10th Annual Oxford Bone Infection Conference (OBIC)

Bacteriophage therapy in BJI: Fact or fiction? From mythology to clinical evidence

> Tristan Ferry, MD, PhD tristan.ferry@univ-lyon1.fr @FerryLyon in

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 Clinical officer ESCMID Study group for Non-Traditional Antibacterial therapy (ESGNTA) Referral center for the management of complex bone and joint infections (CRIOAc Lyon)















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Science and Technology Committee Wednesday 8 February 2023 Meeting

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The antimicrobial potential of bacteriophages

Inquiry

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INFO (i)

09:34:35 Subject: The antimicrobial p	potential of bacteriophages
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RSS

09:34:36 Witness(es): Professor Martha Clokie, Professor of Microbiology, University of Leicester; Professor Cath Rees, Professor of Microbiology, University of Nottingham; Professor Joanne M. Santini, Professor of Microbiology, University College London

10:21:03 Witness(es): Dr James Soothill, Consultant Microbiologist, Great Ormond Street Hospital Laboratory Medicine; Dr Josh Jones, Clinical Phage Specialist, NHS Tayside

11:06:44 Witness(es): Ms Stephanie Lesage, Co-Founder/Director and Chief Executive Officer, Oxford Silk Phage Technologies Ltd; Mr David Browning, Chief Executive Officer, Fixed Phage LTD

Phage-UK

www.phageuk.com

Non-profit, network of 50+ UK clinicians and scientists, in 15 Trusts

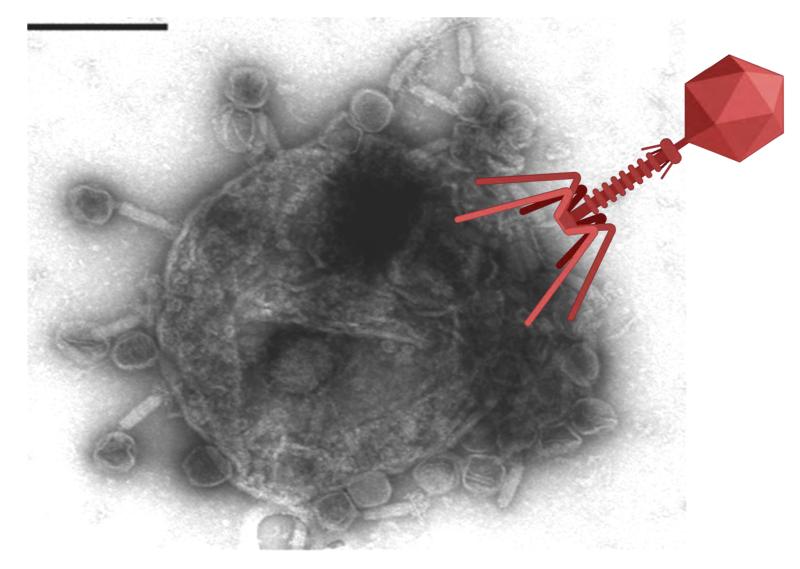
GOALS

- Help establish a standardised way forward for the wider use of phage therapy on a named-patient basis, to provide for patients whose infections no longer respond to antibiotics.
- Connect clinicians to the right research groups, companies and institutes to facilitate the logistics of phage therapy administration.
- Centralise expertise and data gained from the network, to help design clinical trials which will lead to the use of phages as a licensed medicine, helping patients long before they run out of treatment options.
- Inform patients on phage therapy and their options for access to phages.



info@phageuk.com

Bacteria have also their pandemia!



