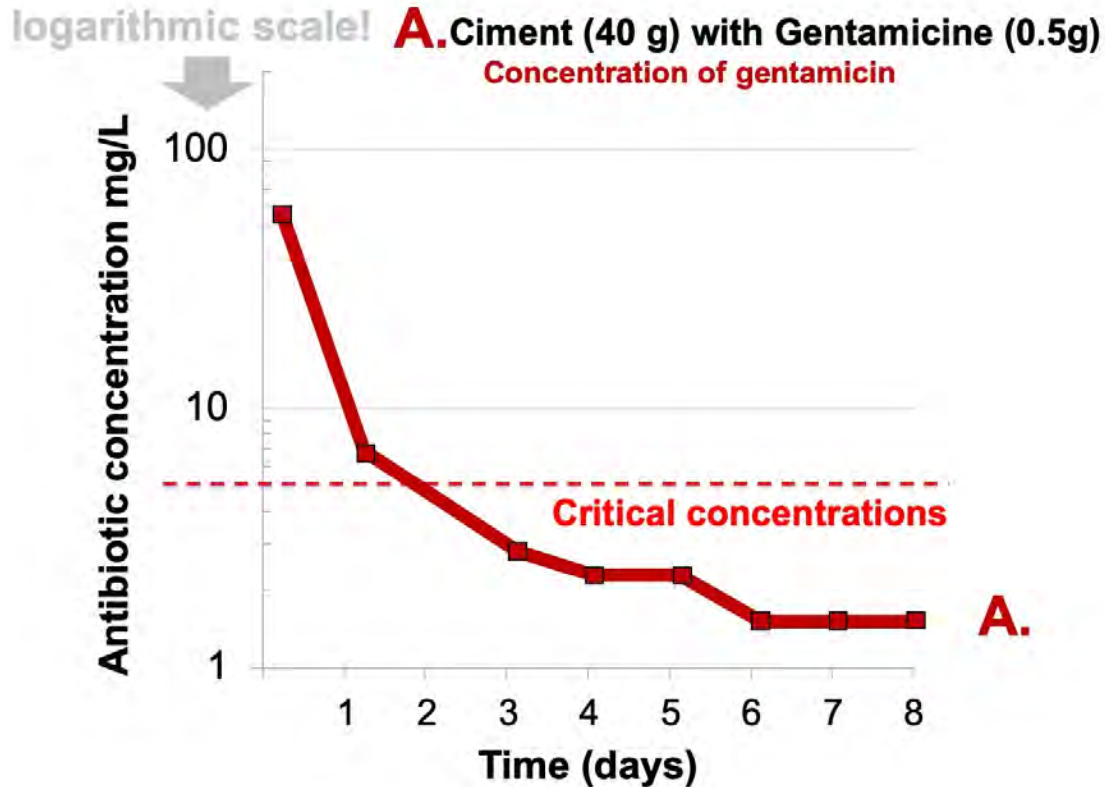
**DISRUPTIVE
Strategy**

**Antibiofilm
agents**

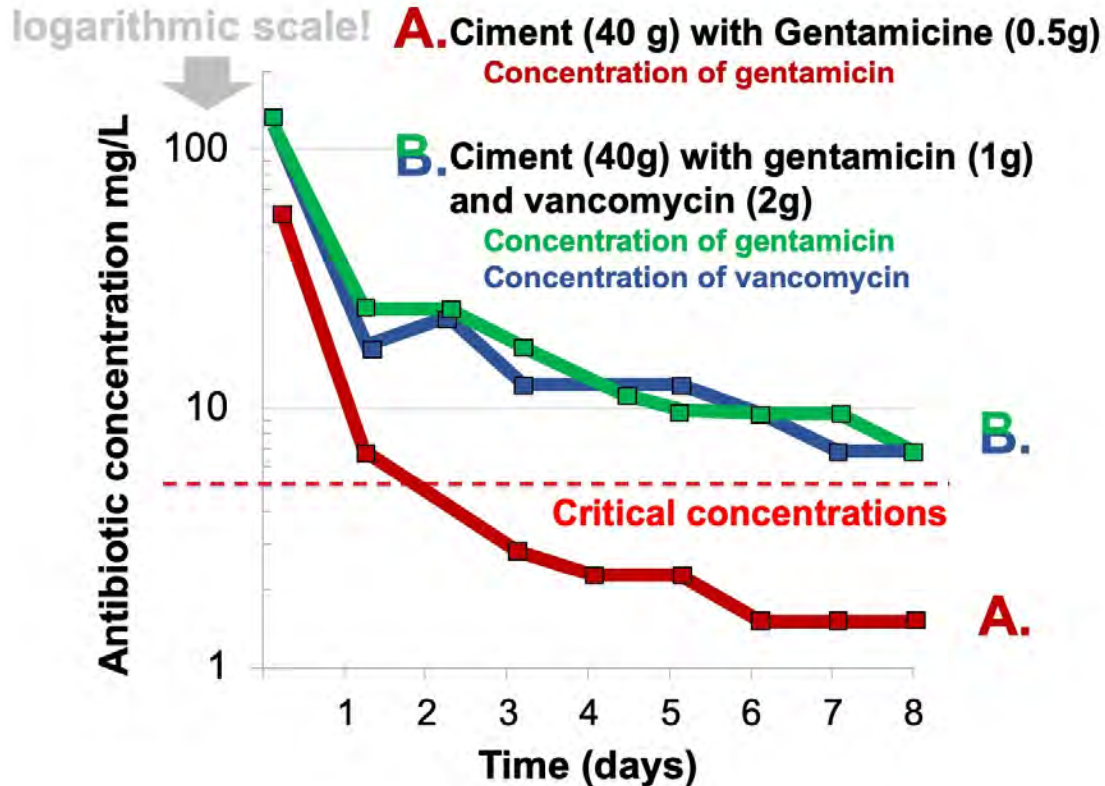
**Local administration
with carriers**



PMMA cements with combination of antibiotics



PMMA cements with combination of antibiotics



PMMA cements with combination of antibiotics

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2021

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de Recherche
en Infectiologie

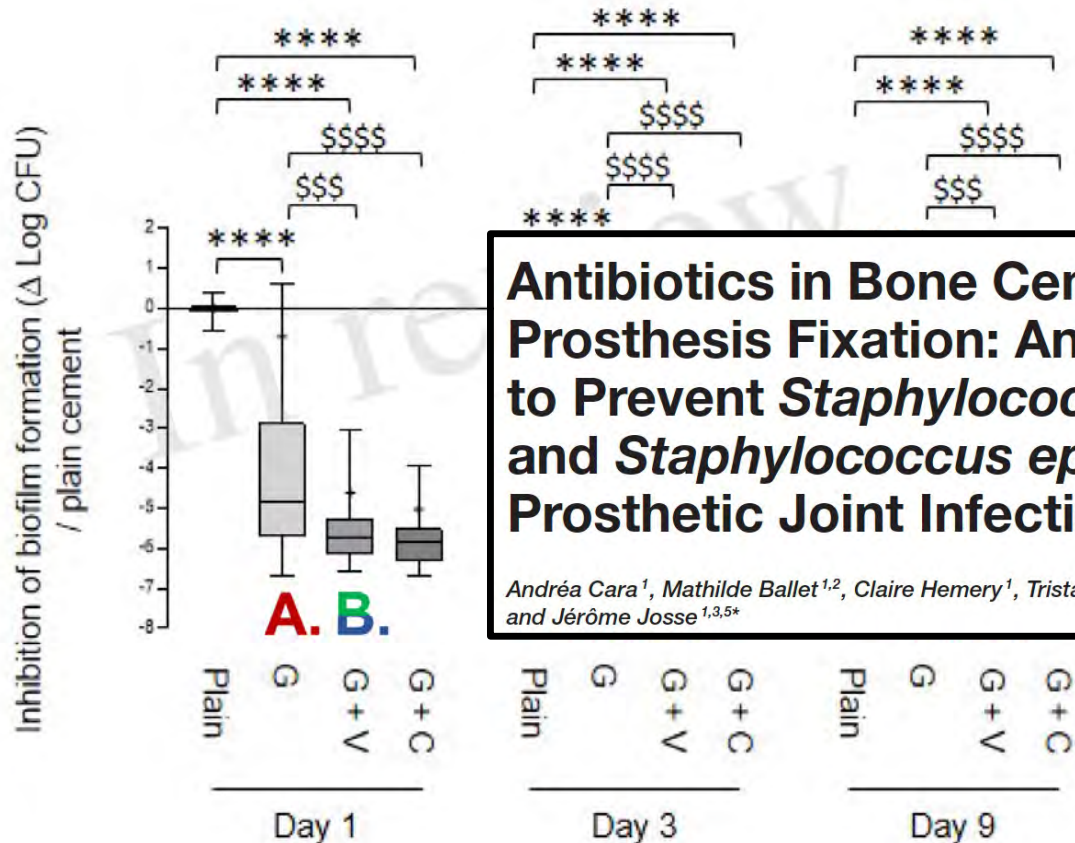
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CRIOAC
LYON

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DE LYON

JNI
22^{es} Journées
Nantes
de
Microbiologie
et
Infectiologie
2022

22^{es} JNI, Mont



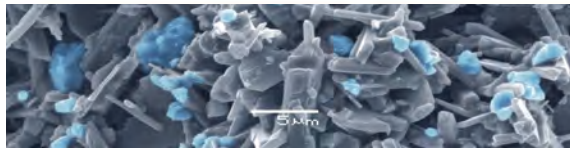
Antibiotic-loaded bone substitutes

BJR

TRAUMA

Pharmacokinetics of gentamicin eluted from a regenerating bone graft substitute

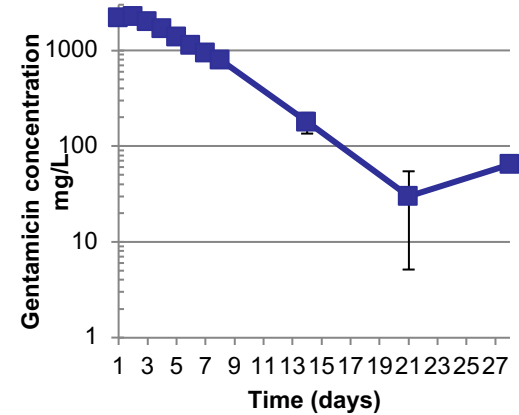
IN VITRO AND CLINICAL RELEASE STUDIES



CERAMENT® G

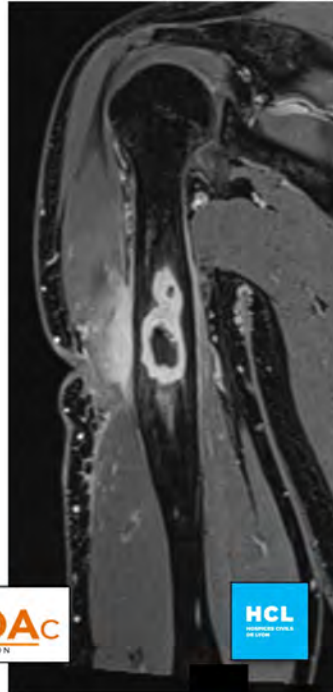


CERAMENT G™
Hydroxyapatite
Calcium sulfate
Gentamicin



- Paste
- Filling of dead spaces
- High local concentration of gentamicin
- Bone regeneration
- Resorbable

