#### Phage therapy experience in France in the field of Bone and Joint Infection

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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...)
- <u>A phage is specific to A type of bacteria</u>
- Largely abundant in the biosphere: 10<sup>31</sup> bacteriophages on the planet, more than every other organism
- Especially in marine environment, sea, lake, backwater, soil, animal and human stools, etc.













## **Bone and joint infections**

Post-trauma long-bone osteomyelitis



Chronic prosthetic-joint infection



Spinal infection with abscess and bone destruction



Surgery (debridement & reconstruction) Antibiotics Surgery (prosthesis explantation) Antibiotics Surgery (debridement & stabilization) Antibiotics





UB

🖐 Inserm

Centre de Ressources Biologiques

#### **Centre de Référence des Infections Ostéo-Articulaires complexes**



#### Réseau des CRIOAc Mandat 2017-2022

le-Tourcoing **STAPHYLOCOOUES** Marine ntre National de Référence Rem Strasbourg Pr. Tristan Ferry Pr. Sébastien Lustig MD. PhD MD, PhD **Multidisciplinar management of** Orthopaedic surgeon Infectiologist the patient Lvon Better understanding of the Pr. Frédéric Laurent PharmD, PhD pathophysiology of BJI Microbiologist

> HOSPICES CIVILS

DE LYON

Centre nternational

de Recherche

en Infectiologie

#### **Promotion of innovative** treatments

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



#### **Centre de Référence des Infections** RIOAC **Ostéo-Articulaires complexes**



LYON



54-year-old man <u>Trauma</u> with open fracture

Post-trauma tibial *S. aureus* **osteomyelitis** 

Surgical debridement

Antibiotics

Failure

Management in Georgia for receiving **phage therapy** bacteriophages 10 years ago

Failure





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Clinical case #1		
54-yea Traum	Partial bone necrosis requiring <u>surgery</u>	
Post-ti <b>osteo</b>	Skin and soft tissue damage requiring surgical coverage	
Surgio Antibio Failure Manag receiv bacter	MAJOR BIOLOGICAL LIMIT: Bacteriophages have not the ability to: perform bone debridement regenerate skin and soft tissue	



#### Docteur André RAIGA

Ancien Interne lauréat des Hôpitaux Ex-Chef de Clinique chirurgicale à la Faculté

. . .

At the stage of bone necrosis, **it will only succeed in stopping the progression of the infection**, but **it will be able to do nothing against the dead bone deprived of circulation; this bone will become sequestered and the lesion is no longer a matter of surgery.** To do otherwise is to commit, in my opinion, an error of therapeutic indication.

Au stade de nécrose osseuse, il ne réussira plus qu'à enrayer la progression de l'infection, mais il ne pourra plus rien contre l'os que la mort a privé de circulation ; cet os va se séquestrer et la lésion ne relève plus maintenant que de la chirurgie. Agir autrement c'est commettre, à mon sens, une erreur d'indication thérapeutique.



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## **Clinical case #2**

80-year-old man

Relapsing S. aureus prosthetic left knee infection (past revision)

#### **Failure**

Complex orthopaedic situation with past femoral fracture

Impossible to walk (painful knee)







Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial











### Lyon Phage team













#### "Debridement And Implant Retention" (DAIR)



#### Ferry T. et al. 2020

### "PhagoDAIR"





One shot peroperative phage application after "DAIR"





## **Clinical case #2**

#### **Post-operative** antibiotics:

Daptomycin + Rifampin

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

Levofloxacin + Rifampin

#### <u>Then:</u>

Cefalexin as suppressive antimicrobial therapy







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

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## **Clinical case #3**

74-year-old man

Melanoma treated with anti-PD1

Catheter-related *P. aeruginosa* bacteriemia in January 2018

Spinal pain summer 2018

Spondylodiscitis with spinal abscess

Pandrug-resistant P. aeruginosa in culture!



## **Clinical case #3**

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Catheter-related *P. aeruginosa* bacteriemia in January 2018

Spinal pain summer 2018

Spondylodiscitis with spinal abscess

Pandrug-resistant P. aeruginosa in culture!