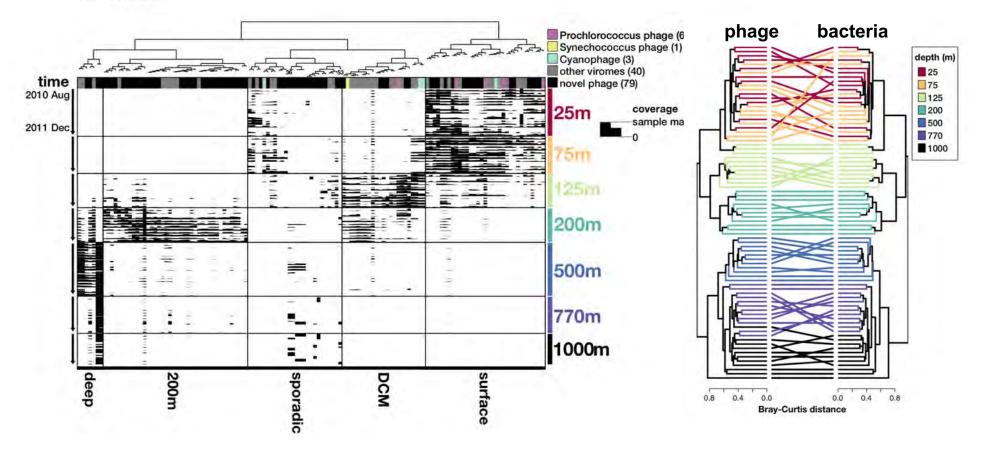
Merabishvili et al. PloS ONE 2009

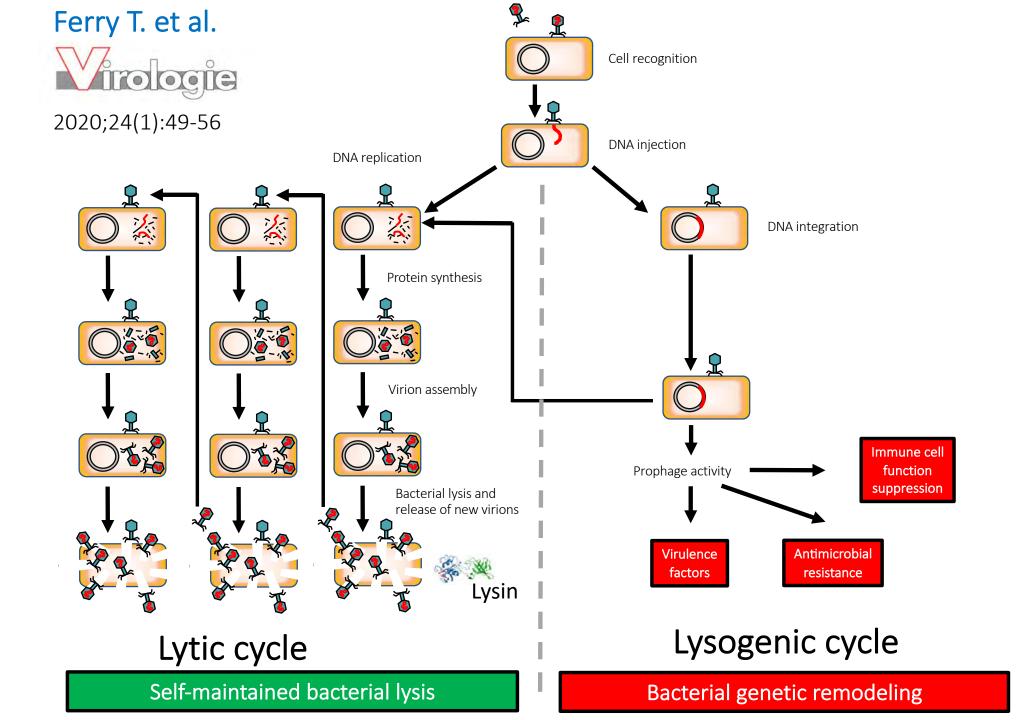
Bacteriophage Distributions and Temporal Variability in the Ocean's Interior



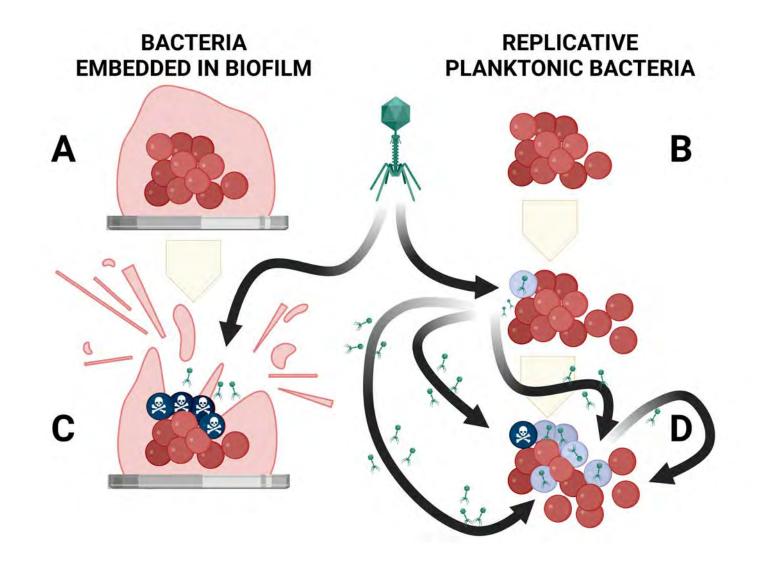
Elaine Luo, Frank O. Aylward,* Daniel R. Mende, DEdward F. DeLong

Daniel K. Inouye Center for Microbial Oceanography: Research and Education, University of Hawaii, Honolulu, Hawaii, USA





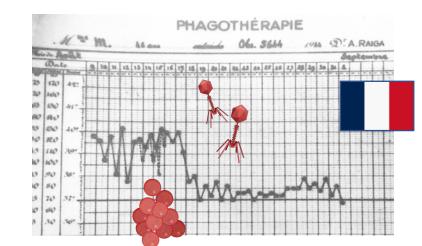
Finally phages have two ways of actions



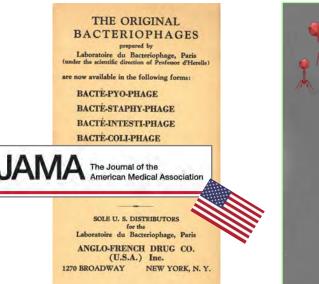
T. Ferry. Springer 2023 In press

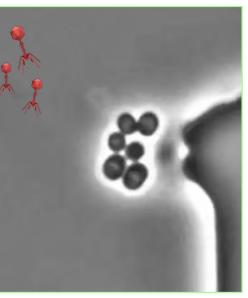
Phage therapy is fascinating

• Viral therapy for bacterial infections



- Story of phage therapy is connected to worldwide geopolicital events
- Failure to implement phage therapy in the west
- Potential <u>incredible</u> preclinical <u>efficacy</u>





S. aureus being lysed by the Sa2 phage

Bacterial DNA appeared in green

Courtesy Pascal Maguin Luciano Marraffini Lab THE ROCKEFELLER UNIVERSITY

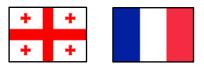








Story of phage Therapy



Creation from F. d'Herelle (dismissed from Pasteur Institute):

2020;24(1):49-56

- Laboratoire du bactériophage (Paris)
- Eliava Center (Georgia)
 - Fixed cocktails to treat digestive-tract infections
 - Fixed cocktails to treat skin and soft tissue infections



	sous le contrôle du PROF: d'HERELLE	
Bacté-coli-phage Colibecilluries. Pyelonephrites. Cystites		Bacté-rhino-phage Grippe-Coryza. Rhino-pharyngites
Bacté - pyo-phage Bacté - pyo-phage Panaris - Phlegmons, Piales Infecties	lé ·intesti ·pl ites Calites.Diarrhees in	age fontiles Baclé-slaphy-phage Furonculose-Anthree

Ferry T. et al.

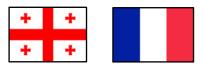
BAC	TÉ-S	TAPH	Y-PI	HAGE	
	BAC	TÉ-PY	'0- F	PHAGE	
T. Ferry				LE LABORATOIRE DU BACTERIOPHAGE IONOÙ FAR LE ROFESSUE OFERILE PS, RUE OUVER DE SERRES - FARS (RV) Téléph. YAUgtrord 65-82	







Story of phage Therapy



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- Eliava Center (Georgia)
 - Fixed cocktails to treat digestive-tract infections
 - Fixed cocktails to treat skin and soft tissue infections



Forbidden to import Georgian phages (not safe for injections)

Don't forget the lessons of the past



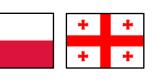
Docteur André RAIGA Ancien Interne lauréat des Hópitaux Ex-Chef de Clinique chirurgicale à la Faculté

1961

At the stage of bone necrosis, [the bacteriophage] will be able to do nothing against the dead bone deprived of circulation; [it] only needs surgery.