CONVICTION clinical trial (PRME 2019)



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**



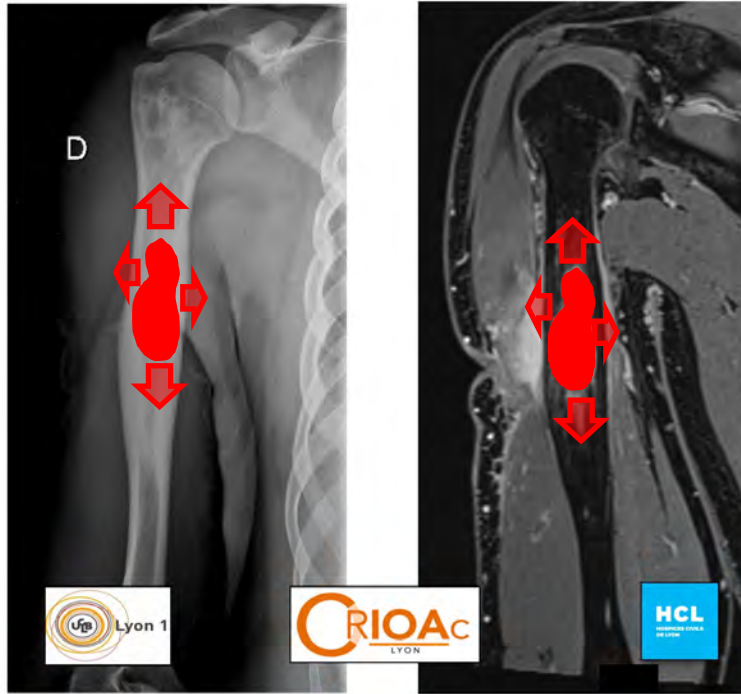
200 patients

2 years

15 CRIOAc centers

T. Ferry (national grant 2019)

CONVICTION clinical trial (PRME 2019)



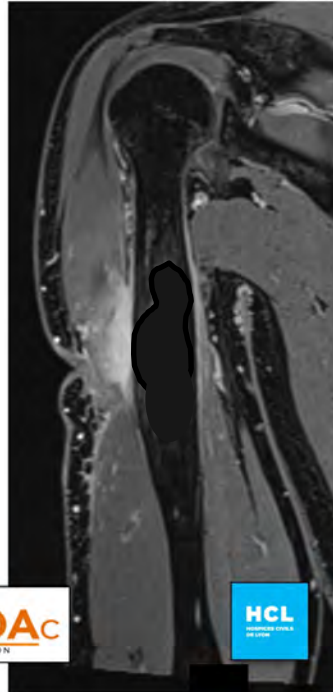
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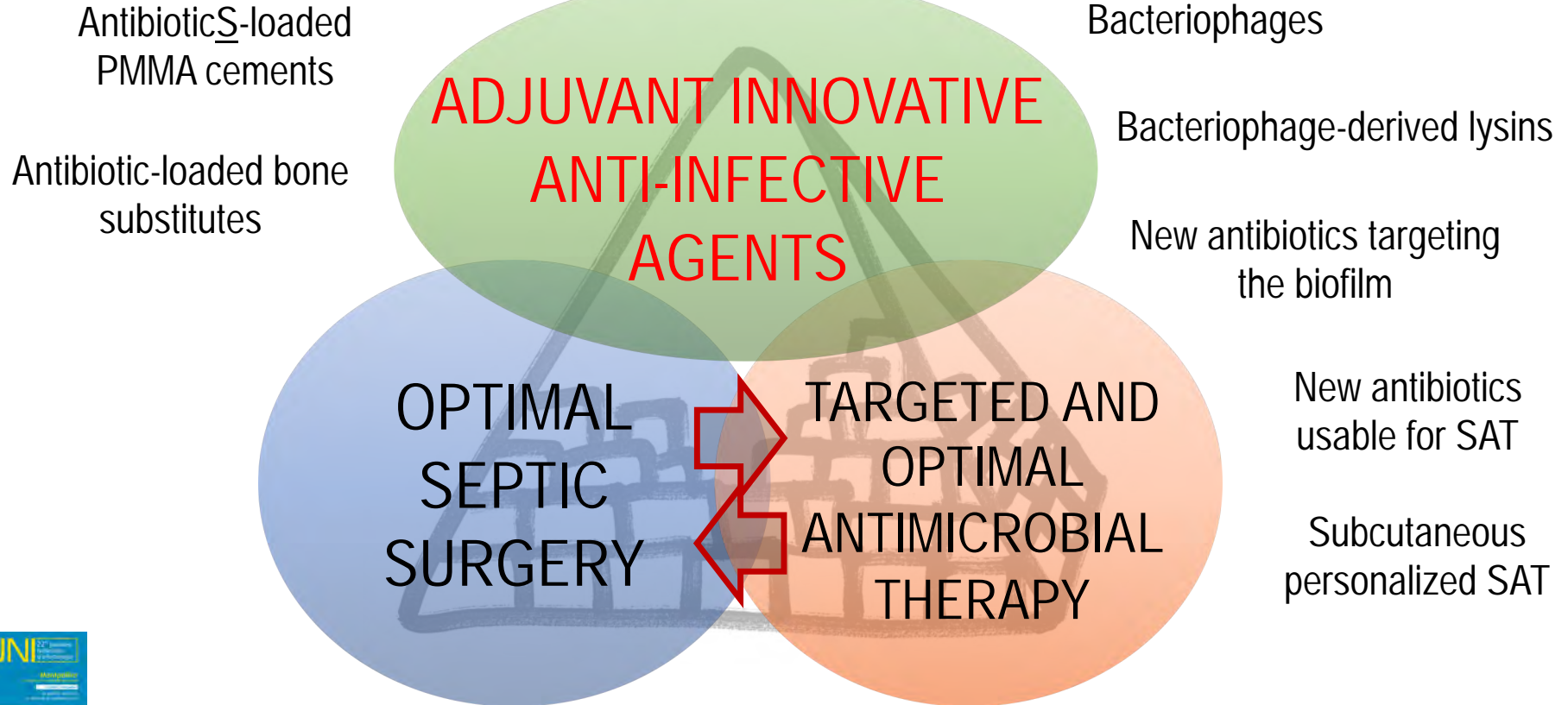
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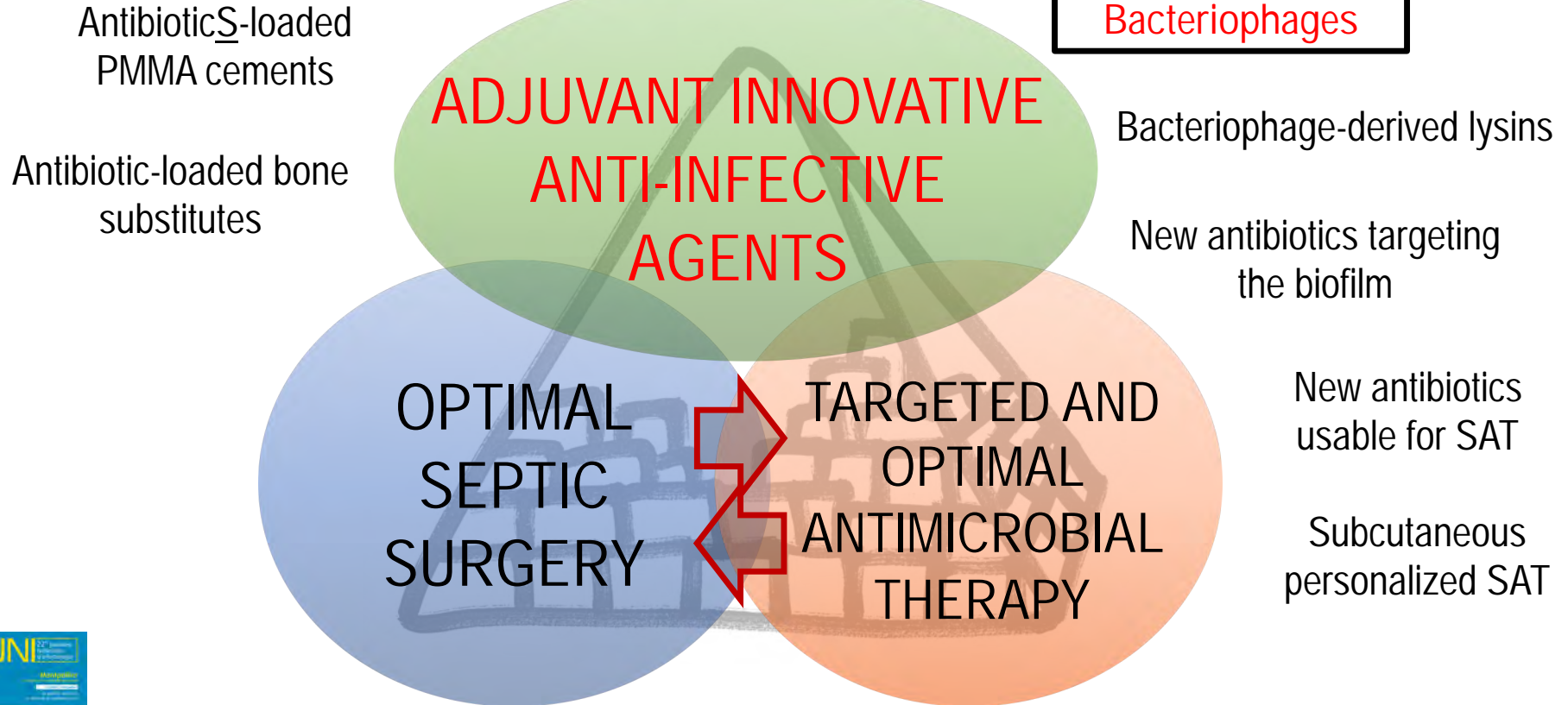
15 CRIOAc centers

