

The Phage lysin CF-301 (Exebacase) in patients with staphylococcal prosthetic joint infection: Experience of a referral clinical centre

Tristan Ferry, MD, PhD

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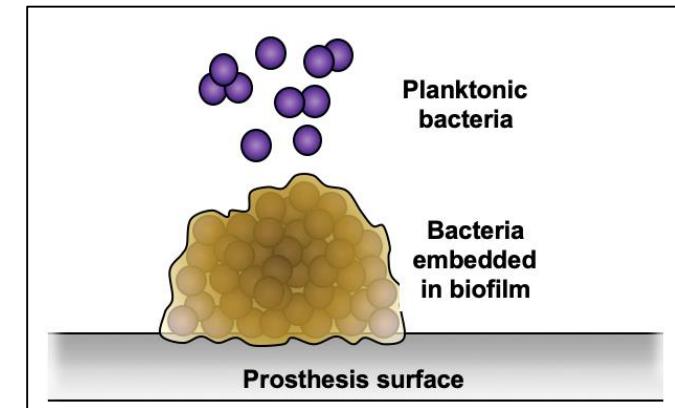
Infectious and Tropical Diseases Unit, Croix-Rousse Hospital , Hospices Civils de Lyon, Claude Bernard Lyon1 University, Lyon
Centre International de Recherche en Infectiologie, CIRI, Inserm U1111, CNRS UMR5308, ENS de Lyon, UCBL1, Lyon, France
Centre de Référence des IOA complexes de Lyon (CRIOAc Lyon)



Chronic bone and joint infection

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

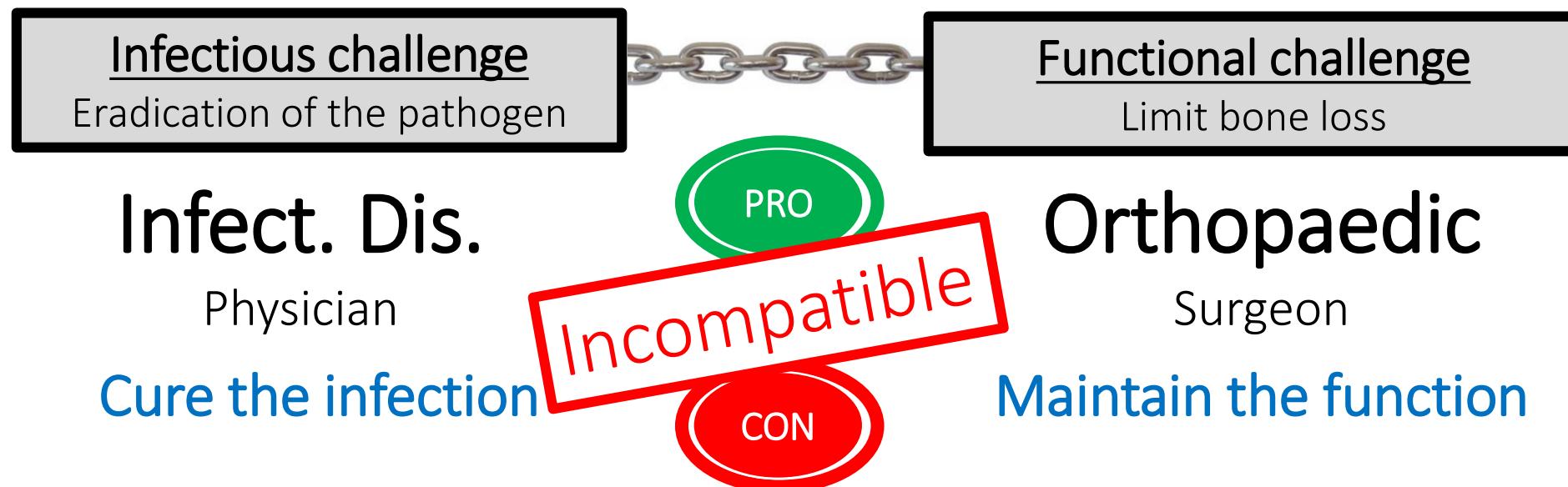
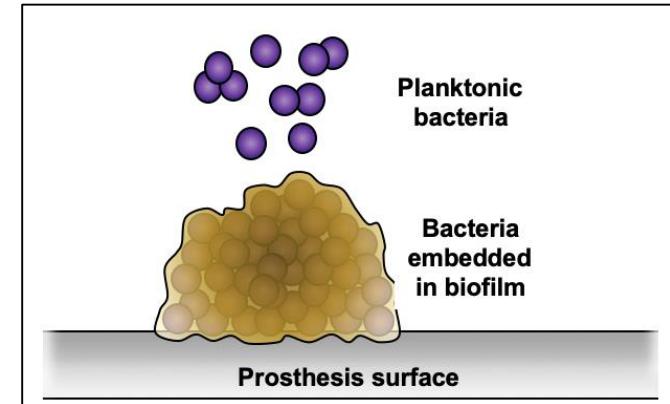
J. JOSSE *Front Microbiol* 2019



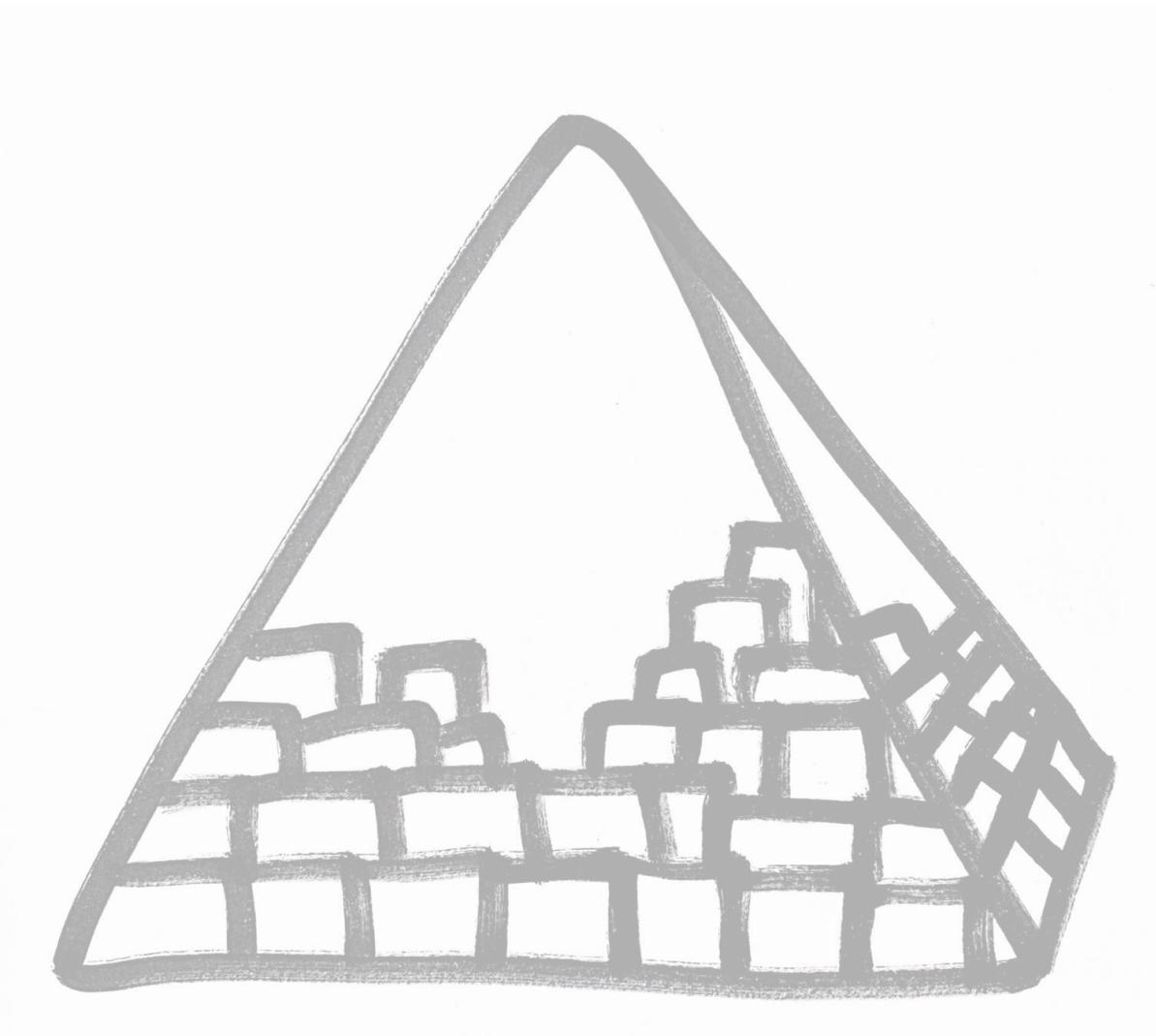
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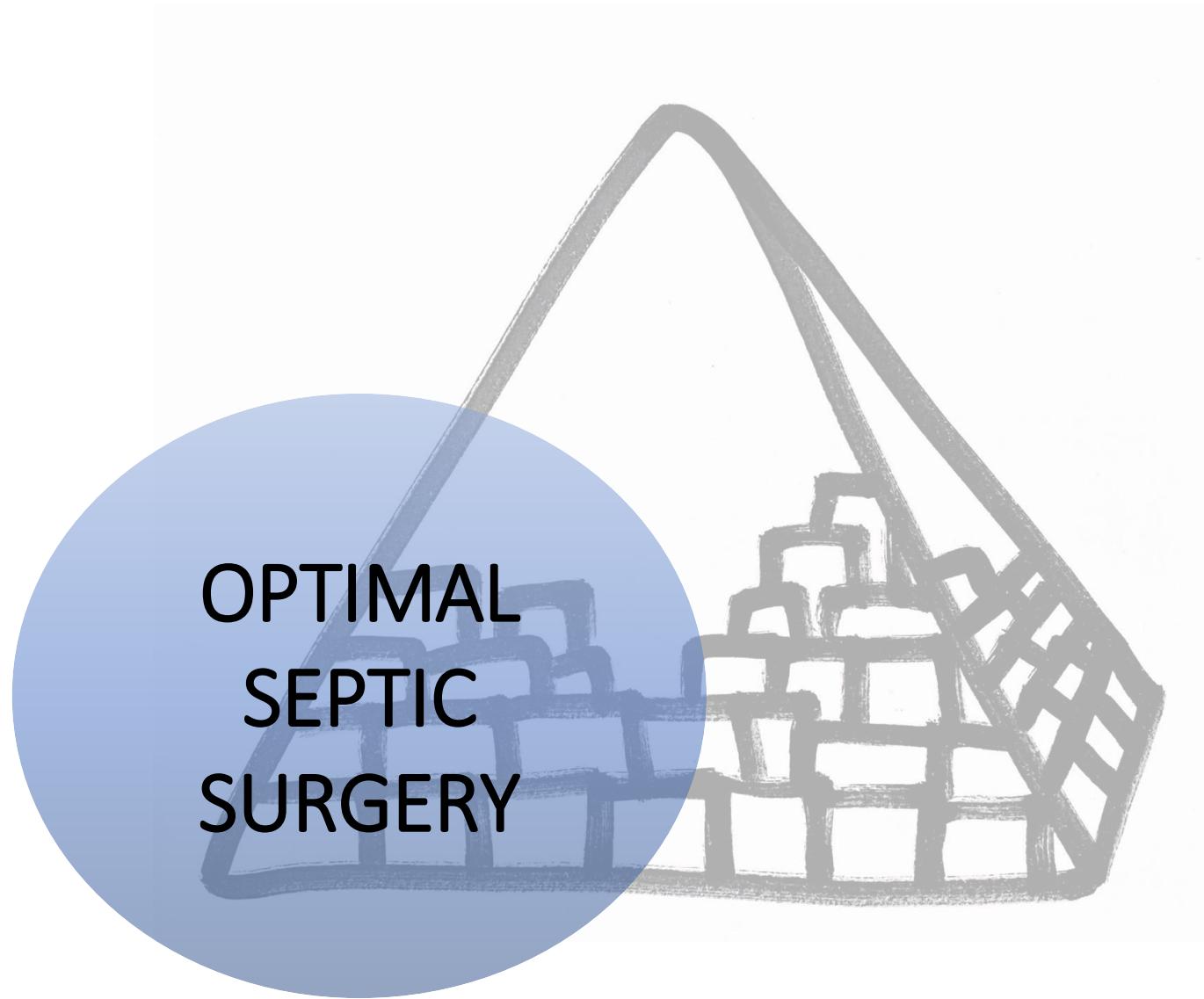
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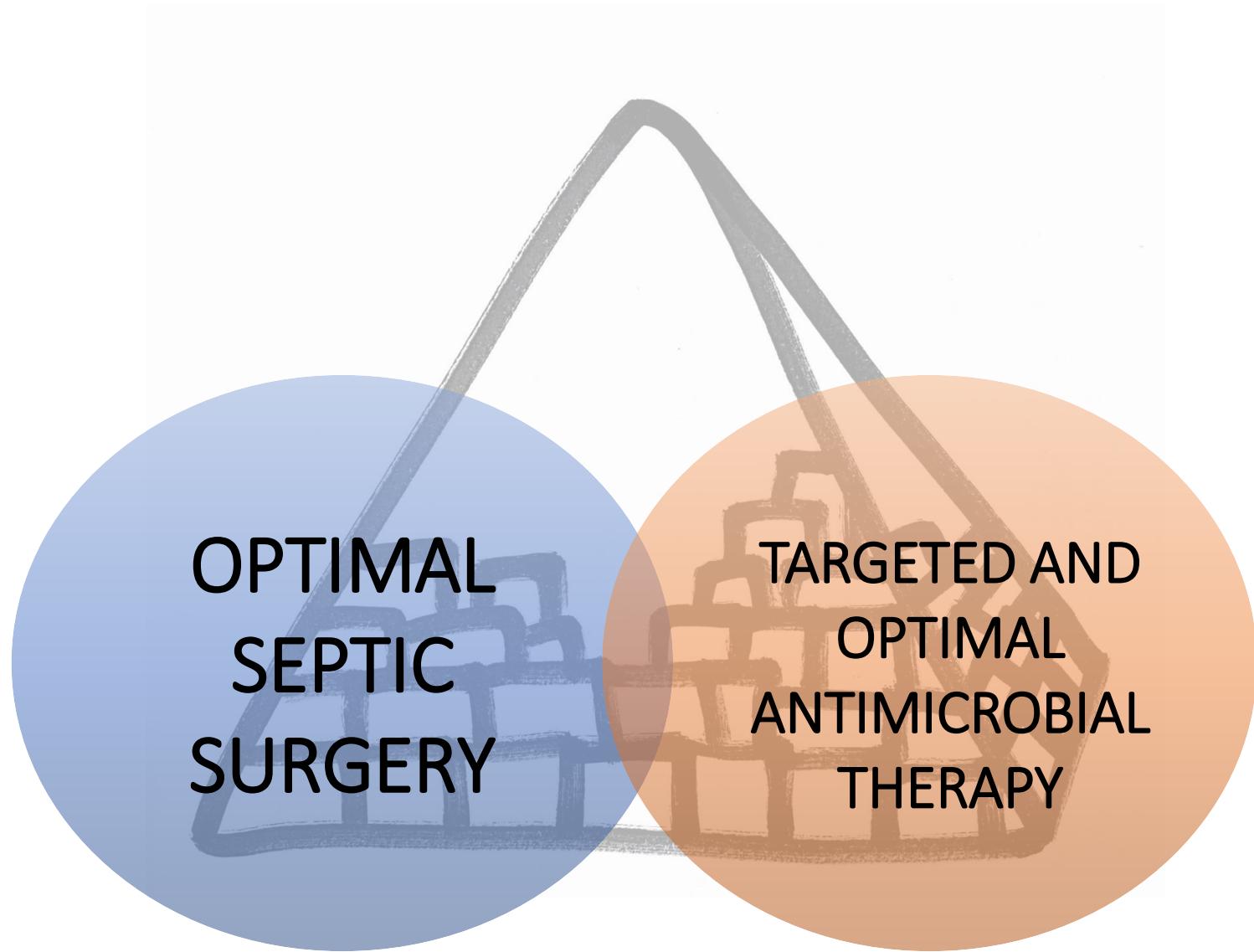
Personalized medicine for BJI