Respect the experience of the East

Ferry T. et al.



2020;24(1):49-56



T. FERRY

PHAGE



KEEP CALM AND USE PHARMACEUTICAL GRADE PHAGES

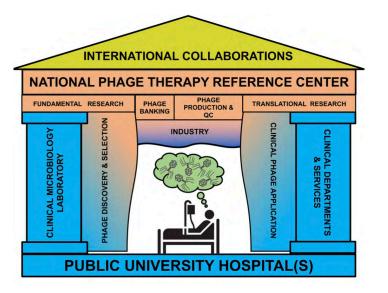


SESGNTA ESCMID STUDY GROUP FOR NON-TRADITIONAL ANTIBACTERIAL THERAPY

European Society of Clinical Microbiology and Infectious Diseases

Elected Executive Committee:

Ran Nir-Paz, Israël Jean-Paul Pirnay, Belgium Clinical officer: Tristan Ferry, France Shawna Mc Callin, Switzerland Zuzanna Drulis-kawa, Poland

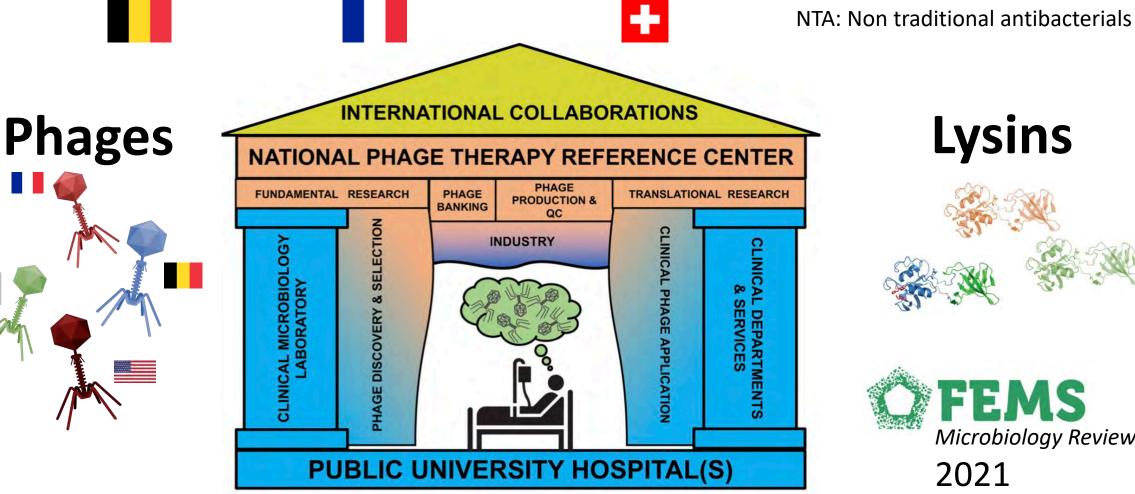


REVIEW ARTICLE

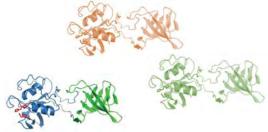
Recent progress toward the implementation of phage therapy in Western medicine

Jean-Paul Pirnay^{1,†}, Tristan Ferry^{2,3,†} and Grégory Resch^{4,*,†}



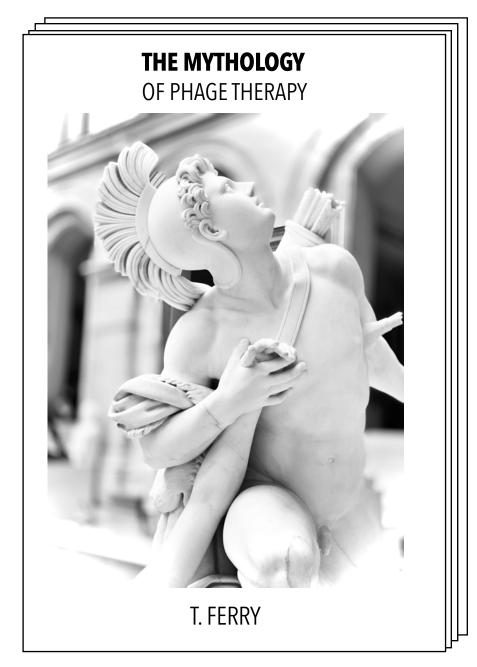


Lysins





2021



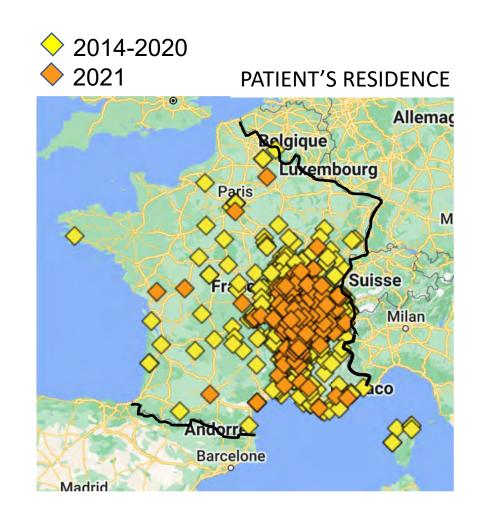
VS.