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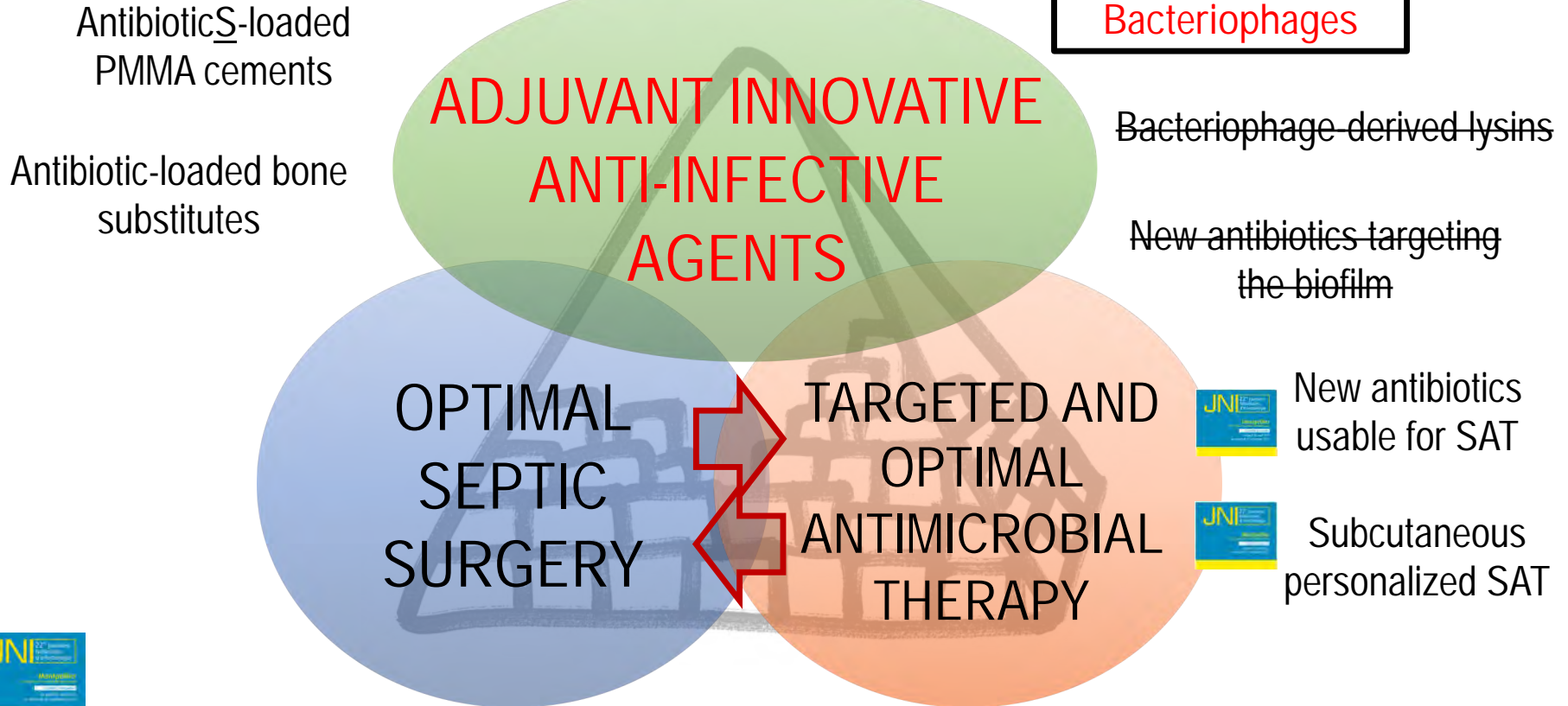
Personalized medicine for BJI



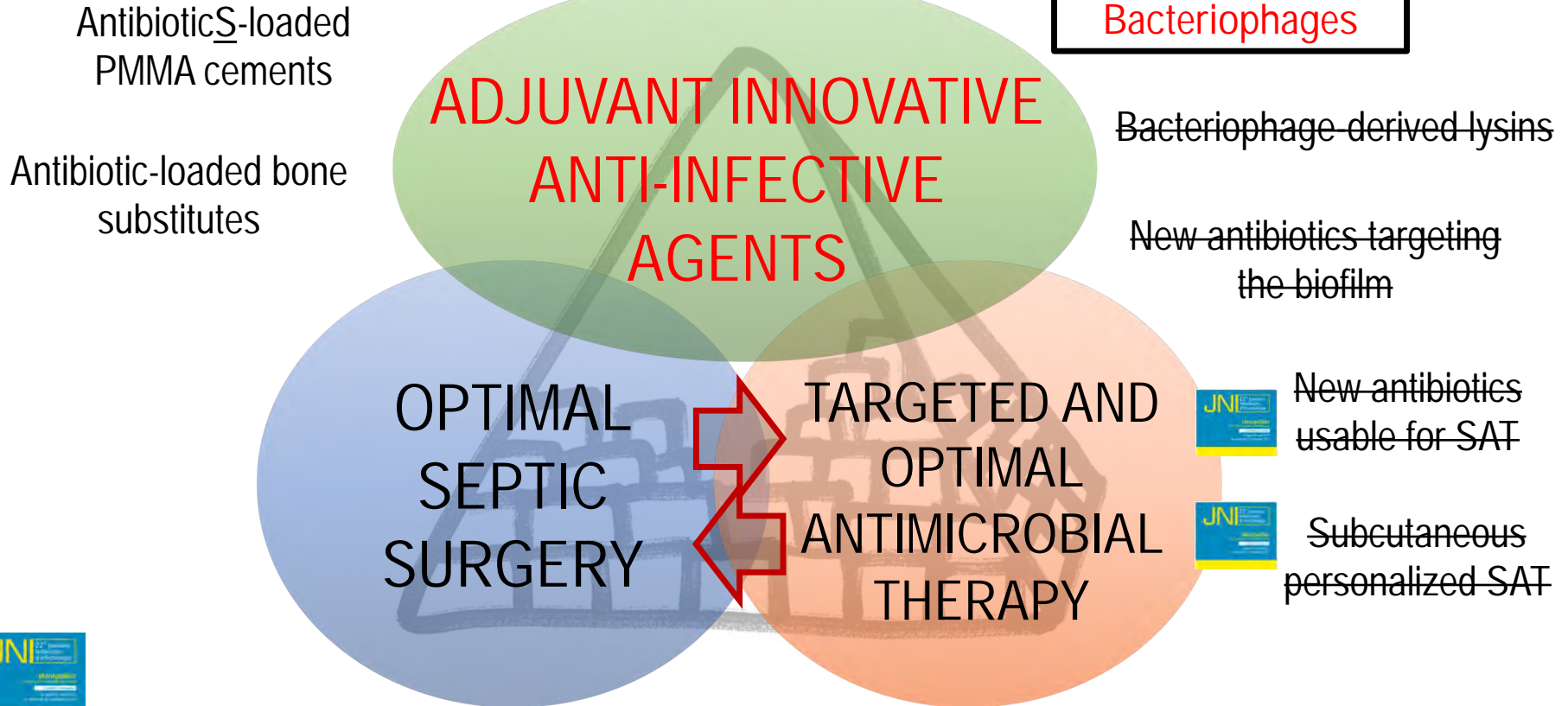
Personalized medicine for BJI



Personalized medicine for BJI



Personalized medicine for BJI



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.

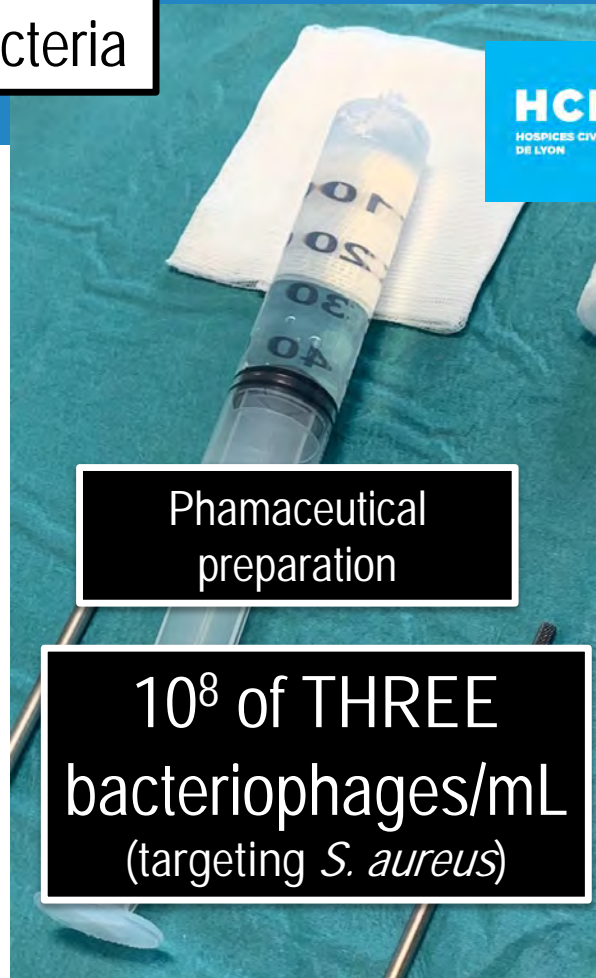


10 to 100 fold smaller than a bacteria

Translucent tap water

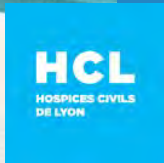


X million of ≠
Bactériophage_S !!!
(targeting environmental bacteria)

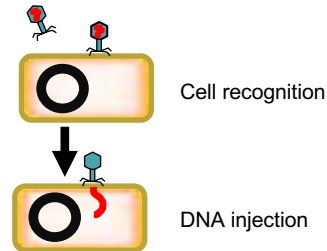


Pharmaceutical
preparation

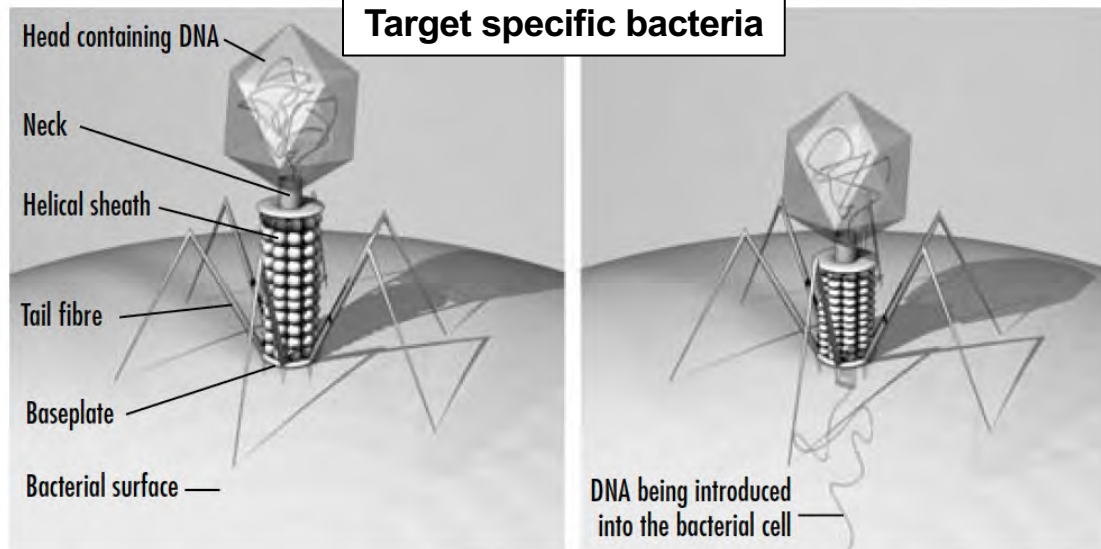
10^8 of **THREE**
bacteriophages/mL
(targeting *S. aureus*)