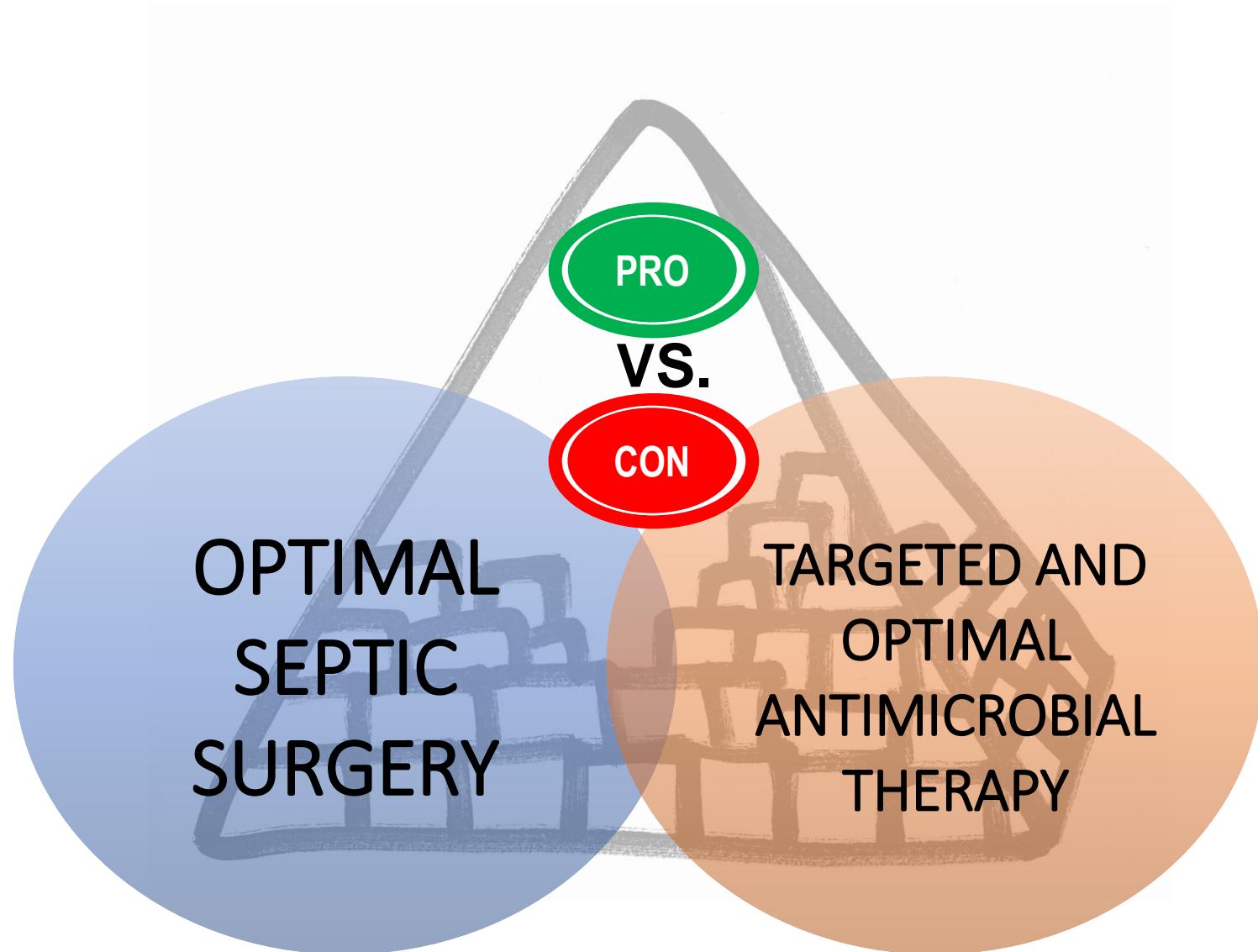
Personalized medicine for BJI



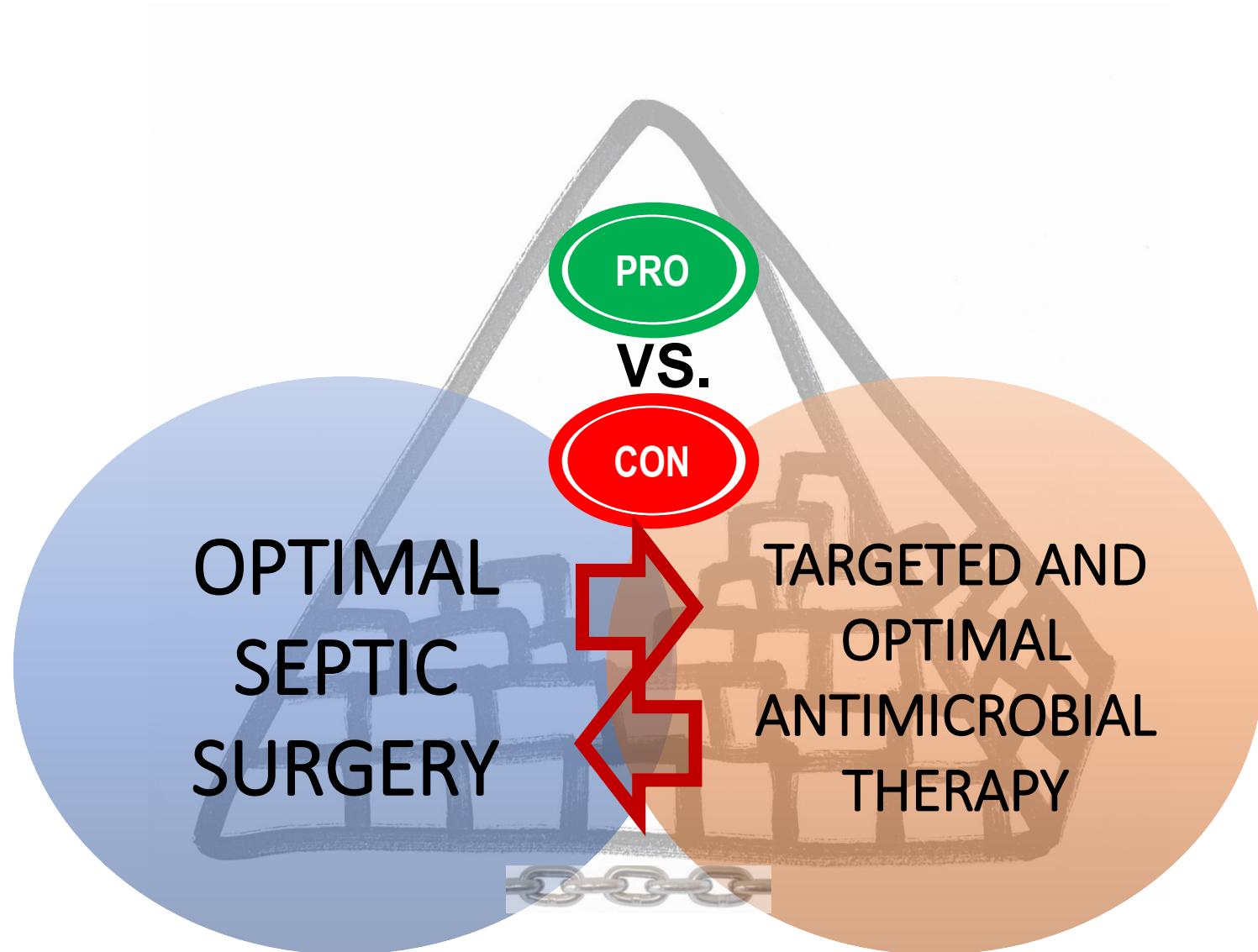
Personalized medicine for BJI



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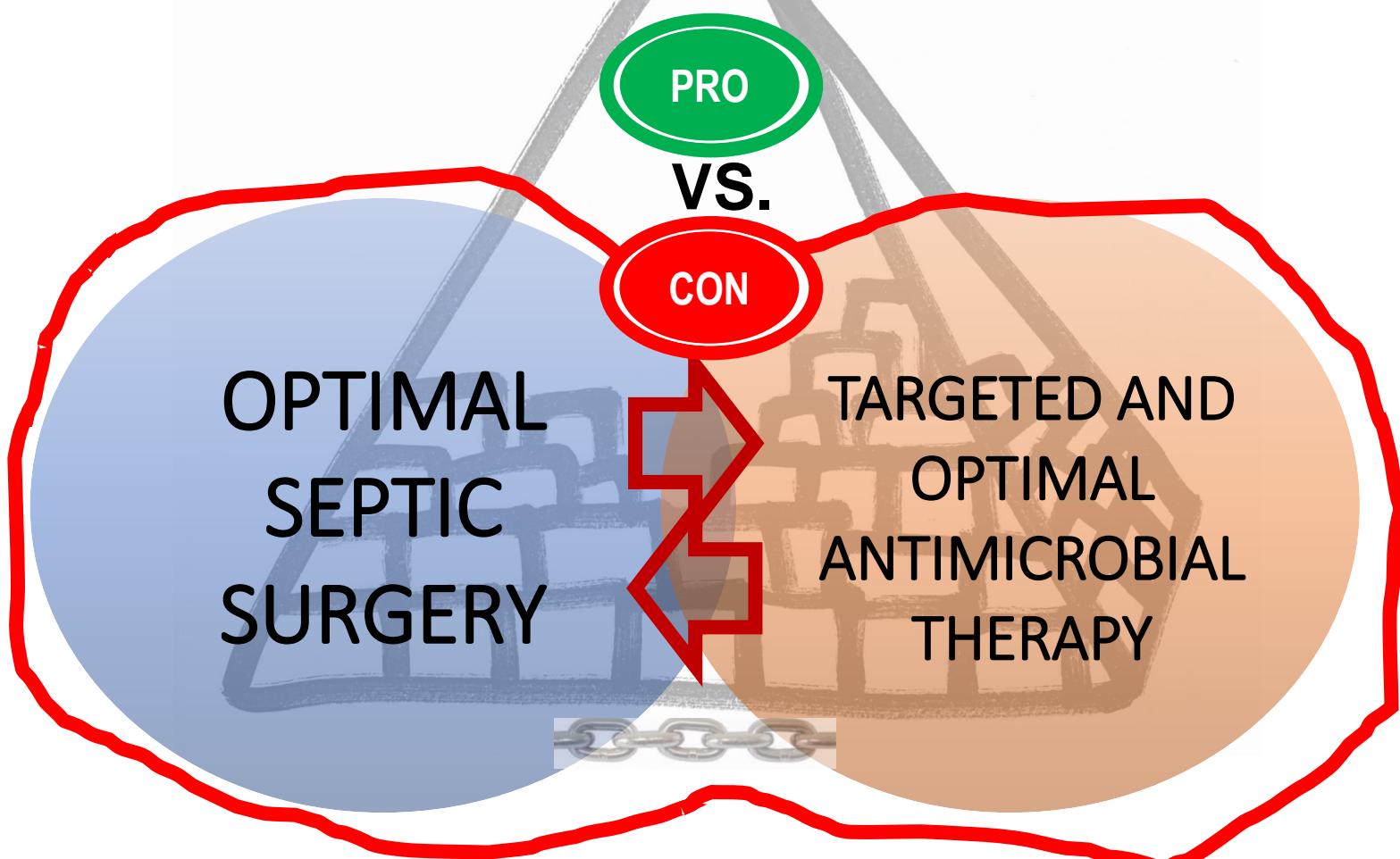


Personalized medicine for BJI



Personalized medicine for BJI

MULTIDISCIPLINAR MEETING THE BEST INDIVIDUALIZED MEDICOSURGICAL STRATEGY