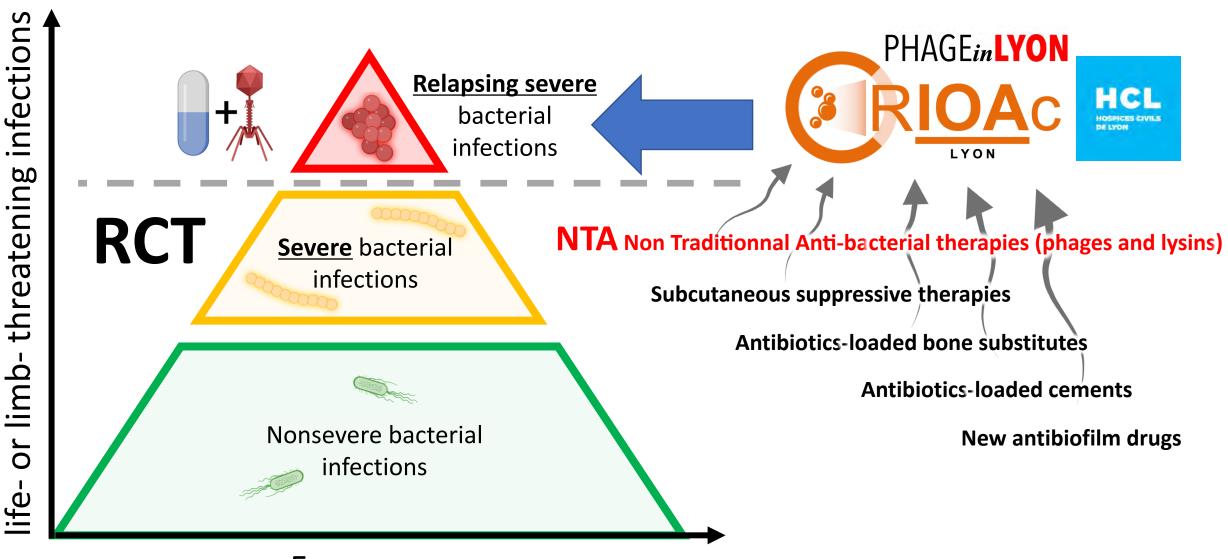
Referral center for the management of complex bone and joint infections (BJI)



Egalité

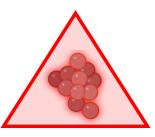


The pyramid of bacterial infectious diseases



Frequency

A large panel of <u>severe</u> bacterial infections



Central nervous system infections

Implant-associated meningitis

Lung infections

Ventilator-associated pneumonia Exacerbation in cystic fibrosis Exacerbations in bronchiectasis

Urinary tract infections

Pyelonephritis Ureteral stent-associated infection



Cardiovascular infections

Endocarditis Cardiac electronic device infection Prosthetic-valve endocarditis Vascular graft infection

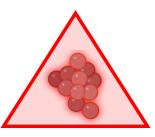
Muskuloskeletal infections

Wound infection Osteomyelitis, fracture-related infection Implant-associated bone and joint infection Prosthetic joint infection

Digestive-tract infections

Typhoid fever, shigellosis Cholera

A large panel of <u>severe</u> bacterial infections



Central nervous system infections

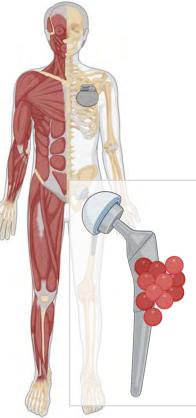
Implant-associated meningitis

Lung infections

Ventilator-associated pneumonia Exacerbation in cystic fibrosis Exacerbations in bronchiectasis

Urinary tract infections

Pyelonephritis Ureteral stent-associated infection



Cardiovascular infections

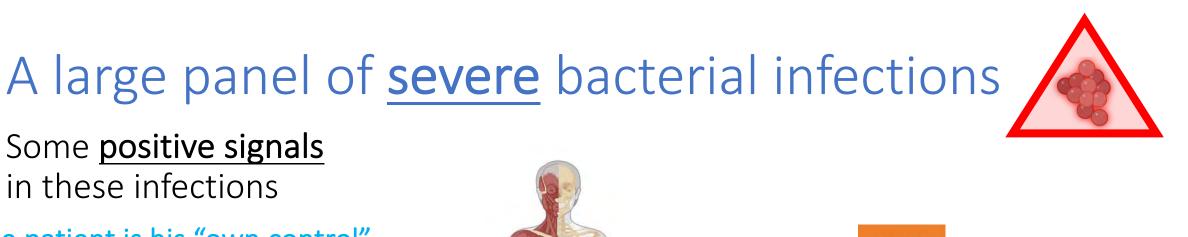
Endocarditis Cardiac electronic device infection Prosthetic-valve endocarditis Vascular graft infection

Muskuloskeletal infections

Wound infection Osteomyelitis, fracture-related infection Implant-associated bone and joint infection **Prosthetic joint infection**

Digestive-tract infection

Typhoid fever, shigellosis Cholera



The patient is his "own control"