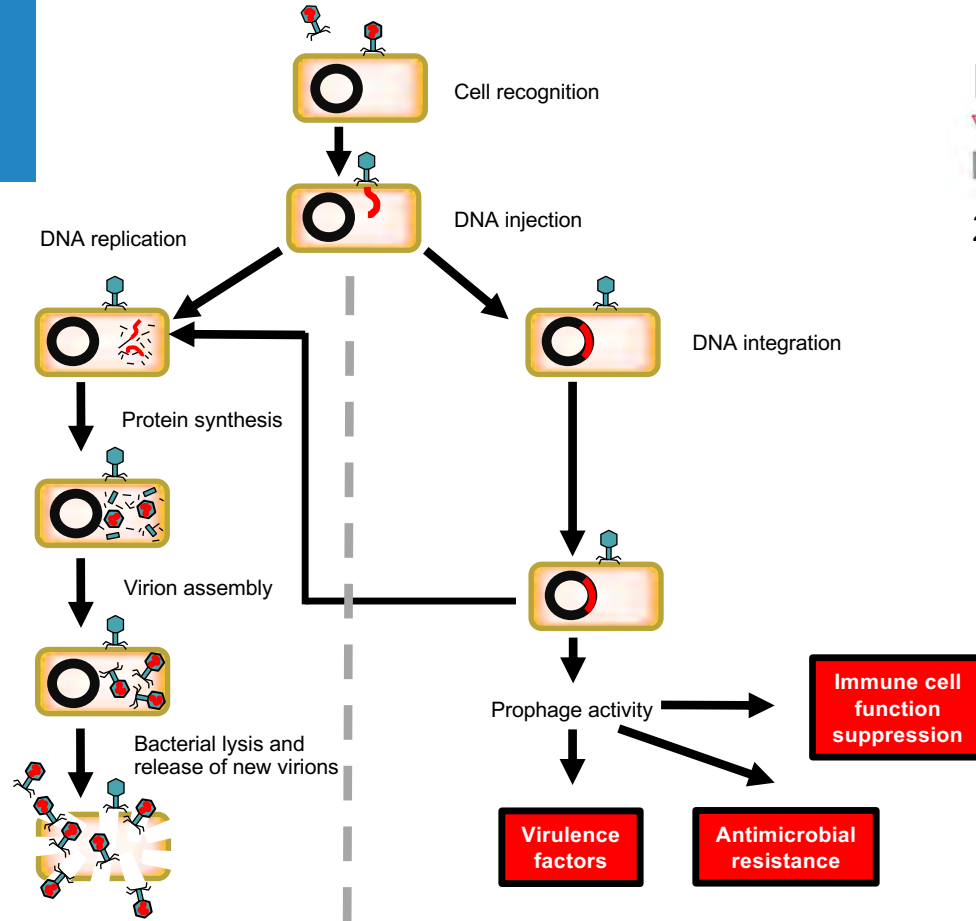
The phage life



Environmental viruses Target specific bacteria



The phage life



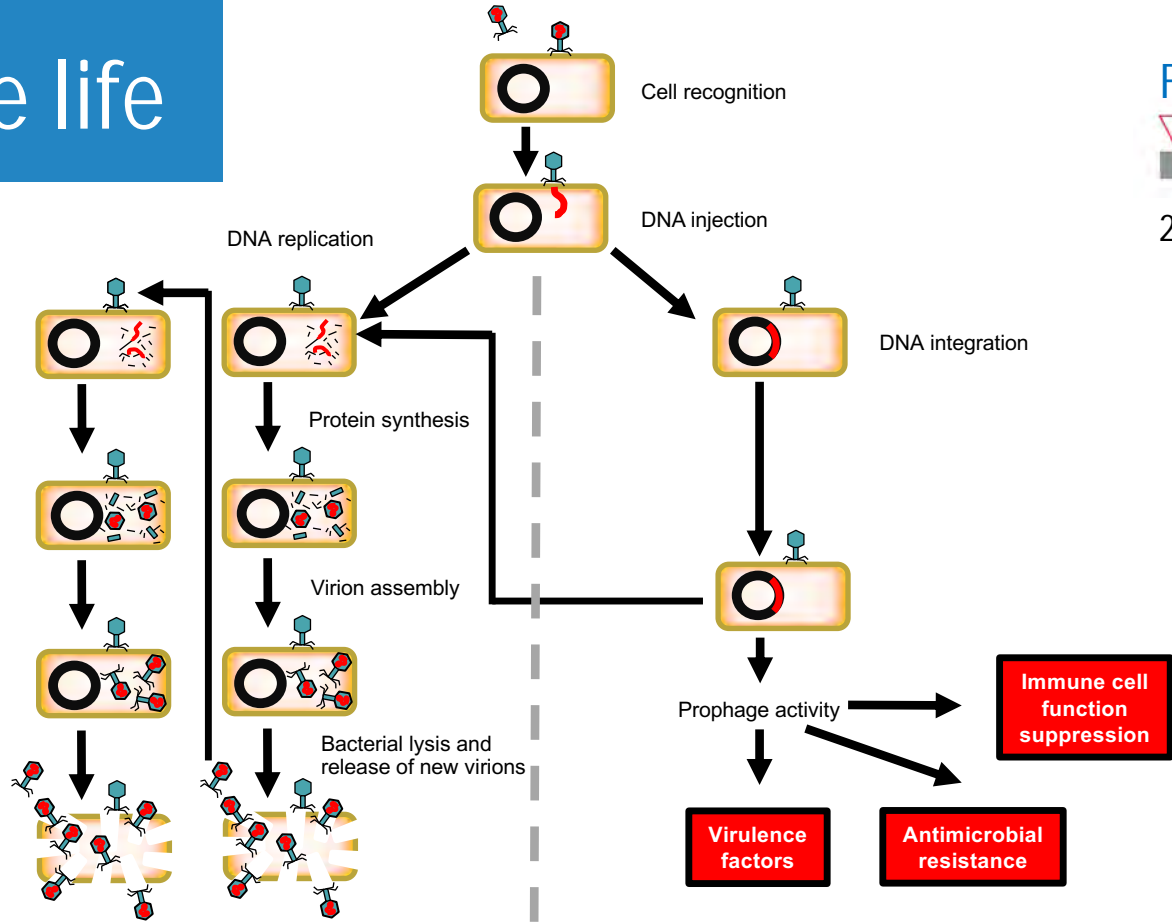
Lytic cycle

Self-maintained bacterial lysis

Lysogenic cycle

Bacterial genetic remodeling

The phage life



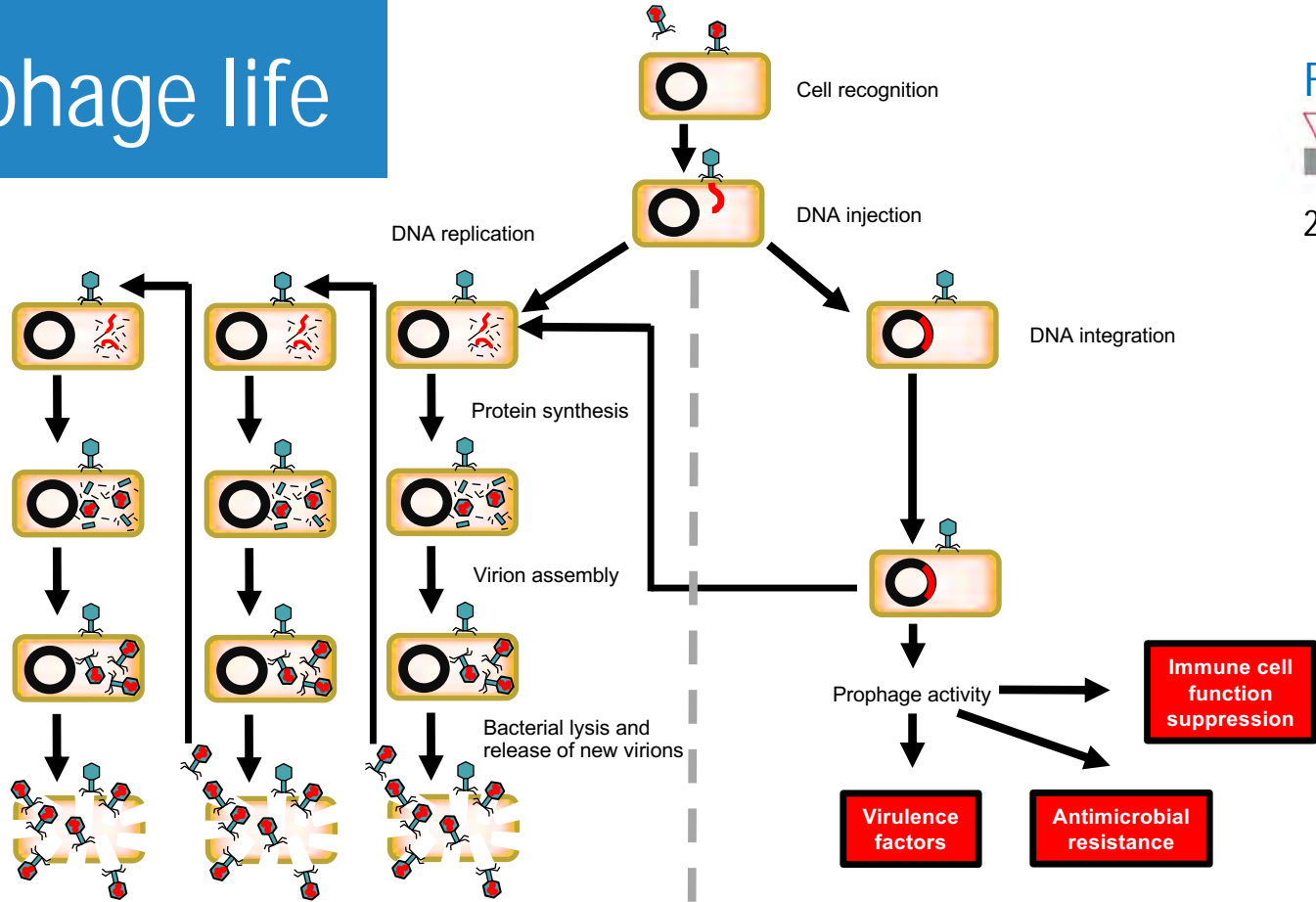
Lytic cycle

Self-maintained bacterial lysis

Lysogenic cycle

Bacterial genetic remodeling

The phage life



Lytic cycle

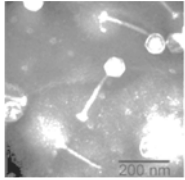
Self-maintained bacterial lysis

Lysogenic cycle

Bacterial genetic remodeling

Only lytic phages have to be used

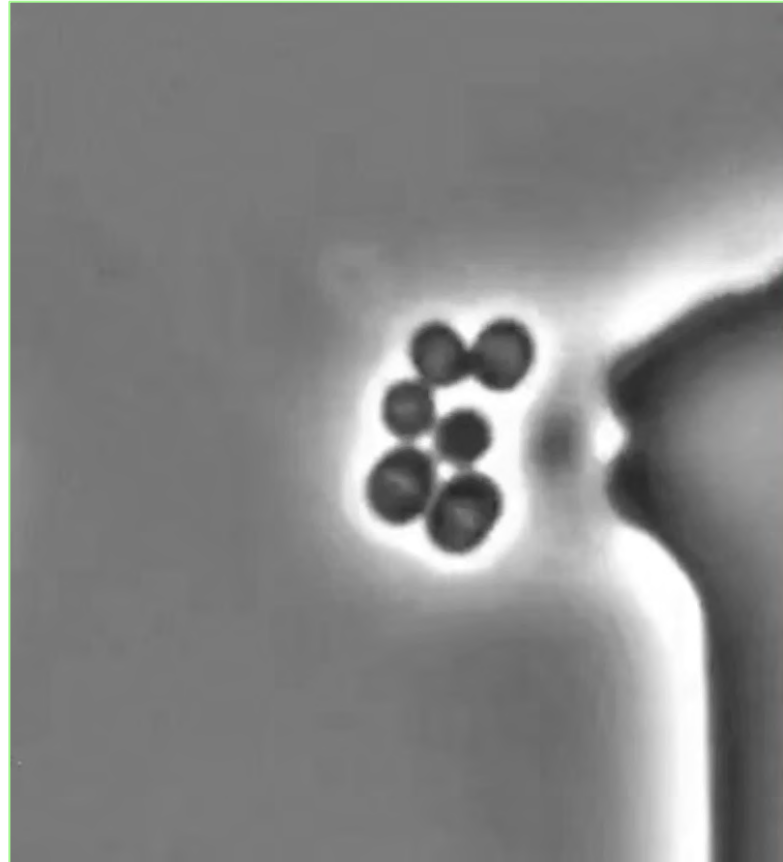
S. aureus being lysed
by the Sa2 phage



Bacterial DNA
appeared in green

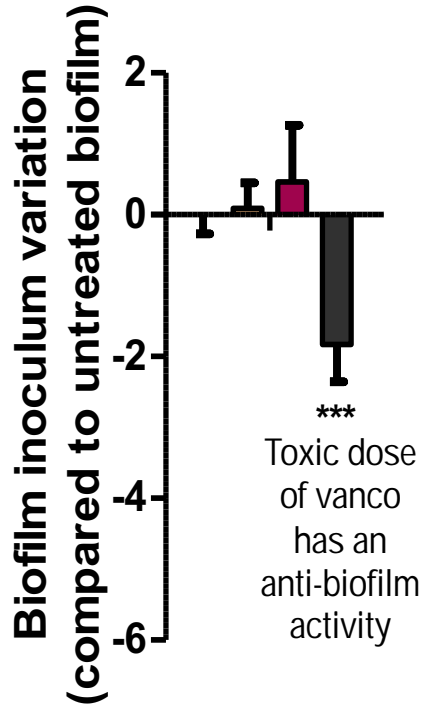
Courtesy Pascal Maguin
Luciano Marraffini Lab

THE ROCKEFELLER UNIVERSITY



Phages have antibiofilm activity

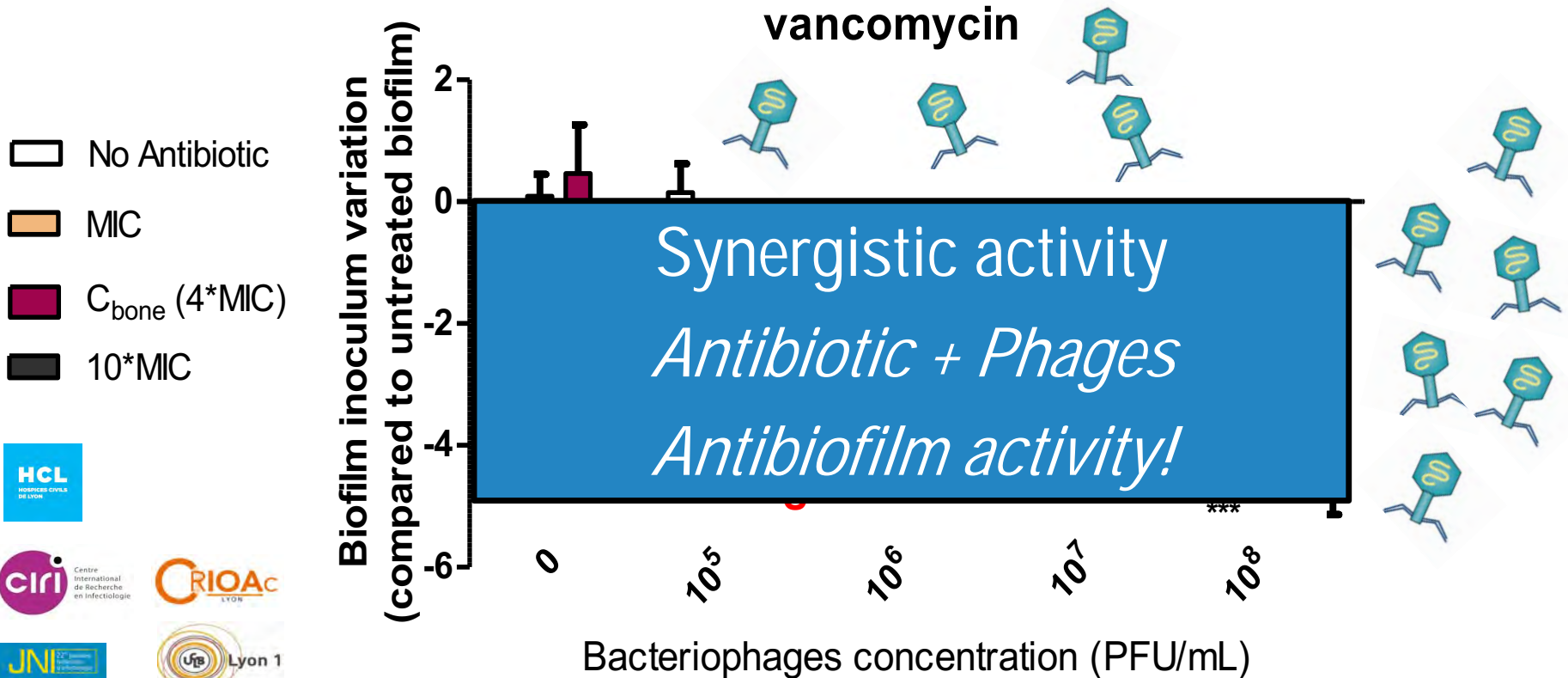
- No Antibiotic
- MIC
- C_{bone} (4*MIC)
- 10*MIC



vancomycin

C. Kolenda et al. Antimicrob Agents Chemother 2019

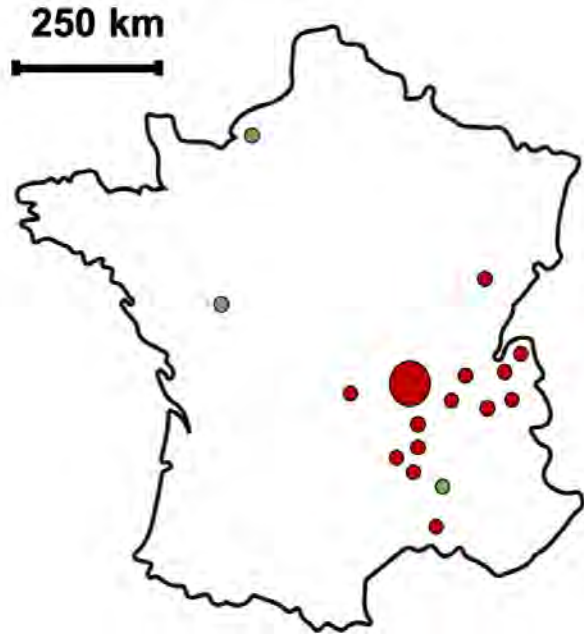
Phages have antibiofilm activity



Bacteriophages concentration (PFU/mL)
C. Kolenda et al. Antimicrob Agents Chemother 2019



Implementation of a Phage Therapy Center in a CRIOAc