Centre de Référence des Infections Ostéo-Articulaires complexes CRIOAc



Réseau des CRIOAc Mandat 2017-2022



Centre de Référence des Infections Ostéo-Articulaires complexes CRIOAc



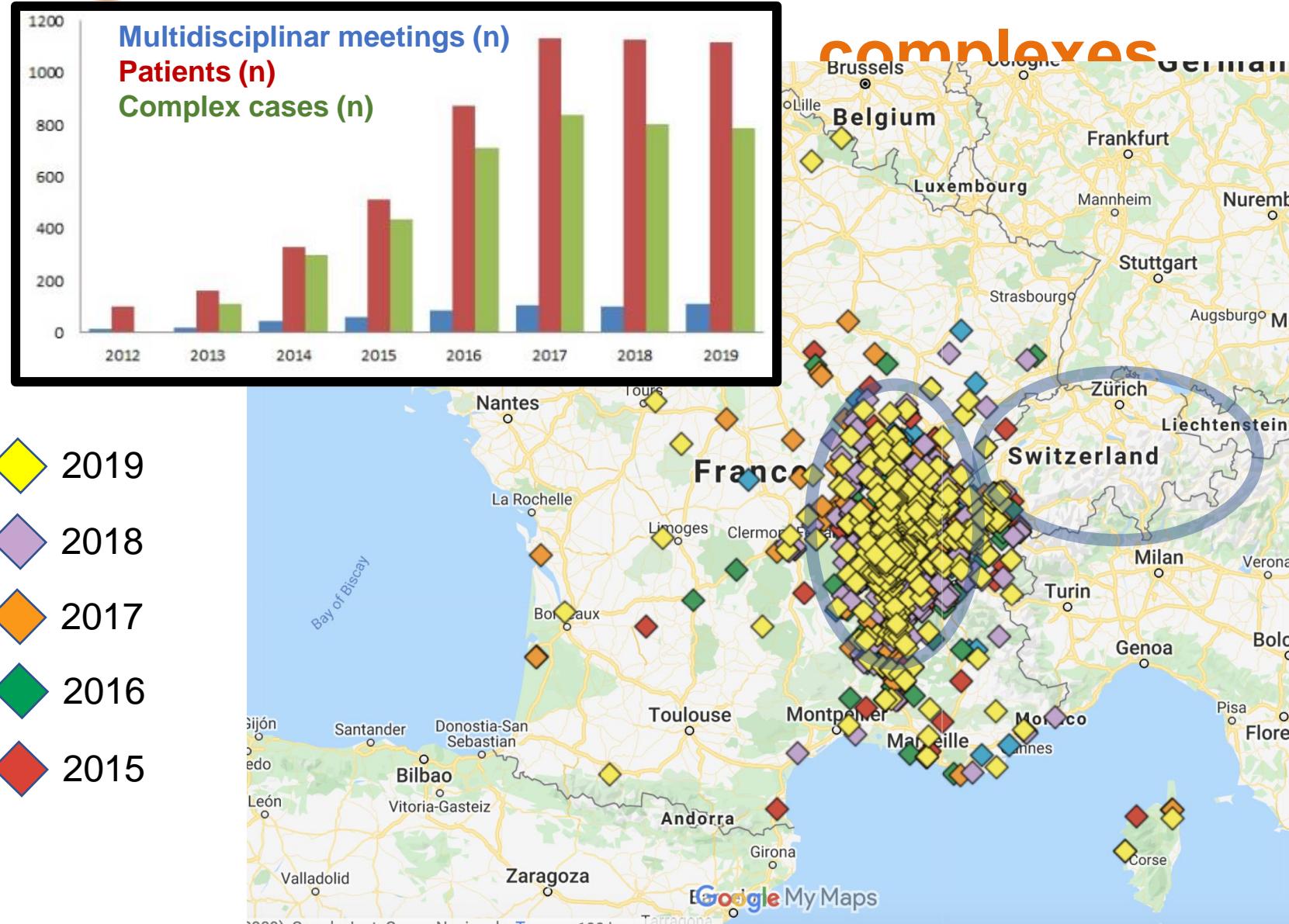
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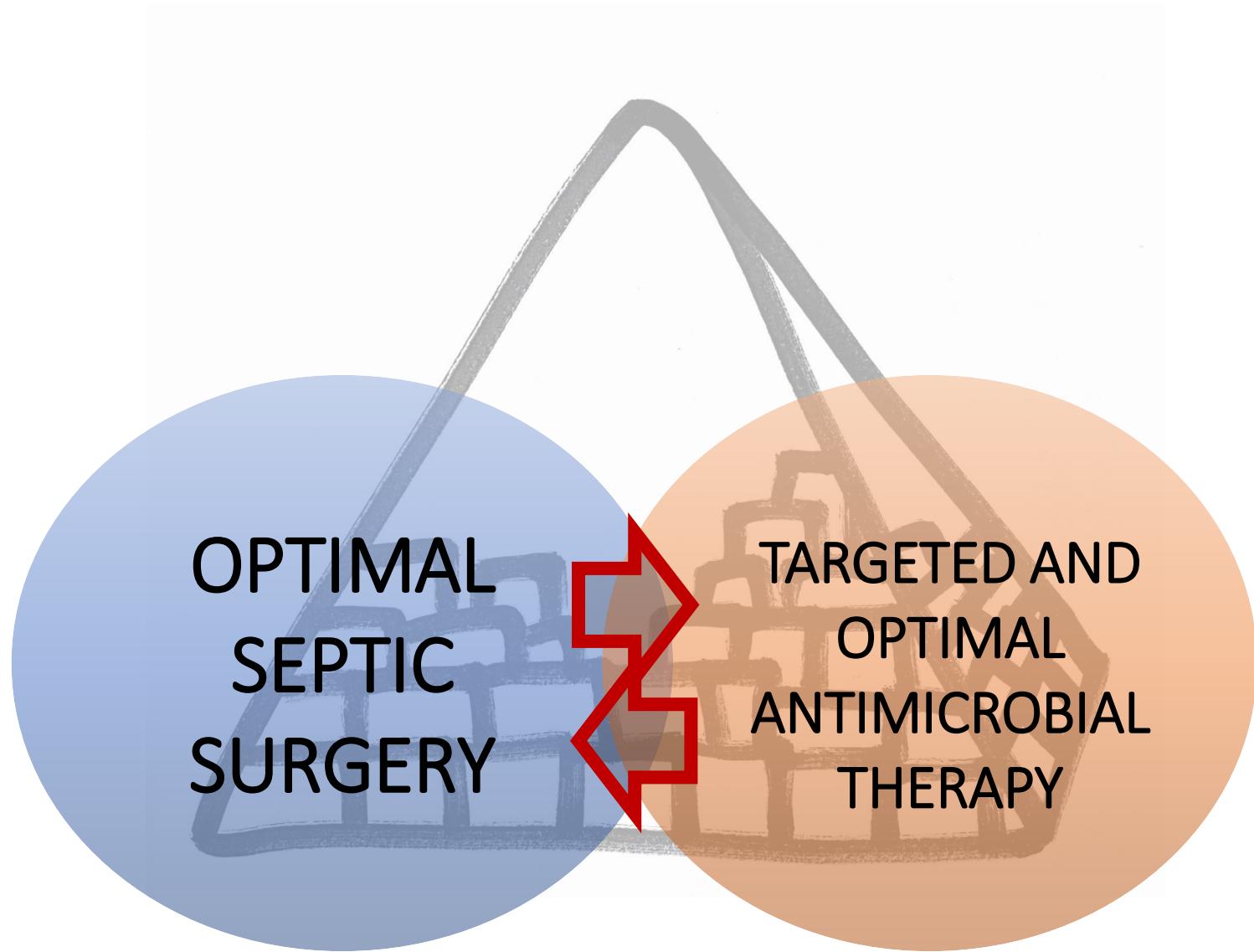
Centre de Référence des Infections Ostéo-Articulaires complexes CRIOAc