Under the supervision of

French Health Authority

Follow-up





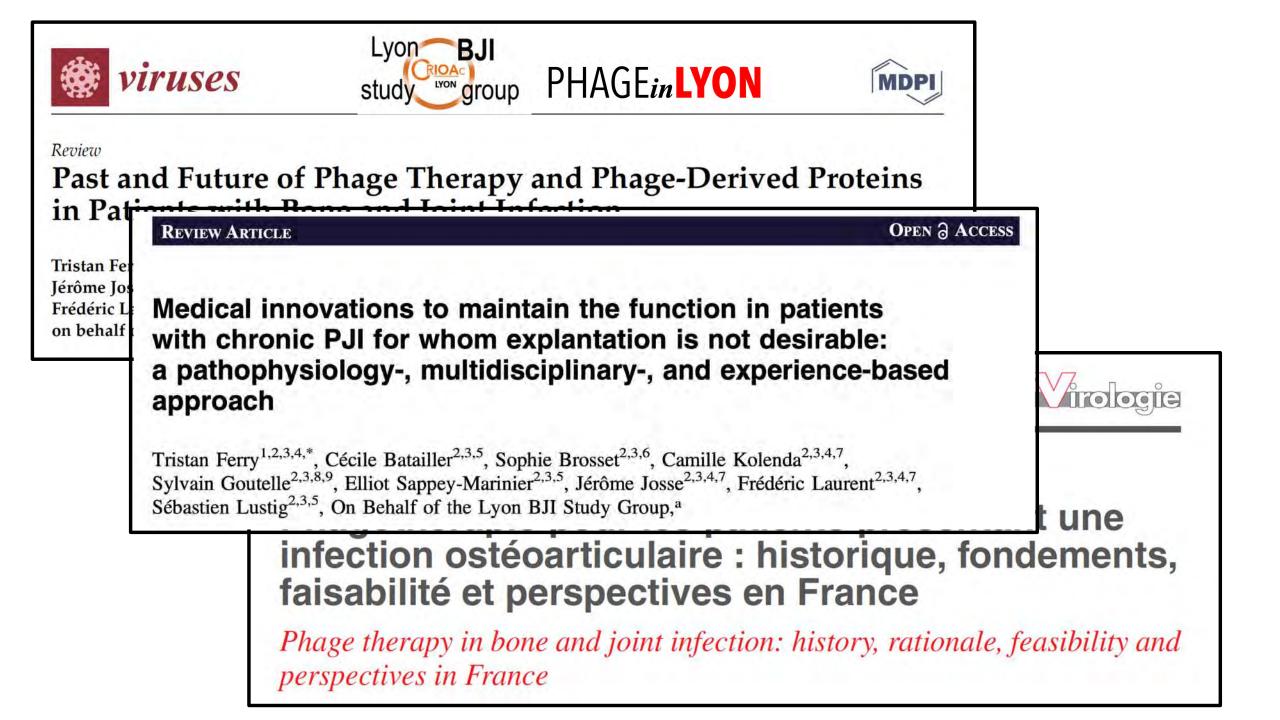
PHAGE*in***LYON** Clinic

- Dedicated program to <u>phage therapy</u> development (Non-Traditional Antibacterials WHO)
- Close relationship with the **French health authority**
- Integrated in our **referral center** for complex BJI
- For patients in **dead-end** clinical situations or at high risk of significant loss of function
- Pharmaceutical grade phages only
- Fulfilling list of quality controls
- **Phagogram** demonstrating the phage susceptibility
- Use in **cocktail** (≥ two active phages), with antibiotics
- Prepared by the **hospital pharmacist** under sterile conditions at the time of injection



PHARMACEUT 5.0 7.5 GRADE PHAGES Time (hours)





Case Report: Arthroscopic "Debridement Antibiotics and Implant Retention" With Local Injection of Personalized Phage Therapy to Salvage a Relapsing *Pseudomonas Aeruginosa* Prosthetic Knee Infection

Tristan Ferry ^{1,2,3,4*}, Camille Kolenda^{2,3,4,5}, Cécile Batailler^{2,3,6}, Romain Gaillard^{3,6}, Claude-Alexandre Gustave^{2,3,4,5}, Sébastien Lustig^{2,3,6}, Cindy Fevre⁷, Charlotte Petitjean⁷, Gilles Leboucher⁸, Frédéric Laurent^{2,3,4,5} and the Lyon BJI Study group **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?

Tristan Ferry,^{1,2,3,4} Gilles Leboucher,⁵ Cindy Fevre,⁶ Yannick Herry,^{2,4,7} Anne Conrad,^{1,2,3,4} Jérôme Josse,^{2,3,4,8} Cécile Batailler,^{2,4,7} Christian Chidiac,^{1,2,3,4} Mathieu Medina,⁶ S. Lustig,⁷ and Frédéric Laurent^{2,3,4,8}; on behalf of the Lyon BJI Study Group



3,743 TOTAL VIEWS



Phage Therapy as Adjuvant to Conservative Surgery and Antibiotics to Salvage Patients With Relapsing S. aureus Prosthetic Knee Infection

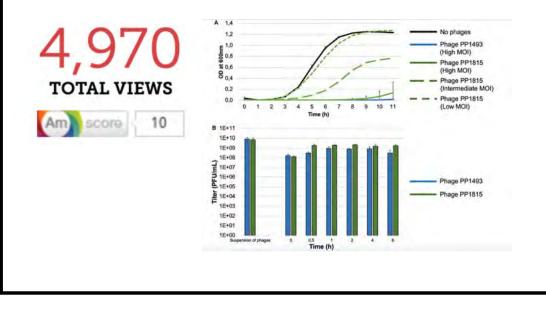
Tristan Ferry^{1,2,3,4*}, Camille Kolenda^{2,3,4,5}, Cécile Batailler^{2,3,6}, Claude-Alexandre Gustave^{2,3,4,5}, Sébastien Lustig^{2,3,6}, Matthieu Malatray^{3,6}, Cindy Fevre⁷, Jérôme Josse^{2,3,4,5}, Charlotte Petitjean⁷, Christian Chidiac^{1,2,3,4}, Gilles Leboucher⁸ and Frédéric Laurent^{2,3,4,5} on behalf of the Lyon BJI Study group





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 ^{1,23,4*}, Cécile Batailler^{2,3,5}, Charlotte Petitjean⁶, Joseph Chateau⁷, Cindy Fevre⁶, Emmanuel Forestier⁸, Sophie Brosset⁷, Gilles Leboucher⁹, 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



J Antimicrob Chemother 2018; **73**: 2901–2903 doi:10.1093/jac/dky263 Advance Access publication 27 July 2018

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

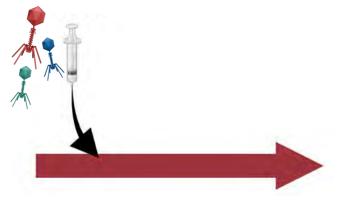
Tristan Ferry¹⁻⁴*, Fabien Boucher^{1,4,5}, Cindy Fevre⁶, Thomas Perpoint^{1,4}, Joseph Chateau^{1,2,4,5}, Charlotte Petitjean⁶, Jérôme Josse^{2-4,7}, Christian Chidiac^{1,2-4}, Guillaume L'hostis⁶, Gilles Leboucher⁸ and Frédéric Laurent^{2-4,7} on behalf of the Lyon Bone and Joint Infection Study Group[†]



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Arthroscopic or open

DAIR





Open DAIR (Arthrotomy)





Courtesy S. Lustig

Case series **ERIOAC** procedure called « **PhagoDAIR** »

Phage Therapy as Adjuvant to Conservative Surgery and Antibiotics to Salvage Patients With Relapsing *S. aureus* Prosthetic Knee Infection







frontiers in Medicine



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

5,711

TOTAL VIEWS

Am score 78

<u>Debridement Antibiotics and Implant Retention</u>

Clinical cases (2nd treated patient)