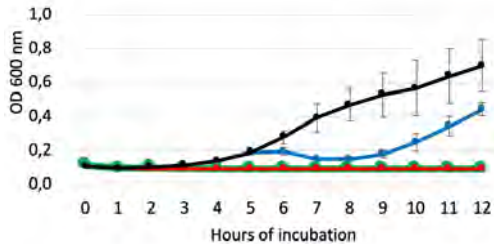
PHAGE*in***LYON**



Number of patients	2017	2018	2019	2020	Total
Managed in CRIOAc Lyon	557	594	647	520	2318
For whom a phagogram was performed	7 (1.2%)	10 (1.7%)	17 (2.6%)	23 (4.4%)	57 (2.4%)
For whom phage therapy was done	4 (0.7%)	2 (0.3%)	8 (1.2%)	7 (1.3%)	21 (0.9%)

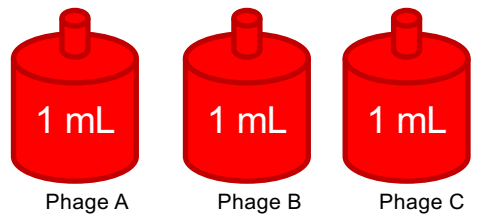


PHAGEⁱⁿLYON team



Phagogram
Selection of active bacteriophages

Active GMP *S. aureus* Bactériophages

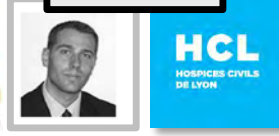


ID Clinic



HCL
HOSPICES CIVILS
DE LYON

Surgery



HCL
HOSPICES CIVILS
DE LYON



Lab



HCL
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DE LYON



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et des produits de santé
French Health Authority

Pharmacy



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Extemporaneous
magistral
preparation of the
mix of
bacteriophages



Case report

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*



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

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





**Septic
arthritis**

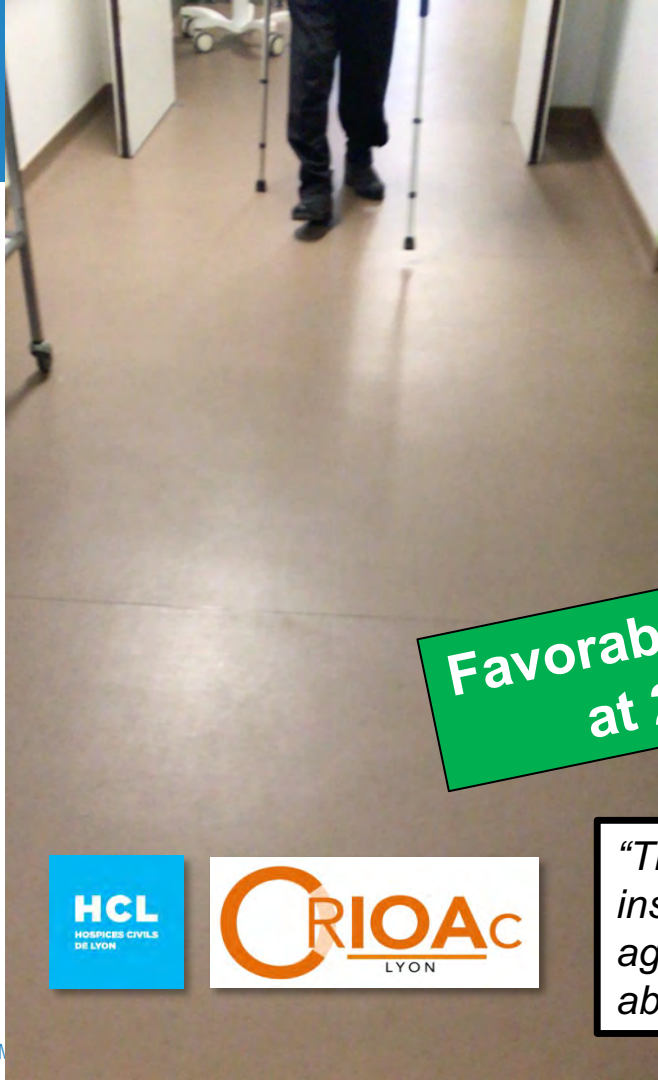
**Fistula and
purulent discharge**



“PhagoDAIR”