PHERECYDES

	Pseudomonas aeruginosa
	CMI (mg/l)
Ticarcilline + Ac. Clav	H (> 64)
Pipéracilline	R (> 64)
Pipéracilline + Tazobactam	R (> 64)
Ceftazidime	R (> 32)
Céfépime	R (> 32)
Aztréonam	R (> 32)
Imipénème	R (> 8)
Meropeneme	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
Ceftolozane-tazobactam (Etest)	R E-test : > 256

Coftazidimo-Avibactam (Etest)

R

E-test: 64

The strain was also spontaneously resistant to 'GMP' bacteriophages !!!

#### **Potential European academic collaborations**



#### Potential European academic collaborations ansm



#### Potential European academic collaborations ansm





#### Potential European academic collaborations answ



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#### Potential European academic collaborations ansm



Personalized production and administration of bacteriophages: lessons learned from a <u>unique European academic collaboration</u> to treat a patient with pandrug-resistant spinal *P. aeruginosa* infection



**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.** 

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Surgery (debridement & reconstruction) Antibiotics Surgery (prosthesis explantation) Antibiotics Surgery (debridement & stabilization) Antibiotics <u>'Debridement And Implant Retention' (DAIR)</u> with local administration of personalized cocktail of bacteriophages (PhagoDAIR) followed by suppressive antibiotherapy as salvage therapy in patients with relapsing prosthetic knee infection



**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.

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



**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.

The Potential Innovative Use of Bacteriophages Within the DAC<sup>®</sup> Hydrogel to Treat Patients With Knee Megaprosthesis Infection Requiring "Debridement Antibiotics and Implant Retention" and Soft Tissue Coverage as Salvage Therapy

Tristan Ferry<sup>1,2,3,4\*</sup>, Cécile Batailler<sup>2,3,5</sup>, Charlotte Petitjean<sup>6</sup>, Joseph Chateau<sup>7</sup>, Cindy Fevre<sup>6</sup>, Emmanuel Forestier<sup>8</sup>, Sophie Brosset<sup>7</sup>, Gilles Leboucher<sup>9</sup>, Camille Kolenda<sup>2,3,4,10</sup>, Frédéric Laurent<sup>2,3,4,10</sup> and Sébastien Lustig<sup>2,3,5</sup> on behalf of the Lyon BJI Study Group





<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 two cases



**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.

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

application of a selected cocl

Tristan Ferry 🖾, Fabien Boucher, Cindy Fevre, Th Jérôme Josse, Christian Chidiac, Guillaume L'ho

Journal of Antimicrobial Chemotherapy, Volume

Open Forum Infectious Diseases





The Potential Innovative Use of Bacteriophages Within the DAC<sup>®</sup> 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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Salvage Debridement, Implant Retention ("D Local Injection of a Se of Bacteriophages: Is I an Elderly Patient Wit Staphylococcus *aureus* Infection?

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

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

Ferry T. 2018



# PHAGE*in*LYON

#### FONDATION HCL HOSPICES CIVILS DE LYON

#### Tristan Ferry Lyon University Hospitals @FerryLyon



Today, we treated @CHUdeLyon a 20th patient with ultrasound injection of #bacteriophages for a relapsing prosthetic joint infection due to multidrug-resistant #Pseudomonas aeruginosa! We hypothethize that #phagetherapy can help to control this kind of dramatic infection!



51

17 11

# PHAG-one

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



Purified <u>academic</u> phages Usable in the next 5 years



## Conclusion



- There is a real place for phage therapy to maximize clinical success in complex bacterial infections
- Need to identify <u>relevant clinical indications</u>
- Expertise of referral clinical centers
- Don't forget Lessons from 20<sup>th</sup> century
- Develop and use <u>purified</u> bacteriophages

21 patients treated in 3 years

- Industry / health authority / academic collaborations
- Need for <u>Phage discovery</u>, <u>banking</u>, <u>susceptibility</u>, to personalize the therapy
- Need for national phage therapy center(s)
- Clinical trials have to be performed <u>to demonstrate</u> a potential benefit in less severe patients



HCI







### 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, Elliot 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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