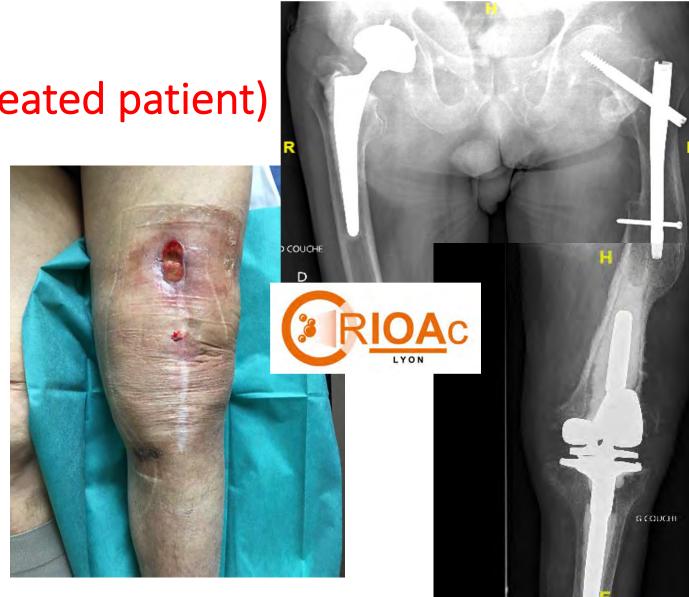
80-year-old man

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

Failure

Complex orthopaedic situation with past femoral fracture

Impossible to walk (painful knee)













PHAGEinLYON Clinic

Arthroscopic or open

DAIR

PHAGEinLYON Clinic

ECCMID

* 🛪 🛧

TOP RATED

Arthroscopic or open

DAIR

in case of <u>relapse</u> OR <u>after DAIR</u> if no phages were available at the time of the DAIR* OR if <u>no DAIR</u> could be performed

1 week interva

1 week interval

33rd FCCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES 15-18 AU

Copenhagen, Denmark 15–18 April 2023

Abstract number: 2508

"PhagoDAIR"



One shot peroperative phage application after "DAIR"





PhagoDAIR I

A Pilot, Multicenter, Randomized, Non-Comparative, Double-Blind Study of Phage Therapy in Patients with Hip or Knee PJI due to *S. aureus* Treated with DAIR and Antibiotic Therapy

Inclusion Criteria

- 1. S. aureus monomicrobial knee or hip PJI with clinical signs of infection with indication of DAIR and Suppressive Antibiotics Therapy (SAT).
- 2. Phagogram displaying the susceptibility of the strain to at least one of the anti-*Staphylococcus aureus* bacteriophages

Primary Objective

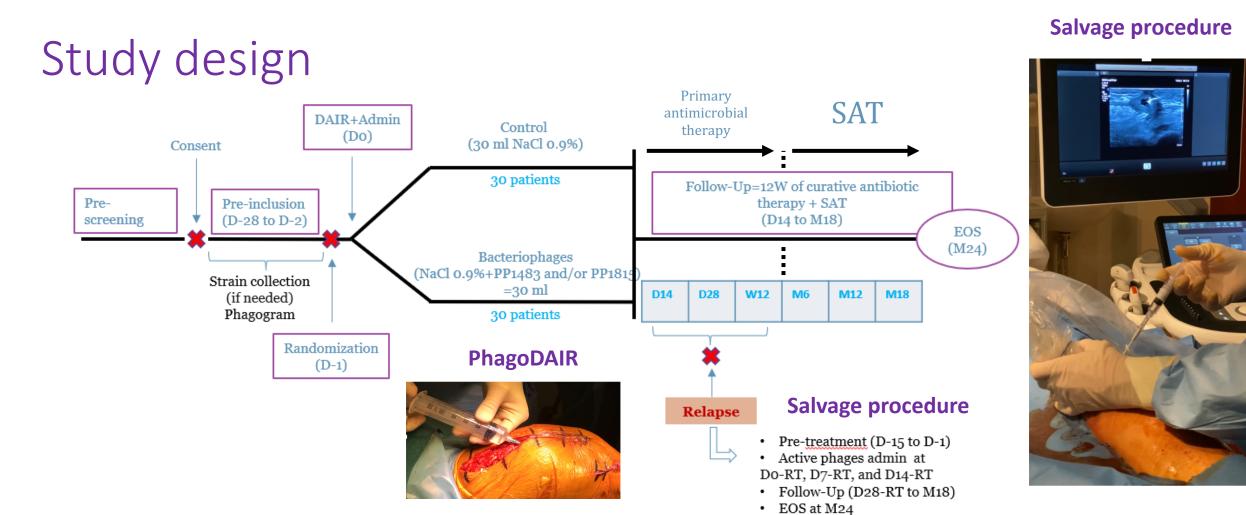
To estimate the rate of clinical control of infection at Week 12 ± 2 which will allow to calculate the sample size for future comparative studies.





PhagoDAIR I

A Pilot, Multicenter, Randomized, Non-Comparative, Double-Blind Study of Phage Therapy in Patients with Hip or Knee PJI due to *S. aureus* Treated with DAIR and Antibiotic Therapy



Clinical case (3rd treated patient)

<u>Arthroscopic DAIR</u> with phages to salvage *P. aeruginosa* prosthetic knee infection