One shot peroperative phage application after “DAIR”



**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**





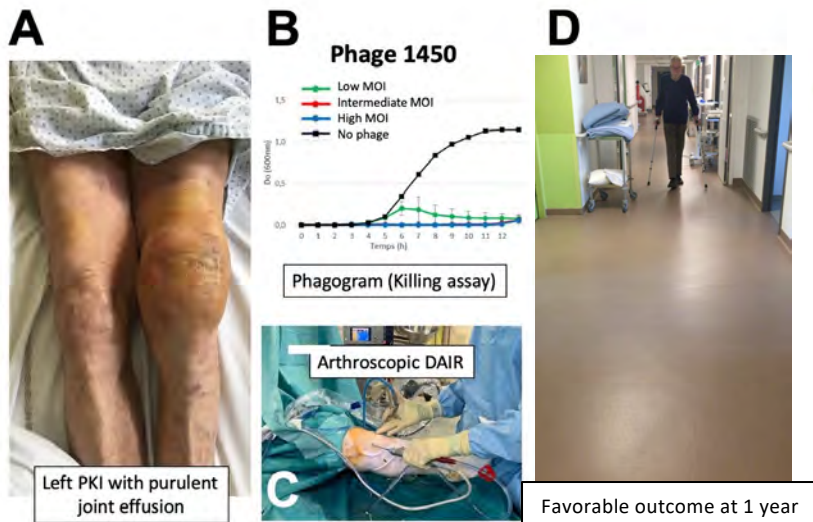


**Favorable outcome
at 1 year**



Arthroscopic “Debridement Antibiotics and Implant Retention” with phages to salvage *Pseudomonas aeruginosa* prosthetic knee infection

**Phago
DAIR**



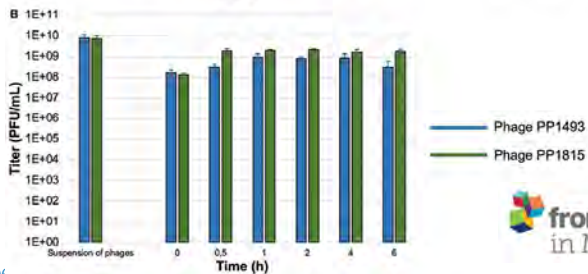
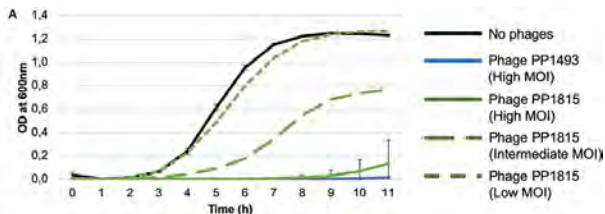
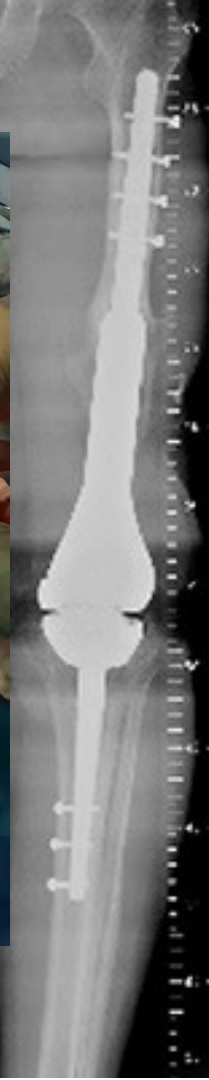
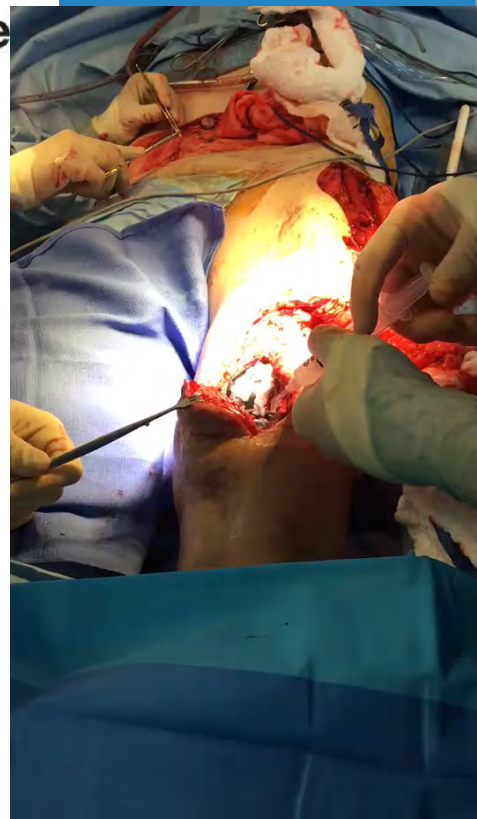
frontiers
in Medicine
2021

CRIOAc
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 Petitjean⁶, Joseph Chateau⁷, Cindy Fevre⁶, Emmanuel Forestier⁸, Sophie Brosset⁷, Gilles Lebourcier⁹, 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



Where to find phages for clinical use?

- Pherecydes Pharma
- Phage directory 
- Phage community

 **PHERECYDES**
PHARMA

Phage Directory

Under the supervision of

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Agence nationale de sécurité du médicament
et des produits de santé
French Health Authority



Where to find phages for clinical use?

- Pherecydes Pharma  PHERECYDES PHARMA
- Phage directory  Phage Directory
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Under the supervision of

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et des produits de santé
French Health Authority

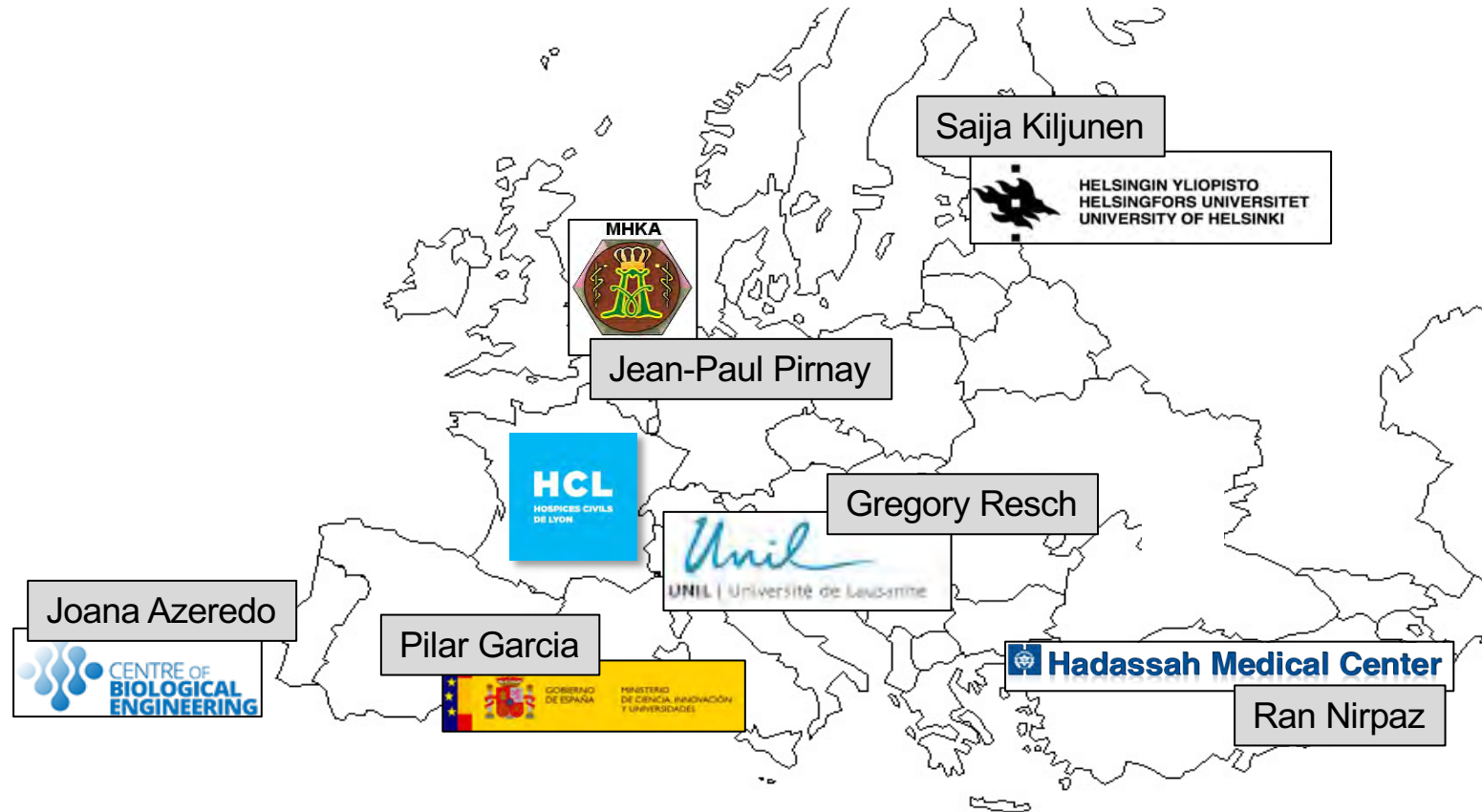
	<i>Pseudomonas aeruginosa</i> CMI (mg/l)
Ticarcilline + Ac. Clav	R (> 64)
Pipéracilline	R (> 64)
Pipéracilline + Tazobactam	R (> 64)
Ceftazidime	R (> 32)
Céfépime	R (> 32)
Aztréonam	R (> 32)
Imipénème	R (> 8)
Meropenème	R (> 8)
Gentamicine	R (> 8)
Tobramycine	R (> 8)
Amikacine	R (> 32)
Ciprofloxacine	R (> 2)
Lévofloxacine	R (> 4)
Cotrimoxazole	R
Colistine	S (8) ⇨ R
Colistine (Etest)	S E-test : 1 ⇨ R
	R E-test : > 256
	R E-test : 64

 PHERECYDES
PHARMA

 AMPLI PHI
BIOSCIENCES CORPORATION

The strain was also **spontaneously resistant to bacteriophages !!!**

Potential European academic collaborations



Potential European academic collaborations

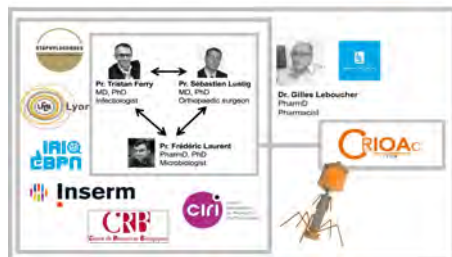
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Agence nationale de sécurité du médicament
et des produits de santé

