



**World Association
Against Infection in
Orthopaedics & Trauma**

2nd WAIOT CONGRESS



**AO
SPINE**
Middle East and Northern Africa

September 1-2, 2022
Grand Nile Tower Hotel, Cairo, Egypt

www.waiot2022.com

Phages therapy: a substitute of antibiotics?

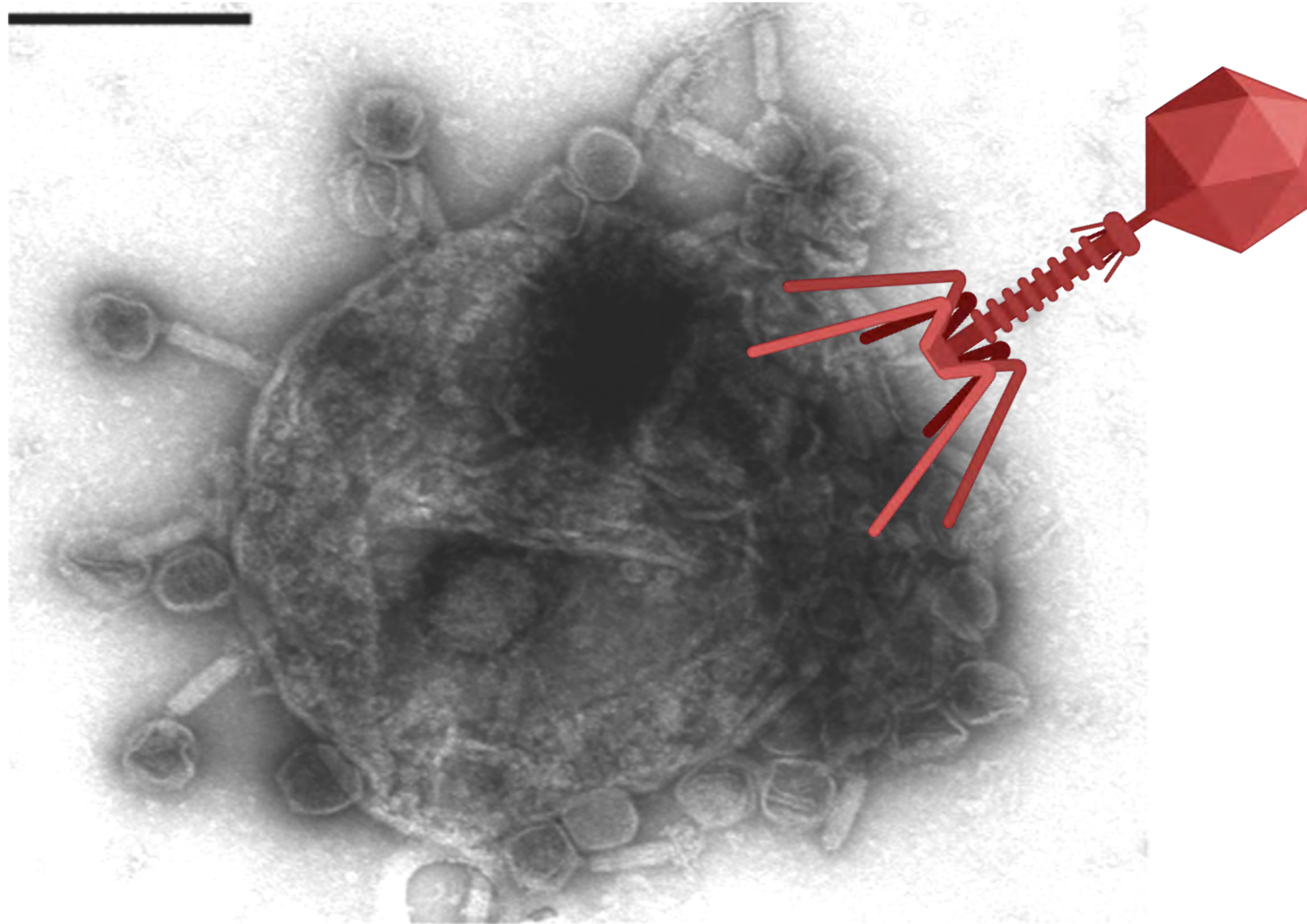