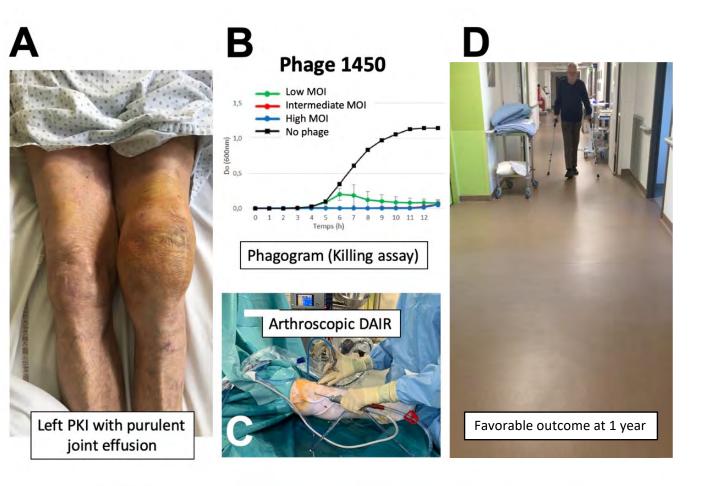


88-year-old man

Relapsing *P. aeruginosa* prosthetic left knee infection

End-stage cardiac failure

Contraindicated to open DAIR









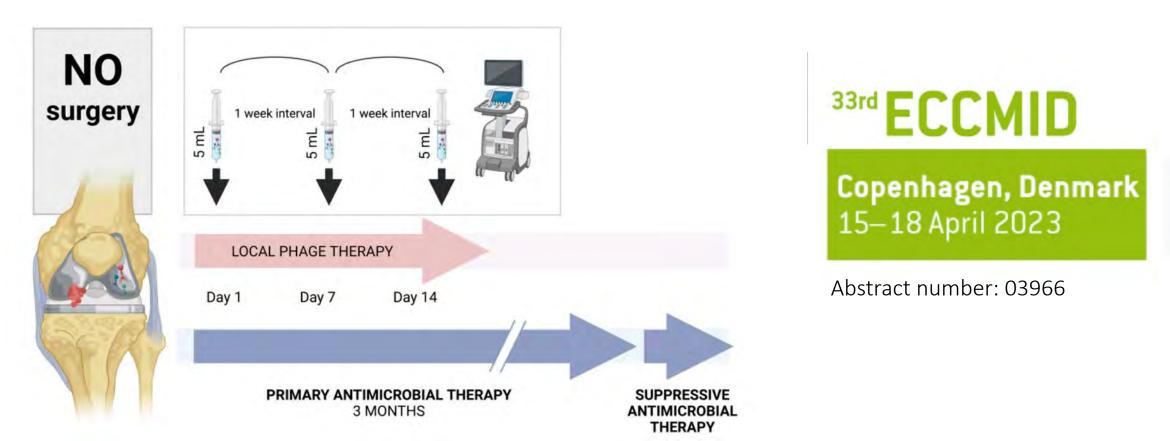
PHAGE*in***LYON**





Exclusive medical treatment combining intraarticular injections of active bacteriophages as adjuvant therapy to antibiotics in patients with *S. aureus* complex PJI contraindicated for, or refusing, surgery

- Five patients (age range 63-79 years) who failed previous treatment for *S. aureus* PJI
- One patient was co-infected with methicillin-resistant *S. epidermidis*



Exclusive medical treatment combining intraarticular injections of active bacteriophages as adjuvant therapy to antibiotics in patients with *S. aureus* complex PJI contraindicated for, or refusing, surgery

- Five patients (age range 63-79 years) who failed previous treatment for *S. aureus* PJI
- One patient was co-infected with methicillin-resistant S. epidermidis
- During the follow-up:
 - <u>All patients were improved by the treatment</u>
 - One experienced a relapse with *S. aureus* at month 8 under SAT
 - The patient co-infected with *S. epidermidis* experienced a relapse due to the *S. epidermidis* at month 17 (but not *S. aureus*)
- The disease was totally under control with disappearance of clinical signs of infection for the three other patients at month 6



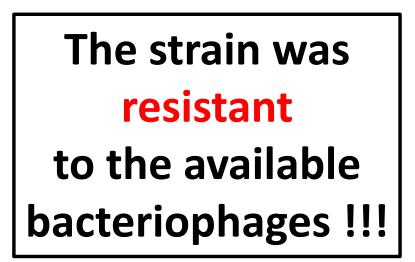
Abstract number: 03966

Unique European academic collaboration

Clinical case (12th treated patient)