French Health Authority

Lyon Phage team



Potential European academic collaborations

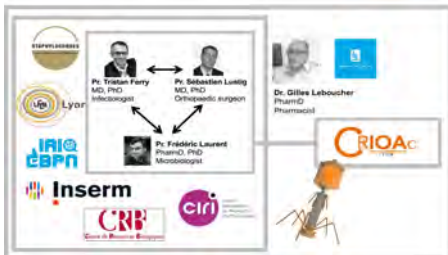


Jean-Paul Pirnay



Gregory Resch

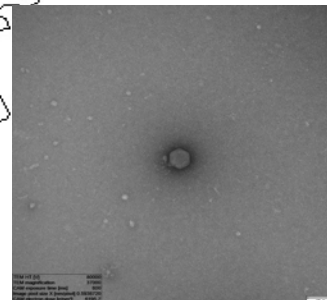
Lyon Phage team



Potential European academic collaborations

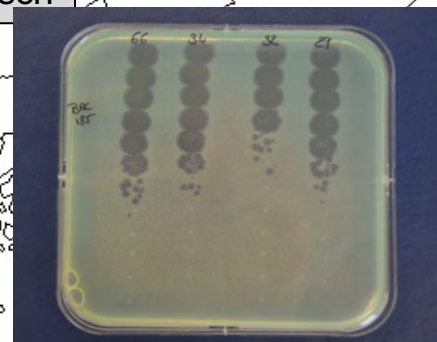
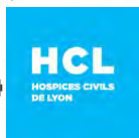
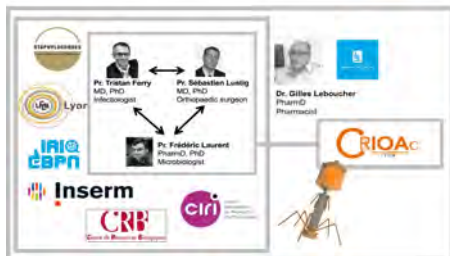


Jean-Paul Pirnay

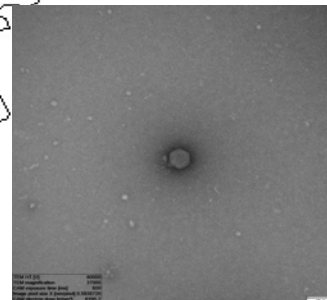


Gregory Resch

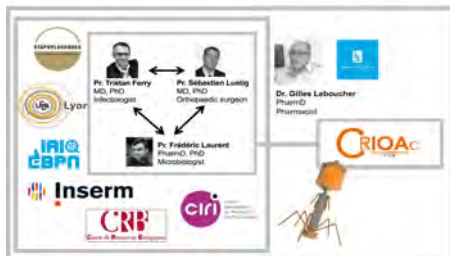
Lyon Phage team



Potential European academic collaborations



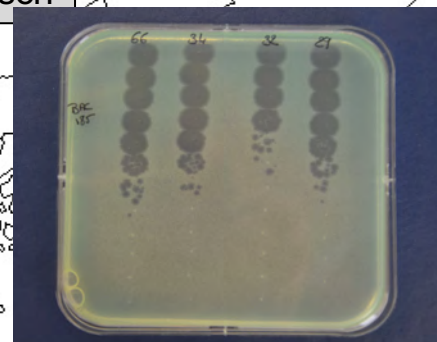
Lyon Phage team



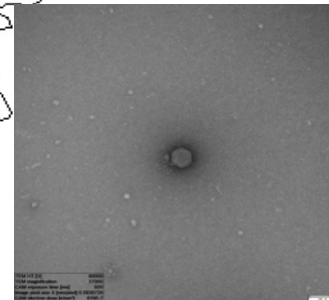
Jean-Paul Pirnay



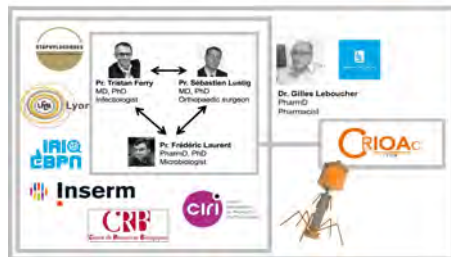
Gregory Resch



Potential European academic collaborations



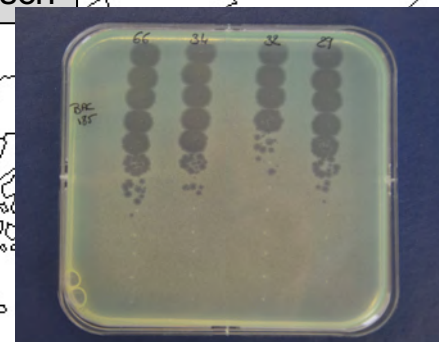
Lyon Phage team



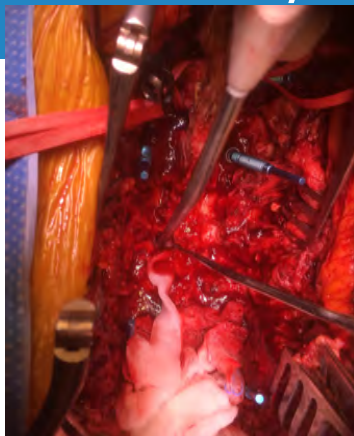
Jean-Paul Pirnay



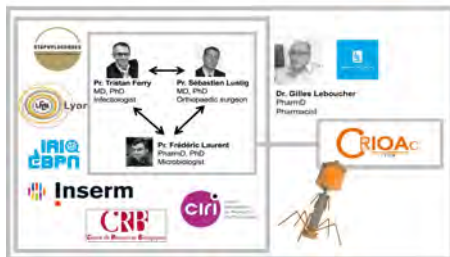
Gregory Resch



Potential European academic collaborations



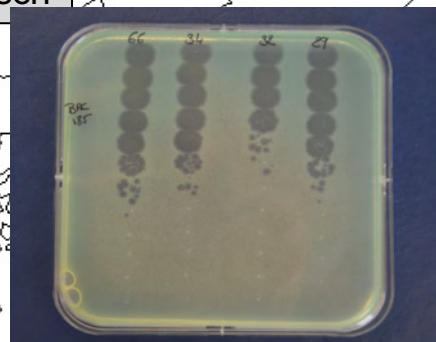
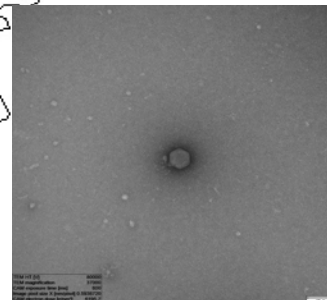
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Gregory Resch



Outcome

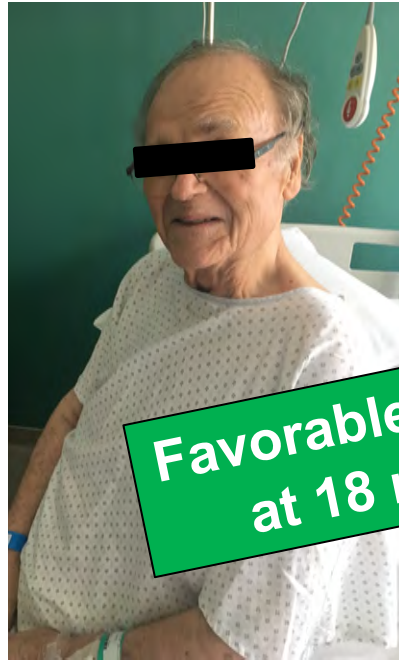


Under the supervision of



Agence nationale de sécurité du médicament
et des produits de santé

French Health Authority



**Favorable outcome
at 18 months**

30th
ECCMID

Paris, France
18 –21 April 2020



Conclusions: Personalized phage therapy is a potential adjunct treatment for patients with complex BJI due to pandrug-resistant bacteria. **In addition to industrial phages under development, academic collaborative research is crucial to develop personalized phage therapy.**



Where to find phages for clinical use?

- Pherecydes Pharma
- Phage directory  Phage Directory
- Phage community



Under the supervision of



Where to find phages for clinical use?

- Pherecydes Pharma 
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PHERECYDES
PHARMA

Phage Directory

Under the supervision of

ANSM
Agence nationale de sécurité du médicament
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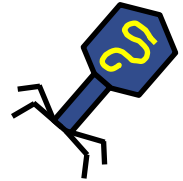


PHAG-one



MINISTÈRE
DE L'ENSEIGNEMENT
SUPÉRIEUR,
DE LA RECHERCHE
ET DE L'INNOVATION

Liberté
Égalité
Fraternité



PHAGE_{in}LYON



Purified academic phages
Usable in the next 5 years



FRI PHARM



Where to find phages for clinical use?

- Pherecydes Pharma  **PHERECYDES**
PHARMA
- Phage directory  **Phage** Directory
- Phage community

Inauguration Committee Members:



Ran Nir-Paz, Israël
Tristan Ferry, France
Patrick Soentjens, Belgium
Zuzanna Drulis-kawa, Poland
Joana Azeredo, Portugal

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 connection 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, Agathe Becker, Claire Triffault-Fillit, Anne Conrad, Cécile Pouderoux, Pierre Chauvelot, Paul Chabert, Johanna Lippman, Evelyne Braun

Surgeons – Sébastien Lustig, Elvire Servien, Cécile Batailler, Stanislas Gunst, Axel Schmidt, Eliott Sappey-Marinier, Quentin Ode, Michel-Henry Fessy, Anthony Viste, Jean-Luc Besse, Philippe Chaudier, Lucie Louboutin, Adrien Van Haecke, Marcelle Mercier, Vincent Belgaid, Aram Gazarian, Arnaud Walch, Antoine Bertani, Frédéric Rongieras, Sébastien Martres, Franck Trouillet, Cédric Barrey, Ali Mojallal, Sophie Brosset, Camille Hanriat, Hélène Person, Philippe Céruse, Carine Fuchsmann, Arnaud Gleizal;

Anesthesiologists – Frédéric Aubrun, Mikhail Dziadzko, Caroline Macabéo, Dana Patrascu;

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

Imaging – Fabien Craighero, Loic Boussel, Jean-Baptiste Pialat, Isabelle Morelec;

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

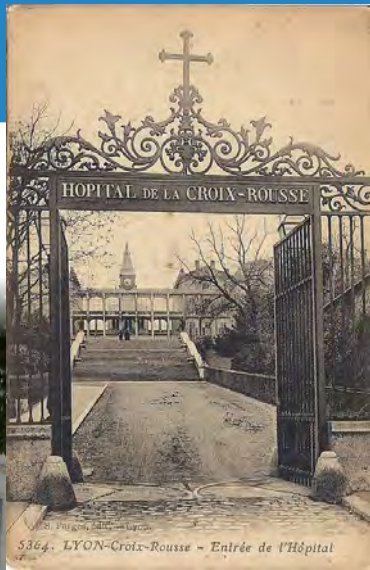
Clinical research assistant and database manager– Eugénie Mabrut

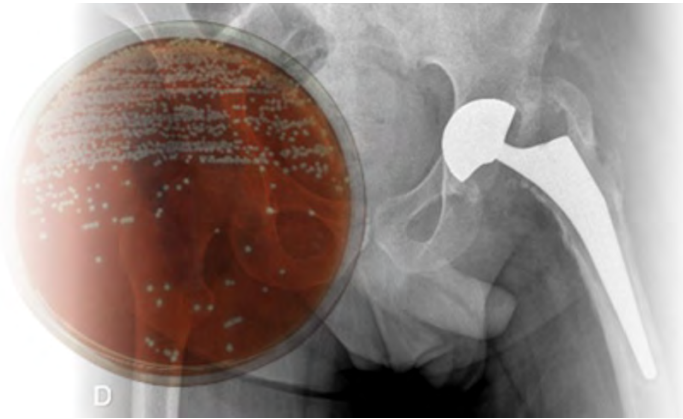


22^{es} JNI, Montpellier du 30/08 au 1^{er}/09/2021



Croix-Rousse Hospital





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



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Vème congrès national des CRIOAc