Tristan Ferry, MD, PhD

tristan.ferry@univ-lyon1.fr

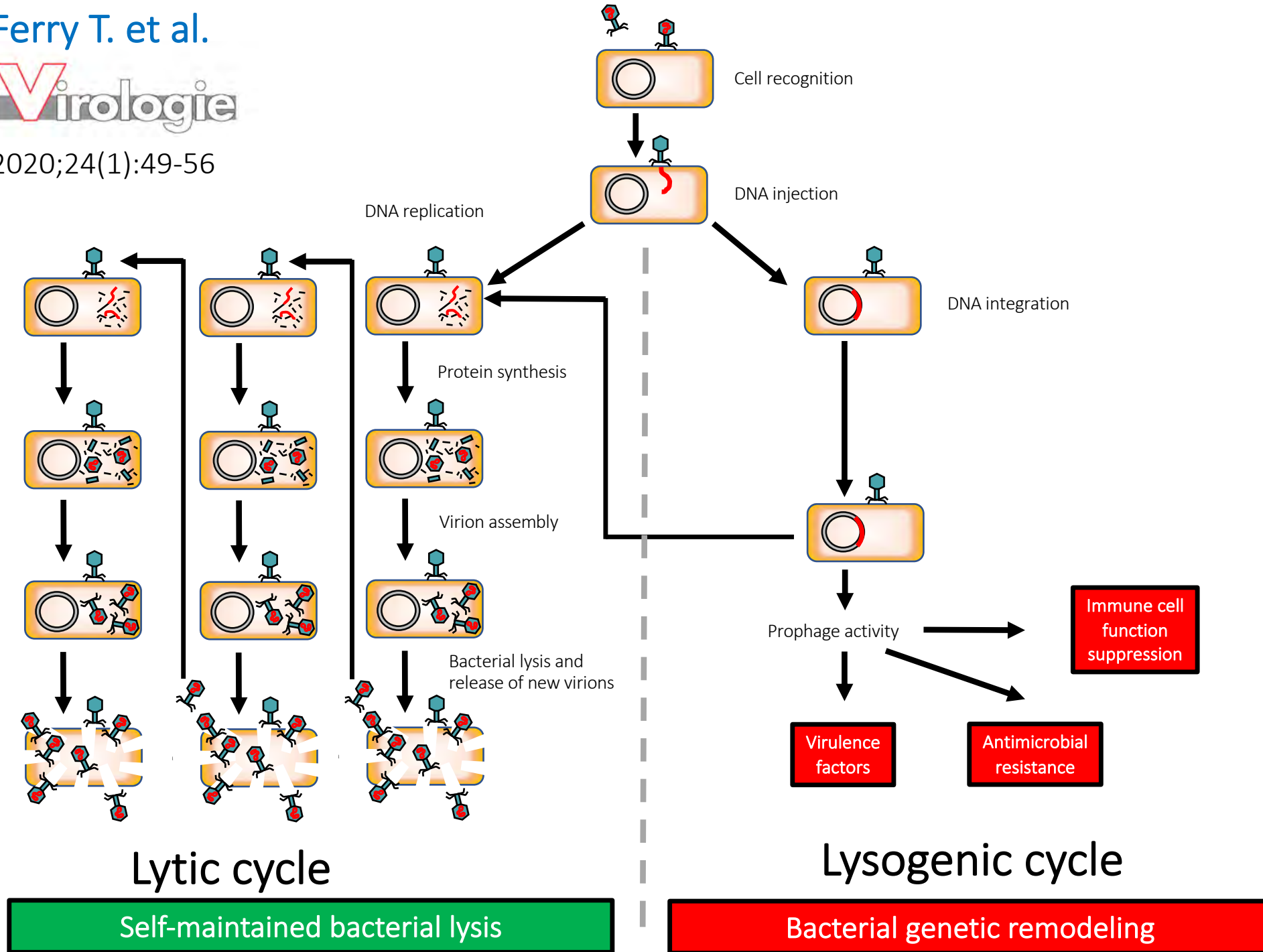
 @FerryLyon 

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)

Bacteria have also their pandemics!

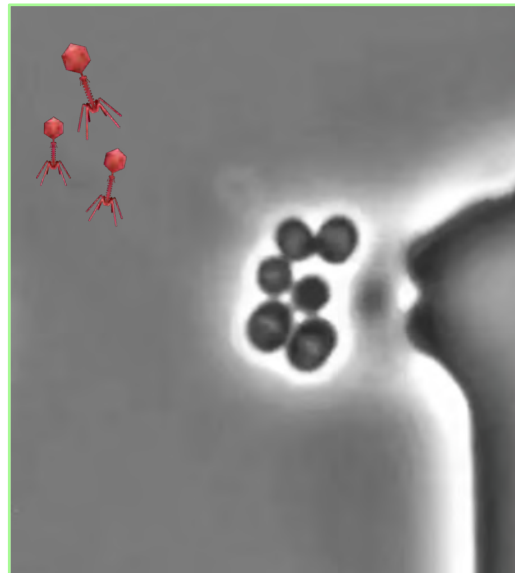
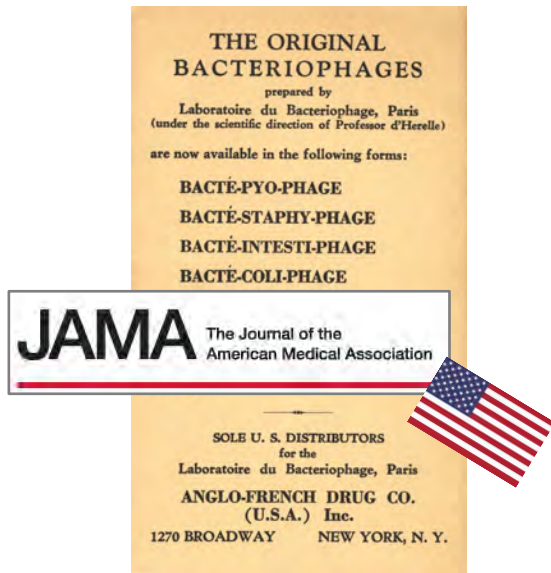
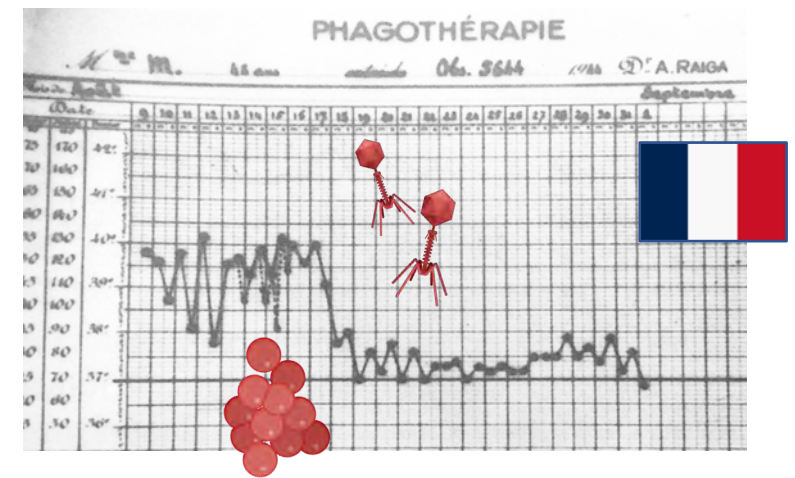