Spondylodiscitis with spinal abscess

Pandrug-resistant P. aeruginosa









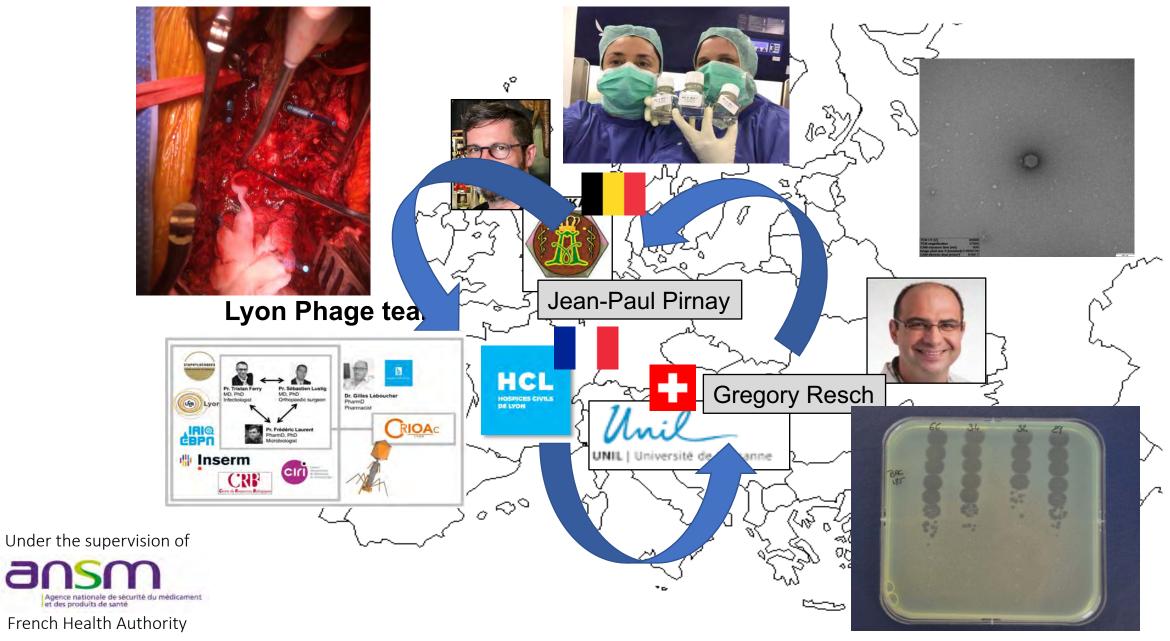


PHAGE*in***LYON**





Unique European academic collaboration



Unique European academic collaboration



UNIL | Université de Lausanne





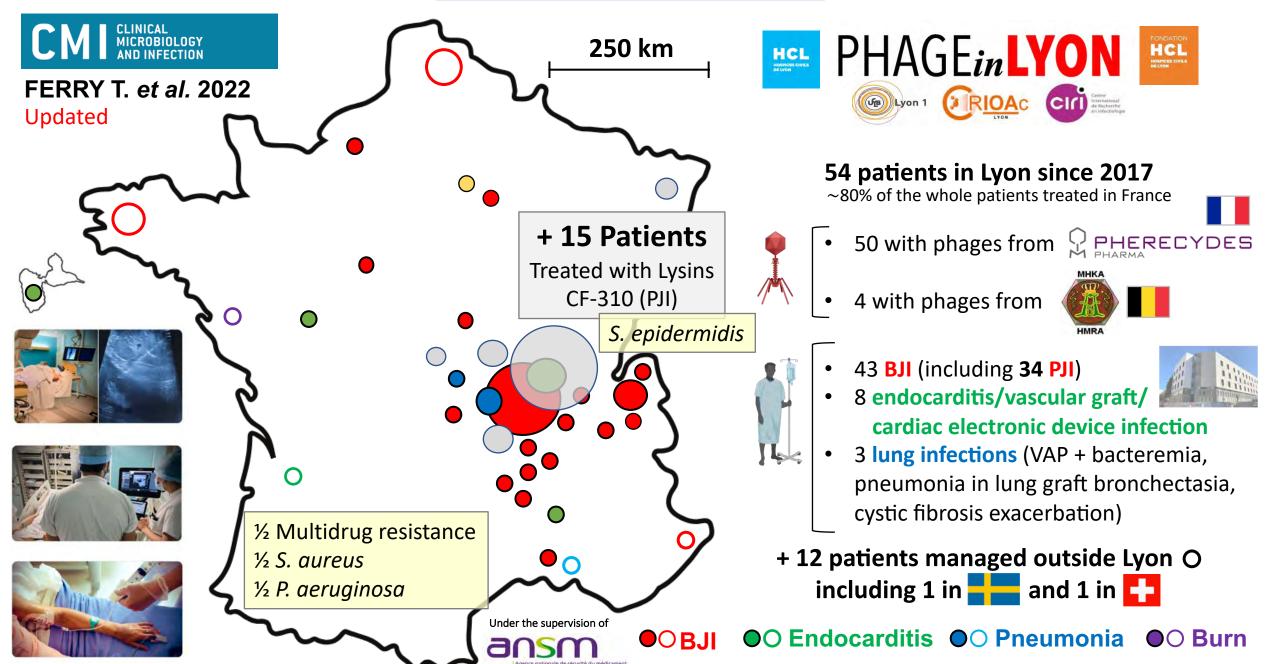


Under the supervision of



Conclusions: Personalized phage therapy is a potential adjuvant 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.**

Implementation of a **Phage Therapy Center** in a CRIOAc



PODCASTS

LE PROGRÈS

News v Departments v Sport v Long format v Culture - Leisure v Magazine v Services v Q

Bone and joint infections: Lyon becomes the national expert center for phage therapy

The reference center for complex bone and joint infections, based at the Hospices Civils de Lyon, will centralize all requests concerning this last resort treatment, using viruses against resistant bacteria.

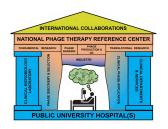
Le Progrès - 23 Feb. 2023 at 17:51 | updated 23 Feb. 2023 at 18:08 - Reading time: 2 min



Conclusion

- Phage therapy has a <u>high potential</u> in patients with BJI, as <u>adjuvant to antibiotics</u>
- Patients with chronic PJI who could be managed with a conservative approach, particular patients in dead-in clinical situation
- Complex personalized therapy (specific to the infecting strain, various scheme of administrations, etc.)
- Few pharmaceutical grade phages are available at this time
- Phage therapy center(s) in each country would be useful to concentrate the experience and to promote interactions
- In addition to industrial phages under development, academic collaborative research is crucial to develop personalized phage therapy.
- Parliament discussions in the UK, and Phage-UK initiative
- Growing <u>clinical evidence</u> and <u>clinical trials are coming</u>









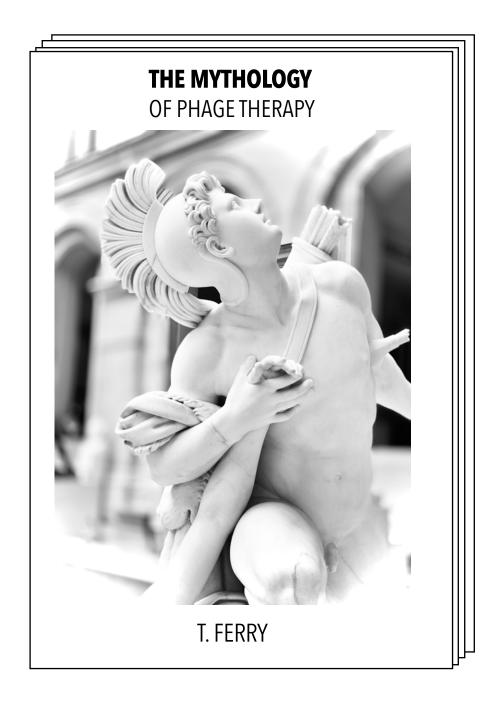




HCL HOSPICES CIVILS DE LYON

ഗ്ള) Lyon 1







T. FERRY

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, Samuel Prive, Philippe Céruse, Carine Fuchsmann, Arnaud Gleizal; Anesthesiologists – Frédéric Aubrun, Mikhail Dziadzko, Caroline Macabéo, Dana Patrascu; Microbiologists – Frédéric 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

Lyon

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Coordinator: Tristan Ferry (clinic); and Frederic Laurent (lab)

Myrtille Le Bouar, Gilles Leboucher, Thomas Briot; Mathieu Medina, Camille Kolenda, Floriane Laumay, Melanie Bonhomme, Leslie Blazere, Tiphaine Legendre, Eline Terrazzoni, Fabrice Pirot, Camille Merienne, Samira Filali, Benjamine Lapras

















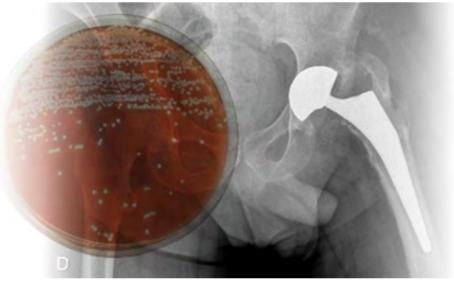






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