21 et 22 octobre 2021
à l'ENS Lyon
PRÉSENTIEL
& VIRTUEL



DIRECTION GÉNÉRALE DE L'OFFRE DE SOINS

Guest international speakers

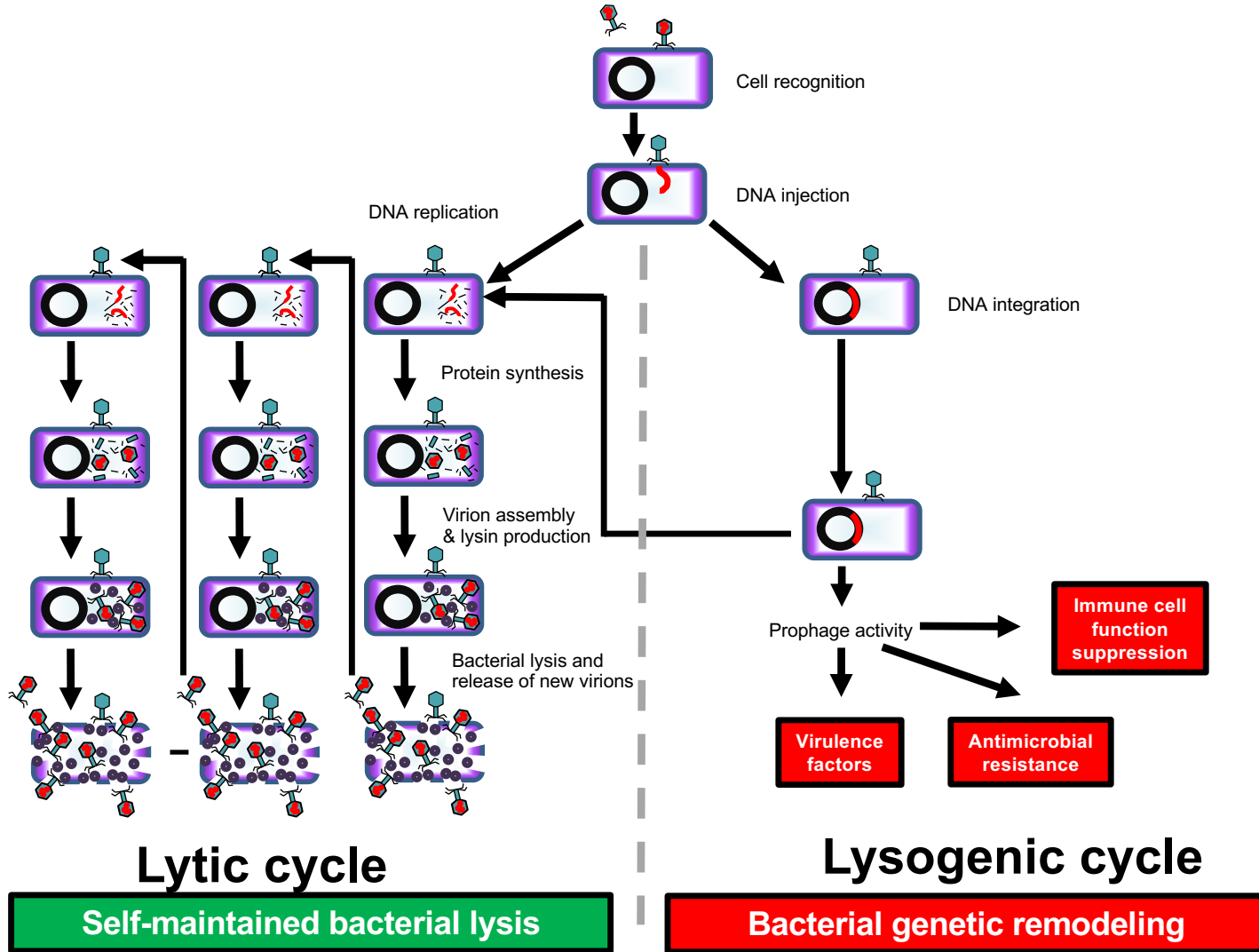
J. Parvizi 
O. Cornu 



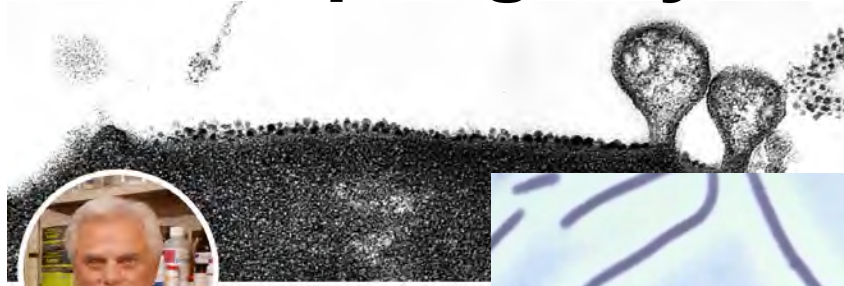
22es JN1, Montpellier du 30/08 au 1er/09/2021

<http://crioac2021.univ-lyon1.fr>





Bacteriophage Lysins



Vincent A Fischetti
@microbepophage



Tristan Ferry Lyon University Hospitals
@FerryLyon

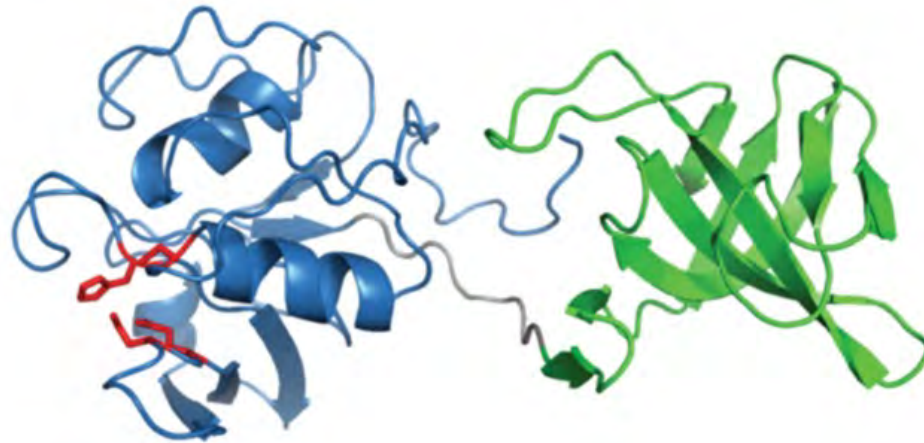
Incredible talk of Pr. Vincent A. Fischetti [@microbepophage](#) @IDWeek2019 about the great potential of [#bacteriophage](#) [#lysins](#) to induce bacterial explosion... and disappearance! It's good to hear that he discovered lysins that are active against [#multidrugresistant](#) [#ESKAPE](#) pathogens!



Combination Therapy With Lysin CF-301 and Antibiotic Is Superior to Antibiotic Alone for Treating Methicillin-Resistant *Staphylococcus aureus*-Induced Murine Bacteremia

Raymond Schuch,¹ Han M. Lee,¹ Brent C. Schneider,¹ Karen L. Sauve,¹ Christina Law,¹ Babar K. Khan,¹ Jimmy A. Rotolo,¹ Yuki Horiuchi,¹ Daniel E. Couto,¹ Assaf Raz,² Vincent A. Fischetti,² David B. Huang,¹ Robert C. Nowinski,¹ and Michael Wittekind¹

¹ContraFact Corporation, Yonkers, NY, and ²Department of Bacterial Pathogenesis and Immunology, The Rockefeller University, New York, New York



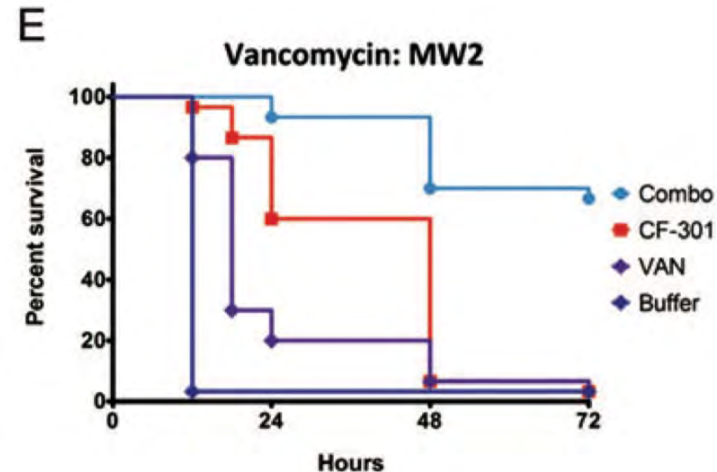
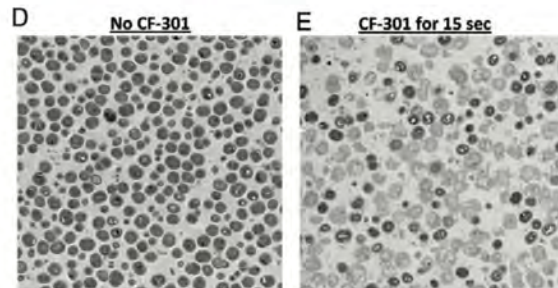
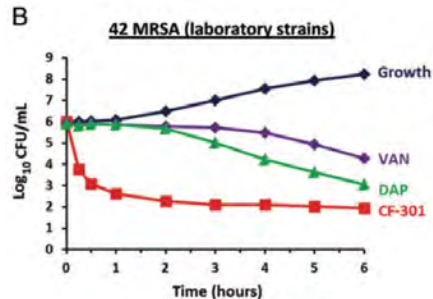
CF-301

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Arthroscopic debridement, antibiotic and implant retention (DAIR) with local administration of Exebacase (Lysin CF-301) (LysinDAIR) followed by suppressive tedizolid as salvage therapy in elderly patients for relapsing multidrug-resistant *Staphylococcus epidermidis* prosthetic knee infection



ContraFect



30th
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Conclusions: Exebacase has the potential to be used as salvage therapy during arthroscopic DAIR in patients with relapsing MDR *S. epidermidis* PKI, to improve the efficacy of suppressive antibiotics, and to avoid considerable loss of function.

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Conclusions: Exebacase has the potential to be used as salvage therapy during arthroscopic DAIR in patients with relapsing MDR *S. epidermidis* PKI, to improve the efficacy of suppressive antibiotics, and to avoid considerable loss of function.



Evaluer l'efficacité du Cerament-G dans le traitement de l'ostéomyélite chronique des os longs en comparant la stratégie innovante (avec le Cerament G) à la stratégie de référence (sans Cerament G)

- **Critère de jugement principal :**
Ratio Différentiel Coût-Utilité (RDCU) estimé à 24 mois entre les deux stratégies de traitement de l'ostéomyélite chronique des os longs