Centre de Référence des Infections Ostéo-Articulaires complexes



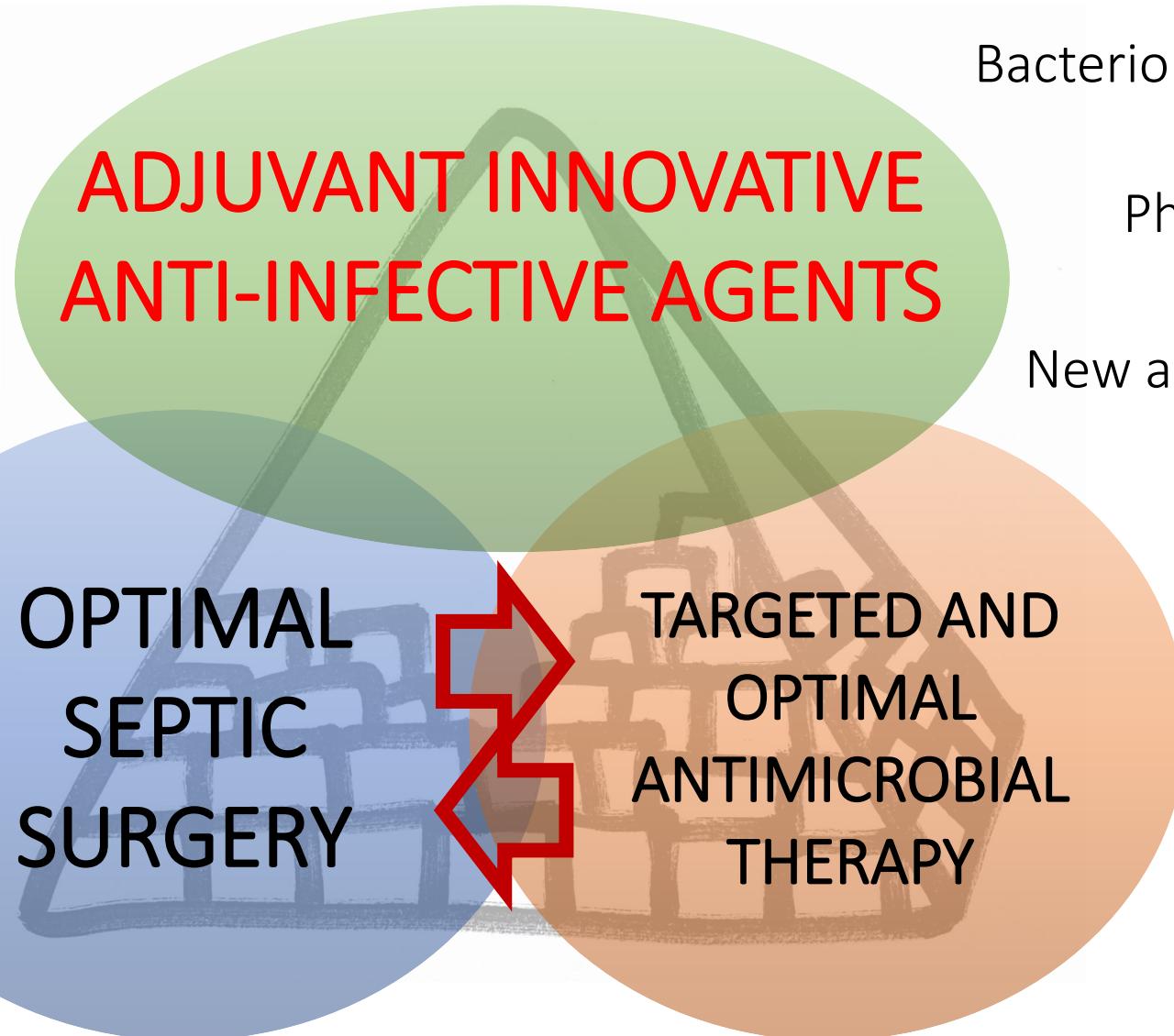
Personalized medicine for BJI



Personalized medicine for BJI

AntibioticS-loaded
PMMA cements

Antibiotic-loaded bone
substitutes



Bacteriophages

Phage-derived lysins

New antibiotics targeting
the biofilm

New antibiotics
usable for SAT

Subcutaneous
personalized SAT

Personalized medicine for BJI

AntibioticS-loaded
PMMA cements

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OPTIMAL
SEPTIC
SURGERY

ADJUVANT INNOVATIVE
ANTI-INFECTIVE AGENTS

Bacteriophages

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New antibiotics targeting
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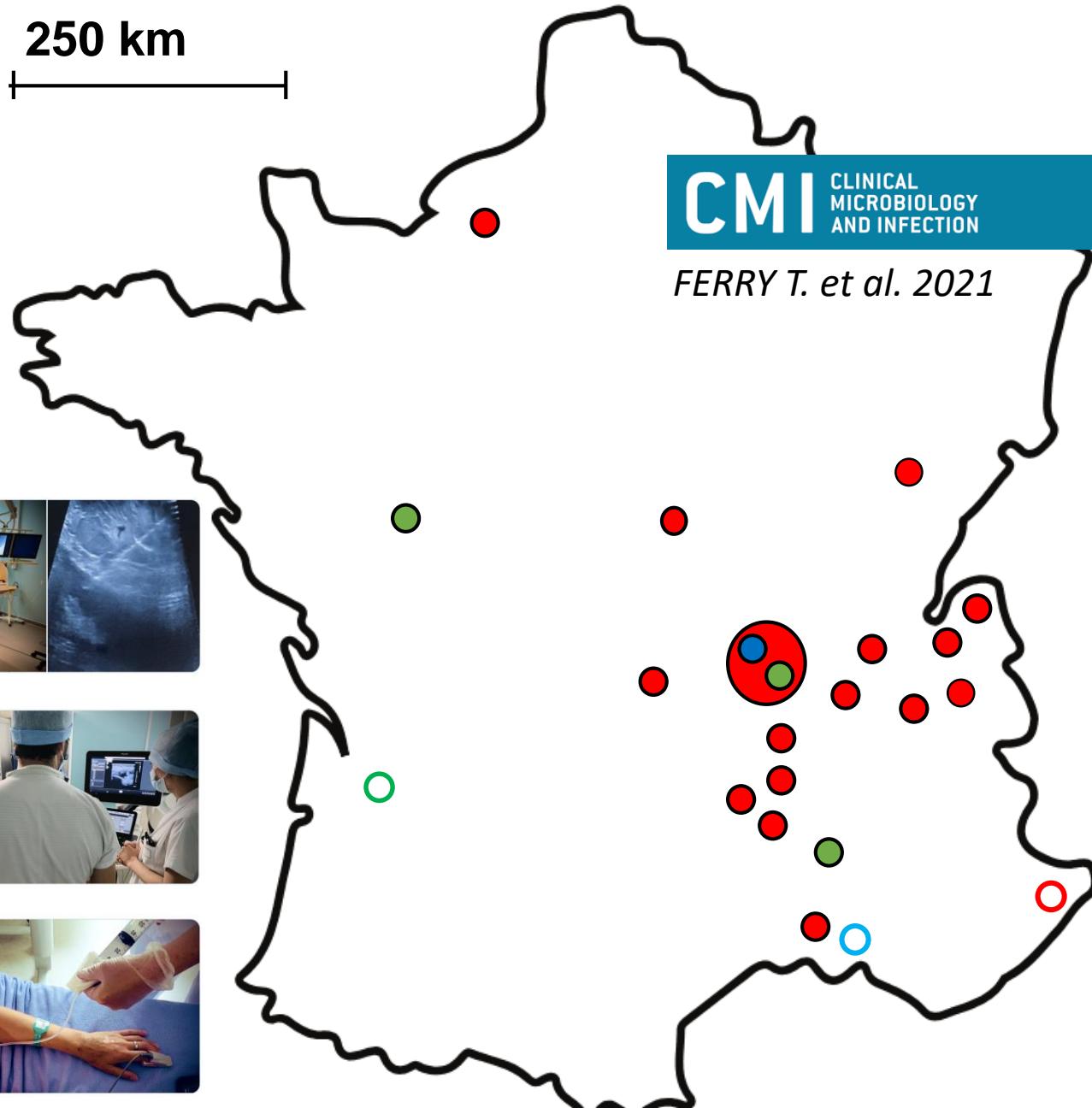
New antibiotics
usable for SAT

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Implementation of a Phage Therapy Center in a CRIODAc

250 km



PHAGES
TARGETTING
S. aureus
P. aeruginosa

NO PHAGE AGAINST *S. epidermidis*

PHAG--ONE

MINISTÈRE
DE L'ENSEIGNEMENT
SUPÉRIEUR,
DE LA RECHERCHE
ET DE L'INNOVATION
Liberté
Égalité
Fraternité



BJI

Endocarditis

Pneumonia

PHAGE *in LYON*



CRIODAc
LYON



FONDATION
HCL
HOSPISES CIVILS
DE LYON

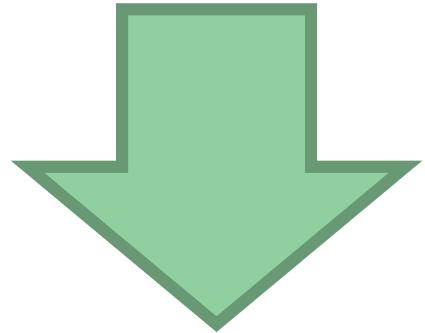
- T. FERRY OFID 2018
- T. FERRY JAC 2018
- T. FERRY Frontiers Med 2020
- T. FERRY Frontiers Med 2020
- T. FERRY SICOT-J 2020
- C. KOLENDRA AAC 2020
- T. FERRY Frontiers Med 2021

ContraFect



Prosthetic joint infection

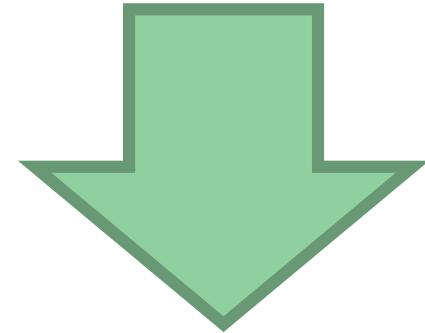
Acute
< 1 month



Open 'DAIR'
Debridement and
Implant Retention
60-80% success

Prosthetic joint infection

Acute
< 1 month



Open 'DAIR'
Debridement and
Implant Retention
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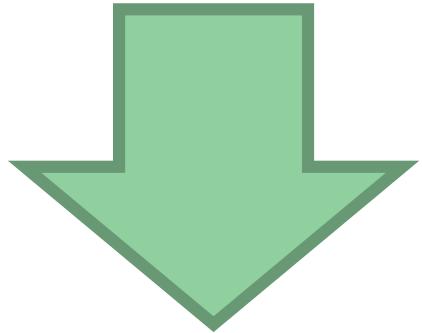
Josse et al.
Front Microb.
2019

Sendi et al.
Clin Infect Dis.
2006

Courtesy S. Lustig

Prosthetic joint infection

Acute
< 1 month



Open 'DAIR'
Debridement and
Implant Retention
60-80% success



No place
For arthroscopic DAIR



Success rate close to 0
Incomplete debridement
Impossible to change the mobile part

More convenient for the patient
Low rate of superinfection
Keep a drug into the joint space

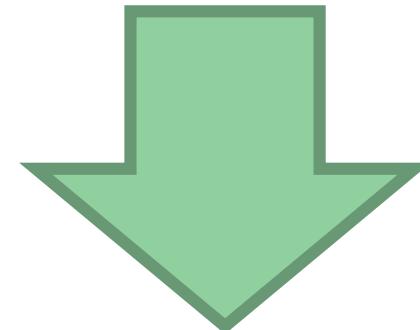
Prosthetic joint infection



Acute
< 1 month

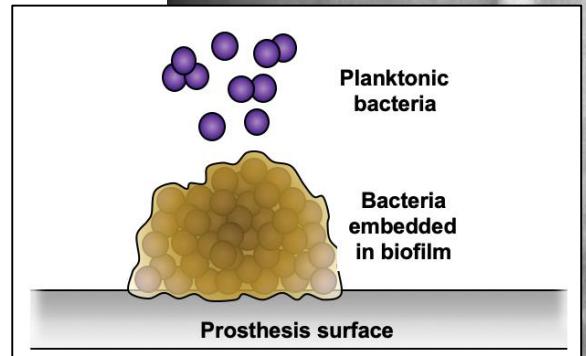


Chronic
> 3 months

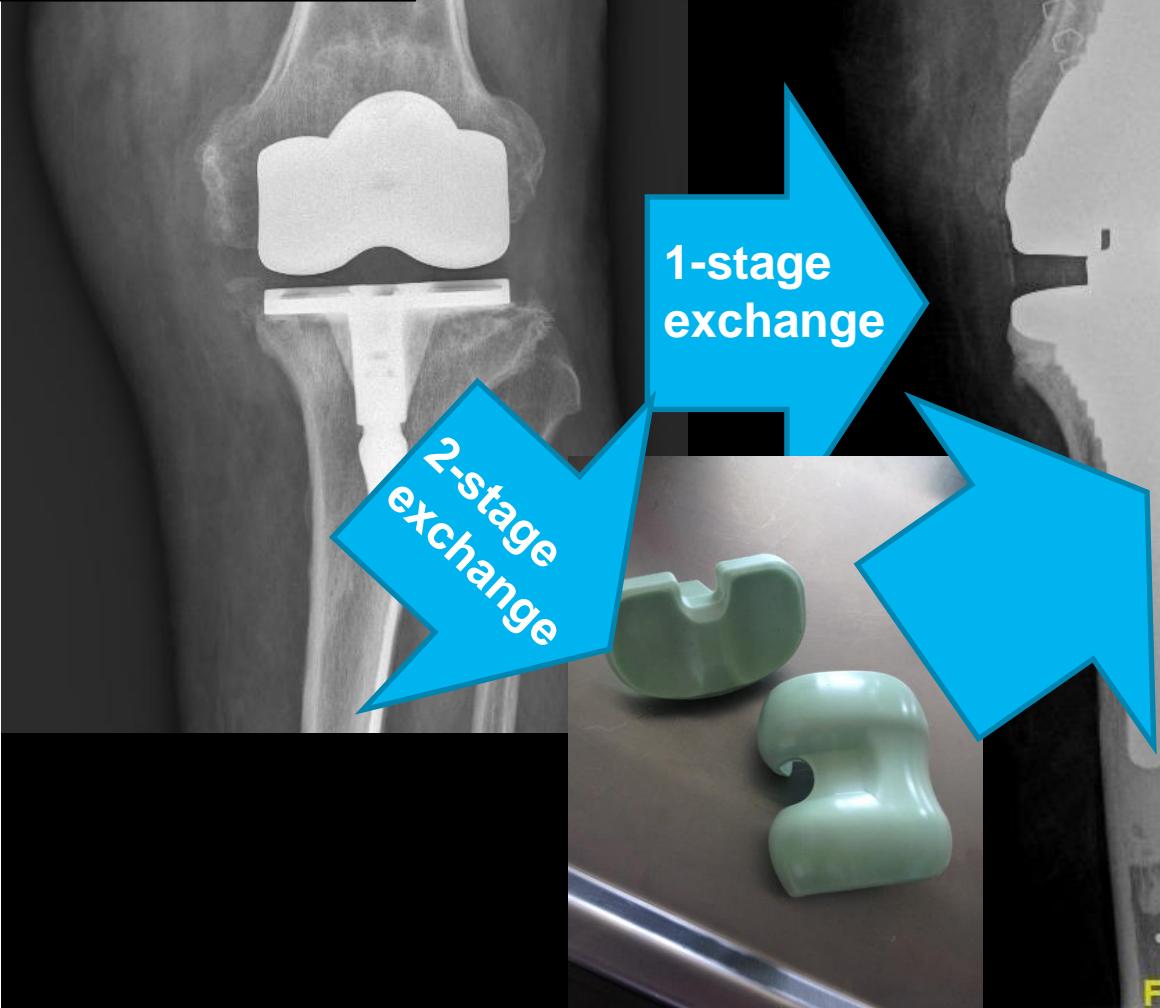


Open ‘DAIR’
Debridement and
Implant Retention
60-80% success

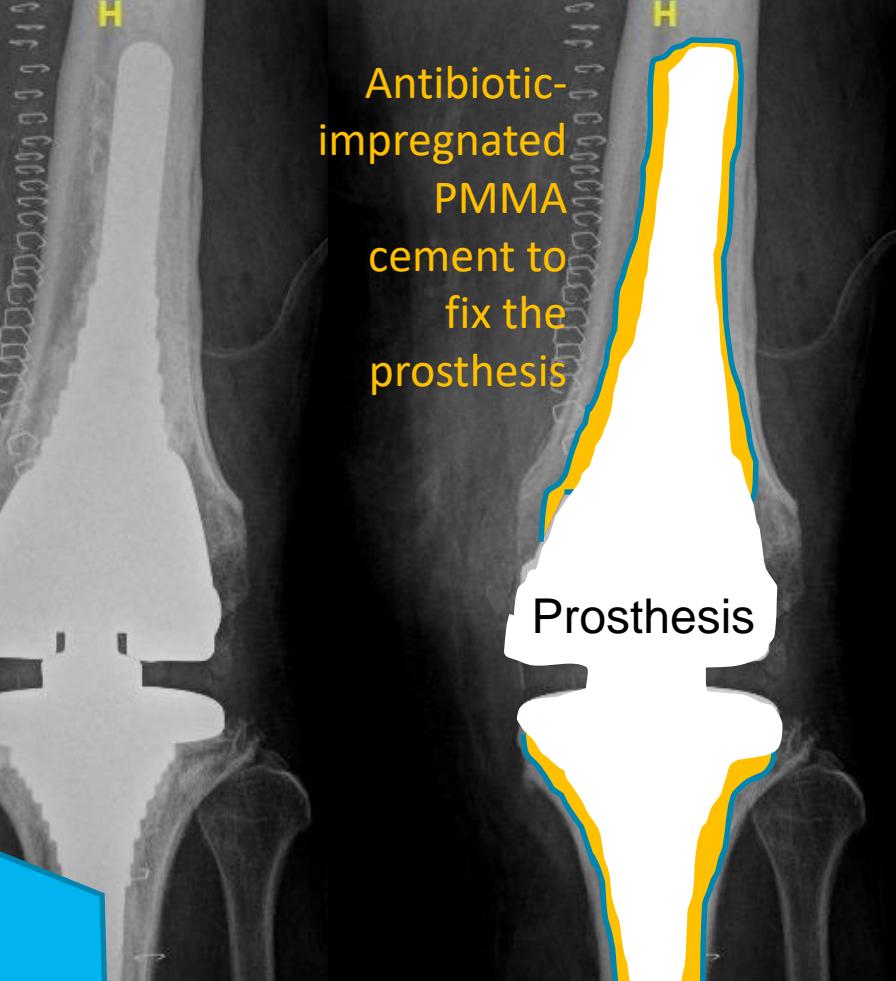
Prosthesis
Explantation
1- or 2- stage exchange
70-90% “success”



G



2-stage
exchange



Iterative surgeries
High cost for healthcare
Loss of function
Loss of bone stock
High risk of superinfection

F

Prosthetic joint infection

Acute
< 1 month

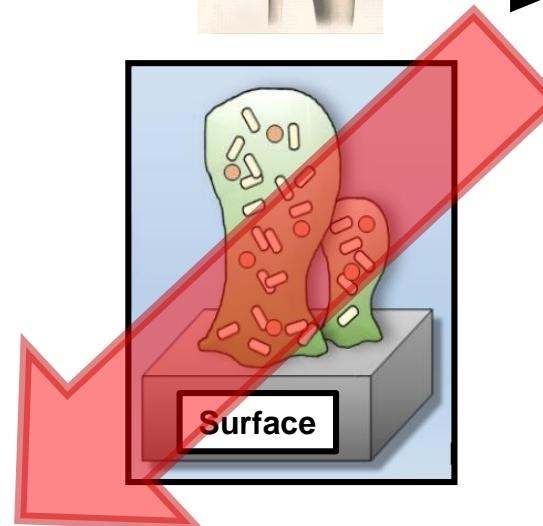


'DAIR'
**Debridement and
Implant Retention**
60-80% success

Low success rate for chronic infections

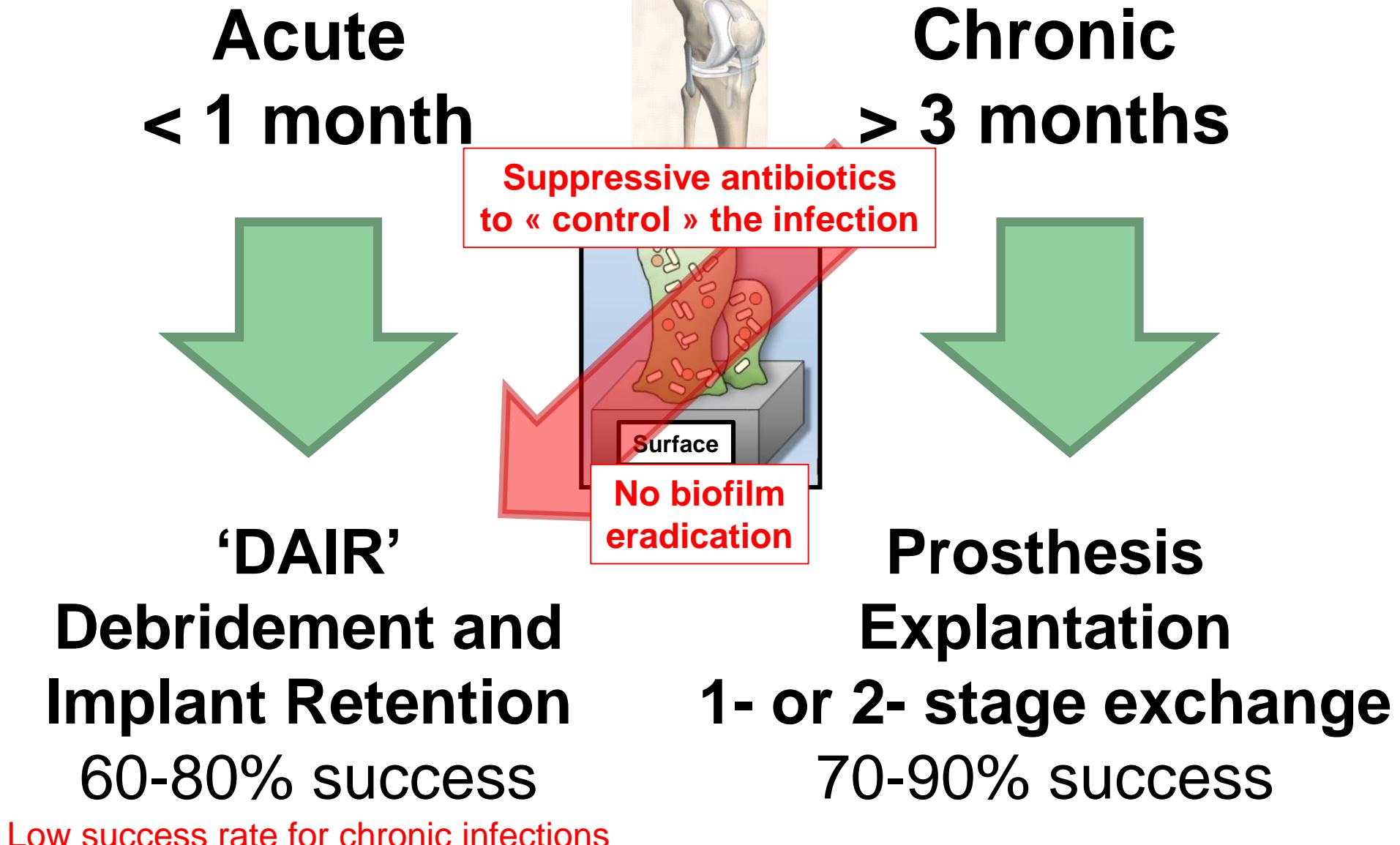


Chronic
> 3 months



**Prosthesis
Explantation**
1- or 2- stage exchange
70-90% success

Prosthetic joint infection



Prosthetic joint infection



'DAIR'
Debridement and
Implant Retention
60-80% success

Controlling the infection

Prosthesis
Explantation
1- or 2- stage exchange
70-90% success

Personalized medicine for BJI

AntibioticS-loaded
PMMA cements

Antibiotic-loaded bone
substitutes

OPTIMAL
SEPTIC
SURGERY

**ADJUVANT INNOVATIVE
ANTI-INFECTIVE AGENTS**

TARGETED AND
OPTIMAL
ANTIMICROBIAL
THERAPY

Bacteriophages

Phage-derived lysins

New antibiotics targeting
the biofilm

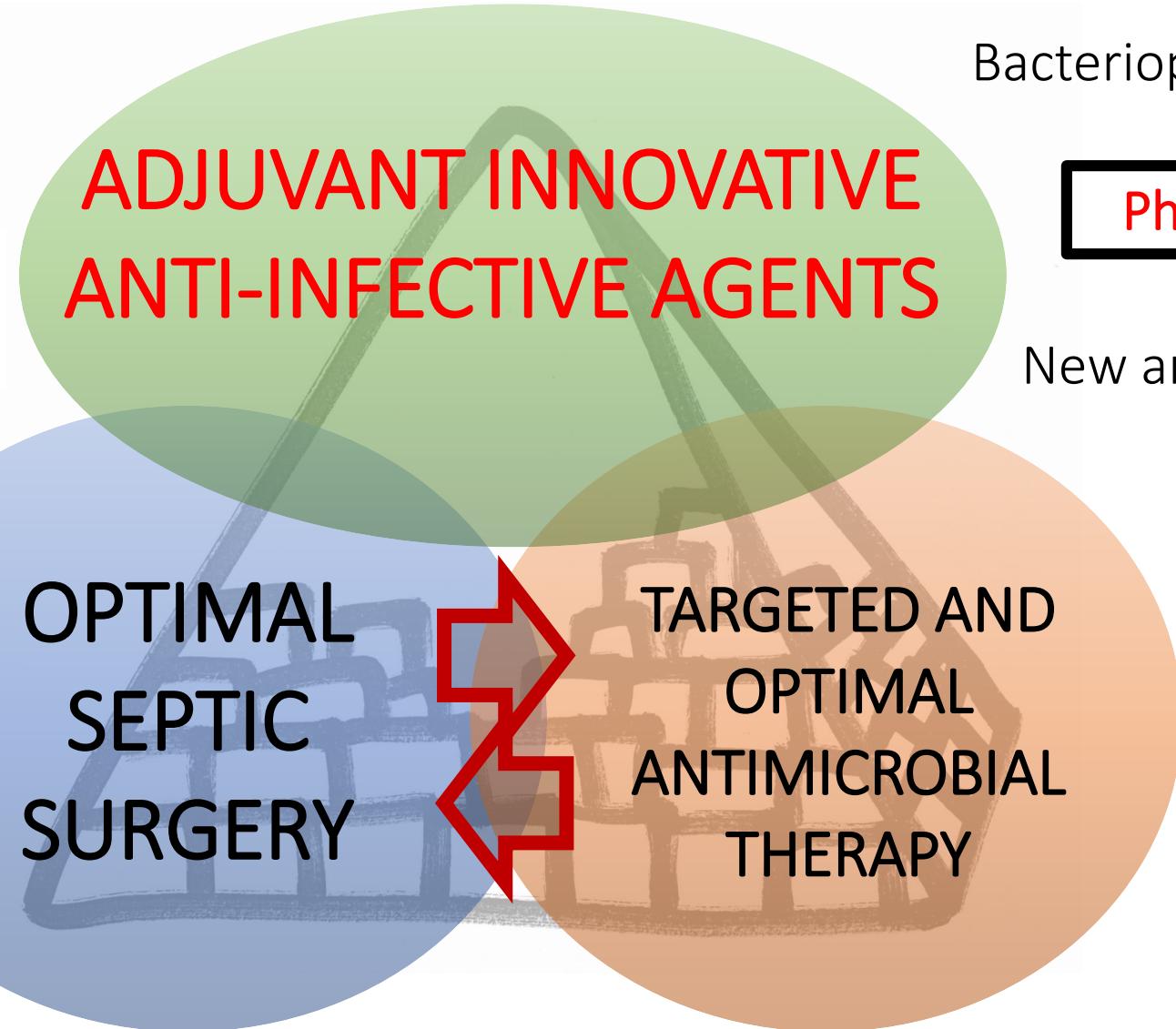
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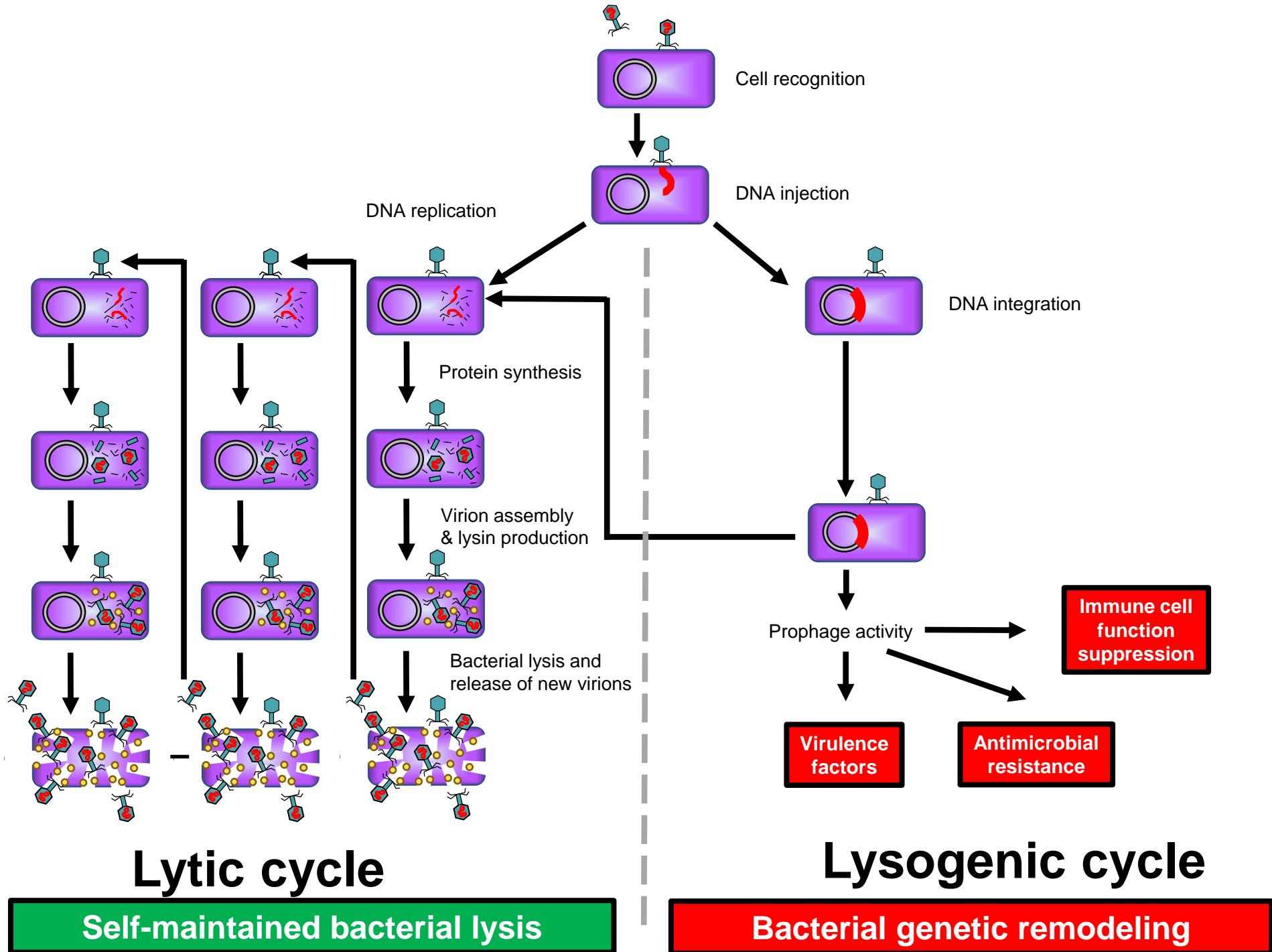
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personalized SAT



Bacteriophage Lysins



Vincent A Fischetti
@microbephage



Tristan Ferry Lyon University Hospitals
@FerryLyon

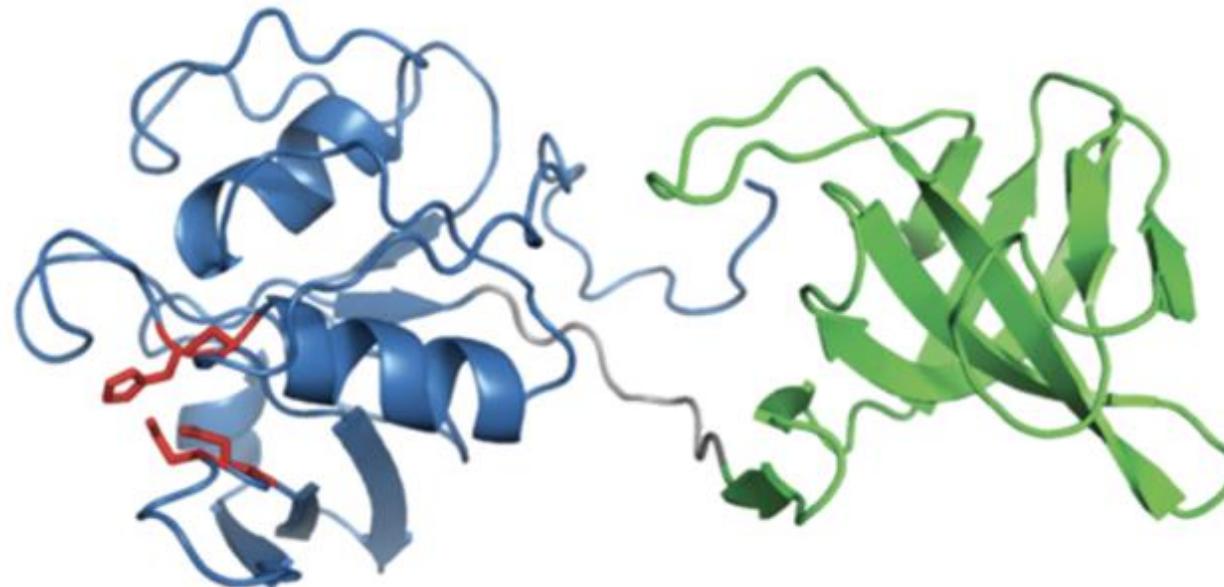
Incredible talk of Pr. Vincent A. Fischetti [@microbephage](#) [@IDWeek2019](#) about the great potential of **#bacteriophage #lysins** to induce bacterial explosion... and disappearance! It's good to hear that he discovered lysins that are active against **#multidrugresistant #ESKAPE** pathogens!

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



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



CF-301

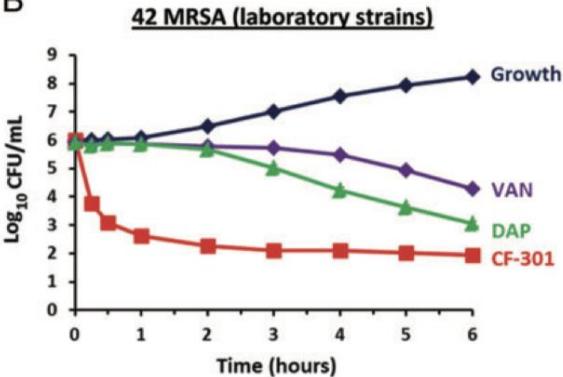
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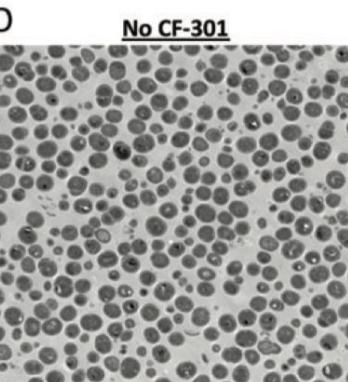
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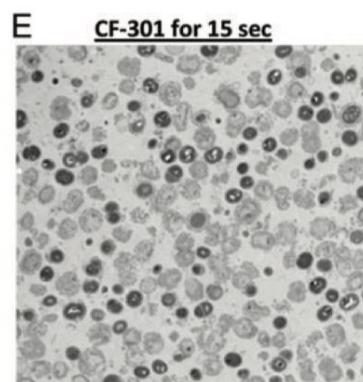
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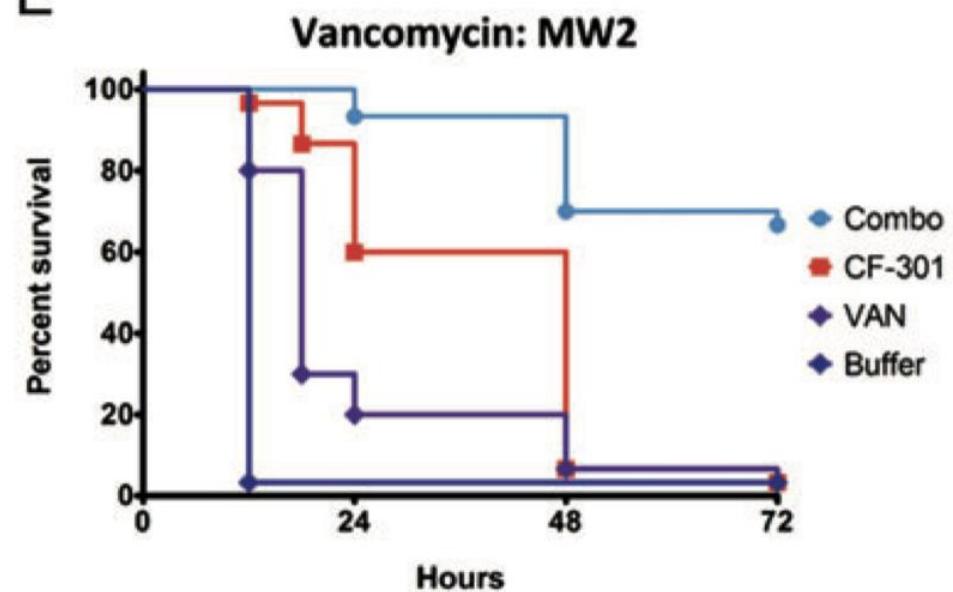
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E

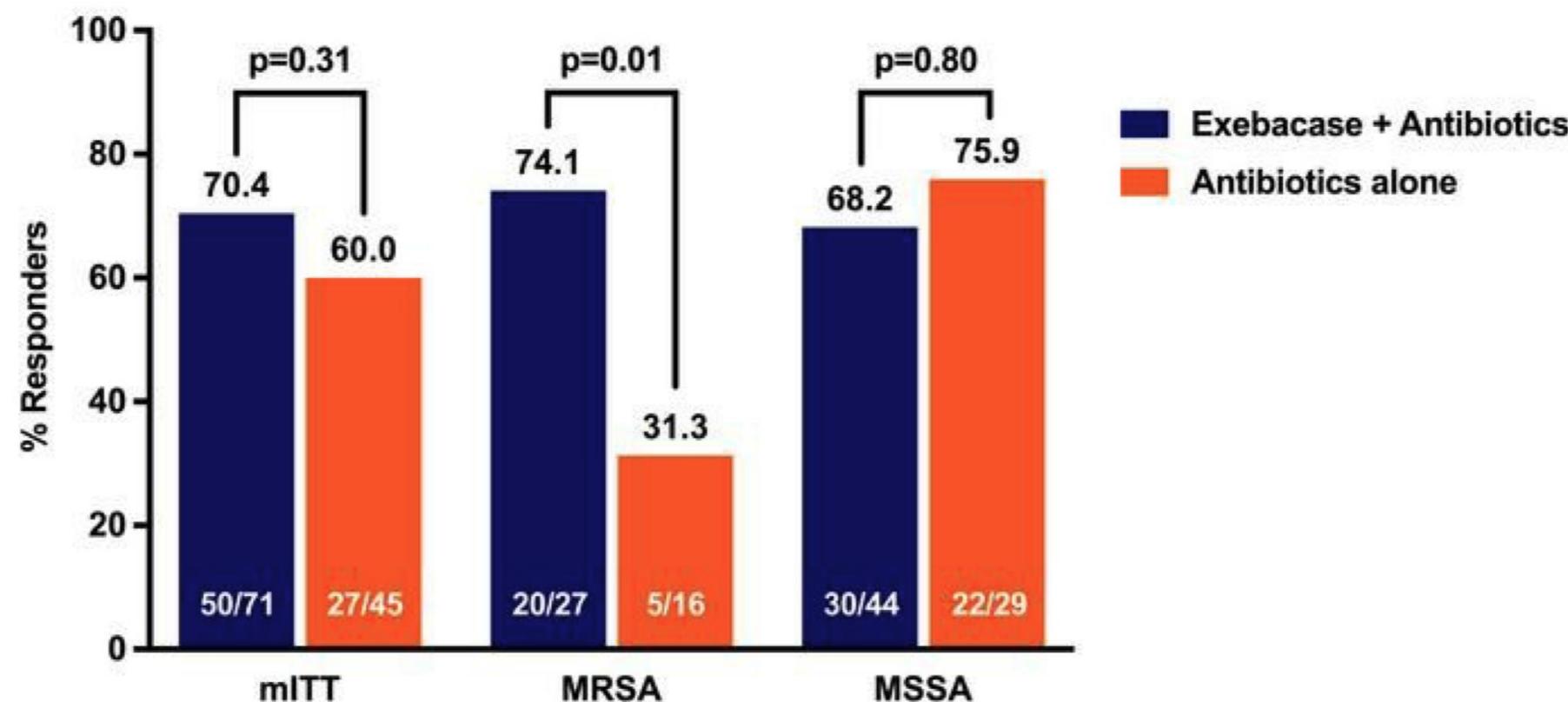


E



Exebacase for patients with *Staphylococcus aureus* bloodstream infection and endocarditis

Vance G. Fowler Jr.,^{1,2} Anita F. Das,³ Joy Lipka-Diamond,⁴ Raymond Schuch,⁵ Roger Pomerantz,⁵ Luis Jáuregui-Peredo,⁶ Adam Bressler,⁷ David Evans,⁸ Gregory J. Moran,⁹ Mark E. Rupp,¹⁰ Robert Wise,¹¹ G. Ralph Corey,¹ Marcus Zervos,¹² Pamela S. Douglas,^{1,2} and Cara Cassino⁵



Bacteriophage Lysin CF-301, a Potent Antistaphylococcal Biofilm Agent

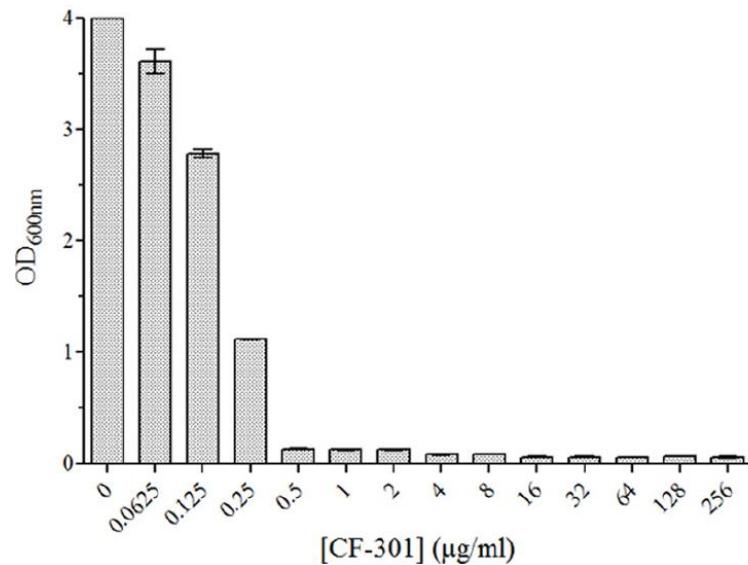
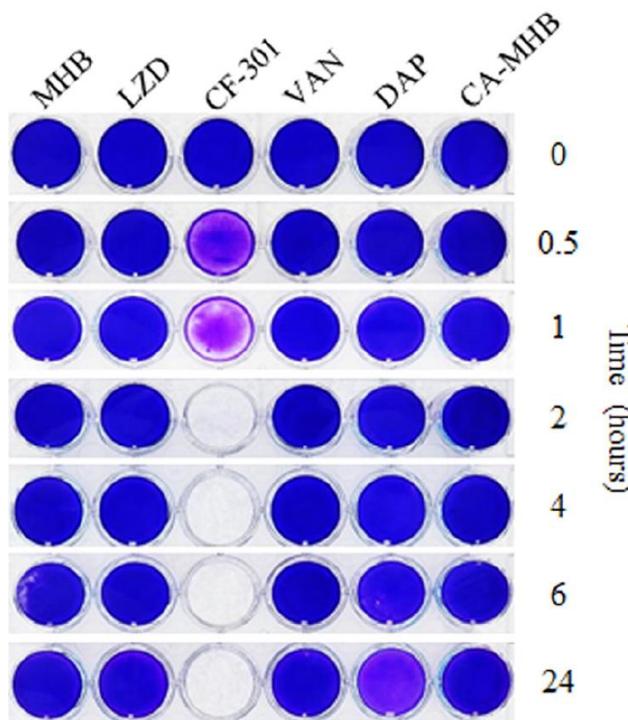
Raymond Schuch,^a Babar K. Khan,^{a*} Assaf Raz,^b Jimmy A. Rotolo,^a Michael Wittekind^a

ContraFect Corporation, Yonkers, New York, USA^a; Laboratory of Bacterial Pathogenesis and Immunology, The Rockefeller University, New York, New York, USA^b

TABLE 1 Activity of CF-301 and DAP against mature biofilms

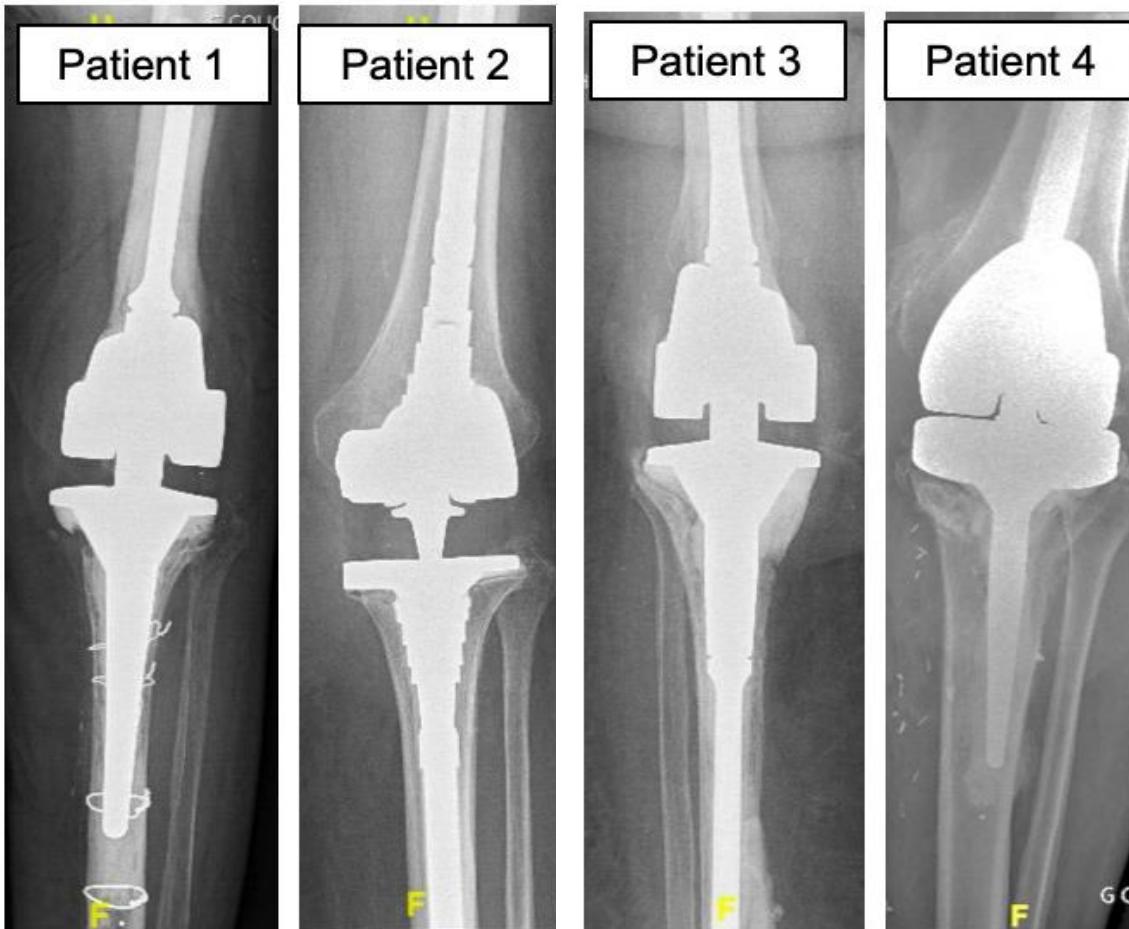
Organism	n	Concn ($\mu\text{g/ml}$) of:			
		CF-301		DAP	
		MBEC ₉₀	Range	MBEC ₉₀	Range
MSSA	40	0.125	0.125 to 1	>1,024	512 to >1,024
MRSA	55	0.25	0.125 to 0.5	>1,024	>1,024
CoNS ^a	46	8	0.125 to 32	>1,024	256 to >1,024
<i>S. pyogenes</i> (group A)	27	0.25	0.03 to 1	>1,024	256 to >1,024
<i>S. agalactiae</i> (group B)	20	0.5	0.03 to 1	>1,024	512 to >1,024

^aCoagulase-negative staphylococci examined in this study include the following (number of isolates in parentheses): *S. epidermidis* (21), *S. warneri* (9), *S. hominis* (5), *S. capitis* (2), *S. saprophyticus* (2), *S. cohnii* (1), *S. hyicus* (1), *S. lugdunensis* (2), *S. sciuri* (2) and *S. simulans* (1).



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

#LysinDAIR procedure



CrioAc
LYON

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

#LysinDAIR procedure

Table 1. Antibiograms and exebacase MIC of the patients' *S. epidermidis* isolates.

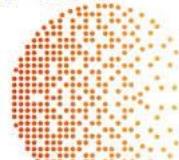
Patient	PJI episode	Sampling date	Exebacase MIC (mg/L)	Antibiotics												
				OXA	K	GM	NN	E	L	TE	OFX	SXT	FA	RA	VA	LZD
Patient 1	Previous episode	04/02/2016	NT	R	R	R	R	R	R	I	R	R	R	R	S	S
	Joint puncture before surgery	17/11/2017	1	R	R	R	R	R	R	I	R	R	R	R	S	S
	At the time of surgery	08/11/2018	2	R	R	R	R	R	R	I	R	R	R	R	S	S
Patient 2	Previous episode	02/12/2013	NT	R	S	S	S	R	R	S	S	R	R	R	S	S
	Previous episode	11/10/2013	NT	S	R	R	R	R	R	S	R	R	R	R	S	S
	Joint puncture before surgery	13/09/2018	0.125	S	S	S	S	S	S	S	S	S	S	NT	S	S
	At the time of surgery*	08/11/2018	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Patient 3	Previous episode	04/02/2011	NT	R	R	R	R	R	R	R	S	R	NT	S	S	S
	Joint puncture before surgery	07/06/2018	0.25	S	R	R	R	R	R	R	S	R	R	S	S	S
	At the time of surgery	10/01/2019	2	S	R	R	R	R	R	R	I	R	R	S	S	S
Patient 4	Previous episode	23/05/2018	NT	S	S	S	S	R	S	S	S	S	R	S	S	S
	Joint puncture before surgery	19/07/2018	ID	S	S	S	S	R	S	S	S	S	S	S	S	S
	At the time of surgery	10/01/2019	NT	R	R	R	R	R	R	S	R	R	R	S	S	S

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#LysinDAIR procedure



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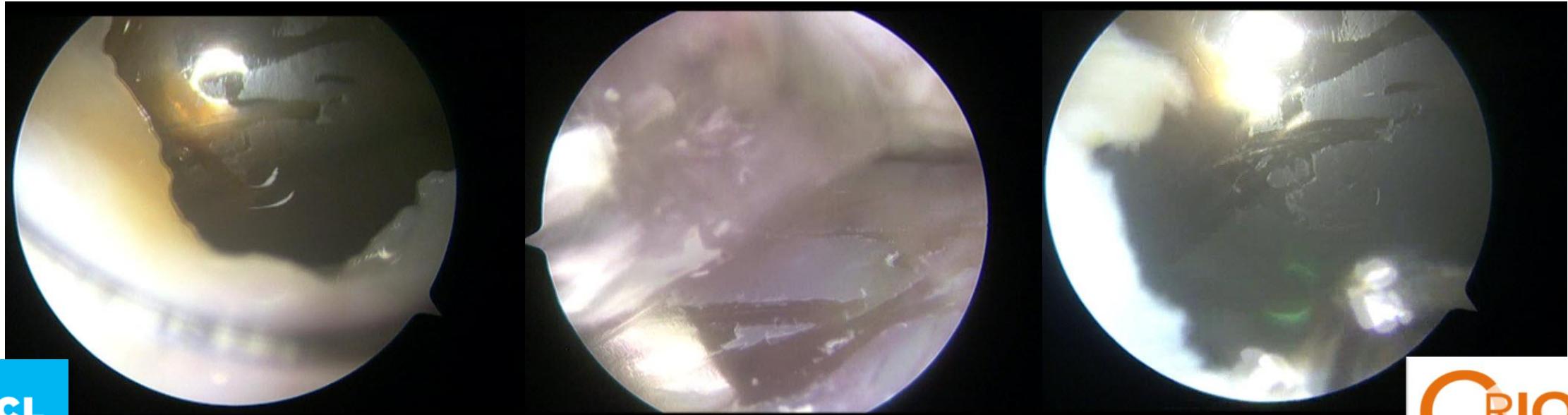
30th
ECCMID
Paris, France
18 –21 April 2020

frontiers
in Medicine

CRIOAc
LYON

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

#LysinDAIR procedure



HCL
HOSPISES CIVILS
DE LYON

CRIoAC
LYON

The biofilm was macroscopically visible

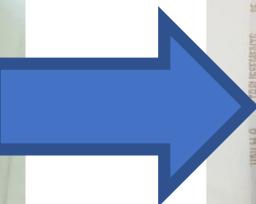
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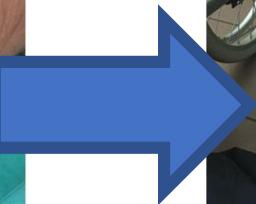


No Lysin-related
adverse event

ContraFect



Relapse
at 2 years



Clinical
response
at 1 year

Favorable
outcome
at 2 years



Conclusion

- Part of patients with chronic PJI need conservative treatments to keep the function
- Dedicated clinical expertise (CRIoAc) is required to select patients and relevant indication of a conservative approach
- No Phage targeting *S. epidermidis* is available in France
- Exebacase (CF-301) is a lysin with bactericidal and anti-biofilm activities
 - Clinical trial in patients with *S. aureus* bacteremia
 - Under the supervision of the French healthcare authority, four patients with relapsing multidrug-resistant *S. epidermidis* prosthetic knee infection were treated with the LysinDAIR procedure
- Clinical response at one year in two of them, with a sustained response at 2 years in one patient
- Exebacase has the potential to be used as salvage therapy during arthroscopic DAIR in patients with relapsing multidrug-resistant *S. epidermidis* prosthetic knee infection, to improve the efficacy of suppressive antibiotics, and to avoid considerable loss of function
- Phase II clinical trial will be done to confirm this hypothesis



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, Elliot 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, Loïc Boussel, Jean-Baptiste Pialat, Isabelle Morelec;

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

Clinical research assistant and database manager– Eugénie Mabrut

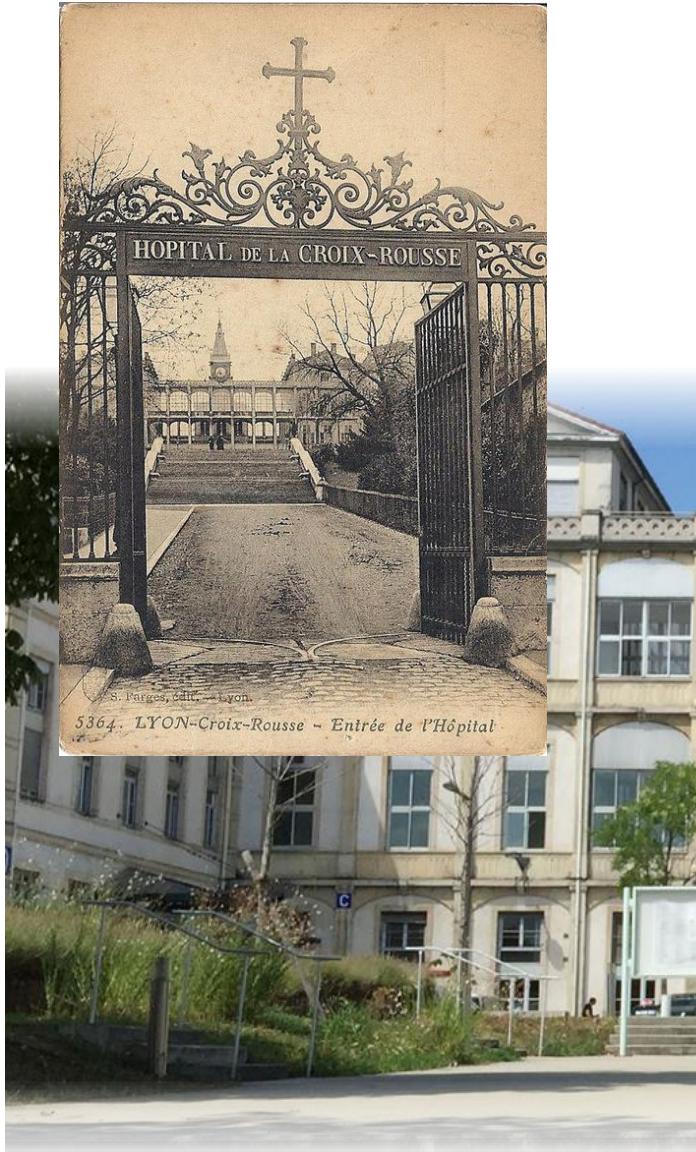
PHAGE *in* LYON

Coordinator: Tristan Ferry and Frederic Laurent

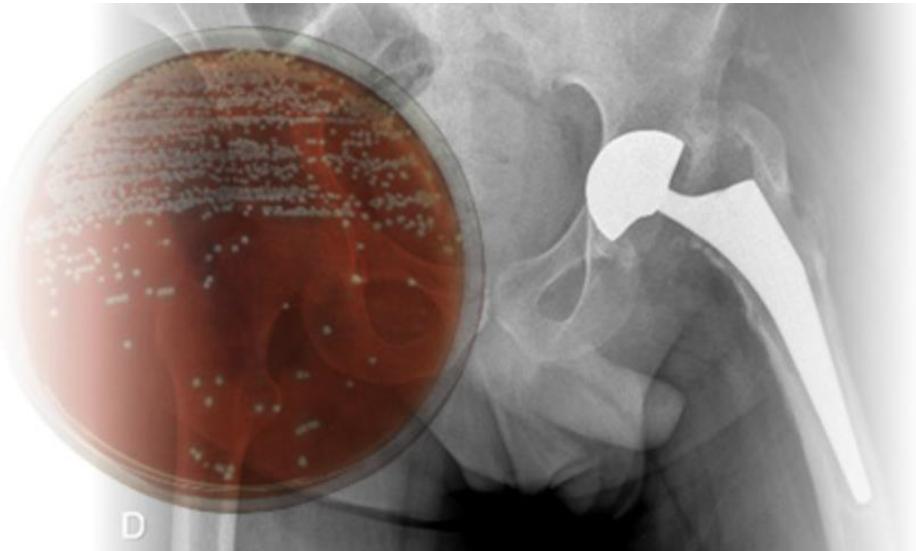
Mathieu Medina, Camille Kolenda, Floriane Laumay, Mélanie Bonhomme, Leslie Blazere, Tiphaine Legendre, Eline Terrazzoni, Fabrice Pirot, Camille Merienne, Samira Filali, Benjamin Lapras, Gilles Leboucher, Thomas Briot



Croix-Rousse Hospital



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