Merabishvili et al. *PLoS ONE* 2009



Phage therapy is fascinating

- Viral therapy for bacterial infections
- Story of phage therapy is connected to worldwide geopolitical events
- Potential incredible preclinical efficacy
- Failure to implement phage therapy in the west



S. aureus being lysed
by the Sa2 phage

Bacterial DNA
appeared in green

Courtesy Pascal Maguin
Luciano Marraffini Lab

THE ROCKEFELLER UNIVERSITY

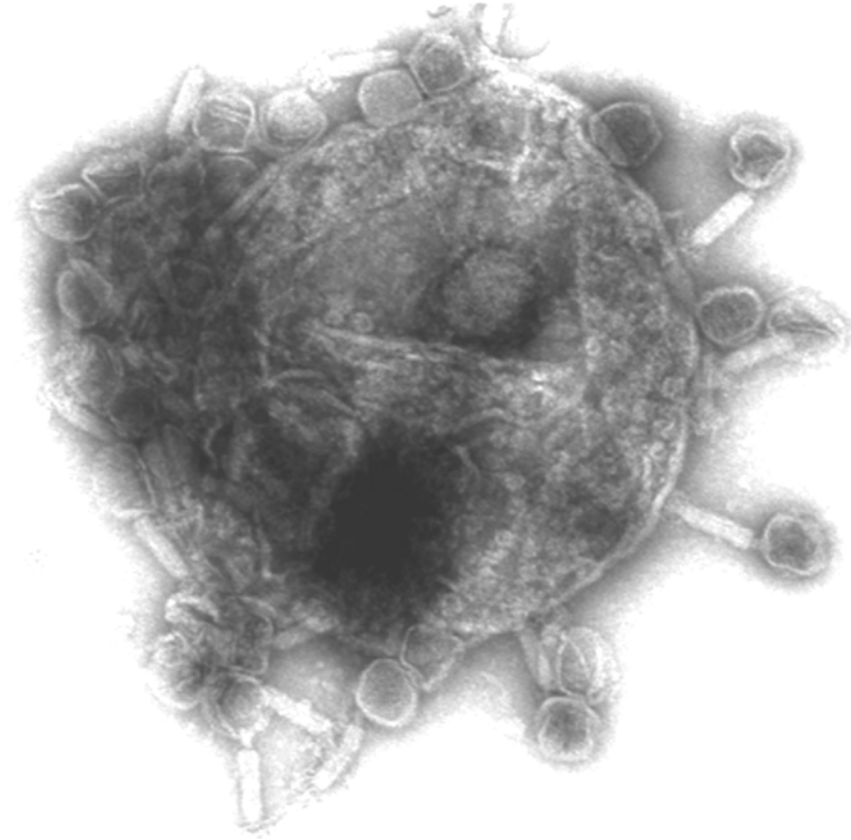


Eliava Institute (Georgia)



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

Bacteriophage (*Myoviridae*) targeting *S. aureus*



Merabishvili et al. PloS ONE 2009





Professor Andrzej Górski



Doctor Ryszard Miedzybrodzki with Anna Kabala, one of the Medical Unit's patients.
Kablar/TFN



The Institute of Immunology and Experimental Therapy's Medical Centre has been looking for a cure for patients who have lost all hope that their ailments could disappear.
Kablar/TFN



"Our centre treats antibiotic resistant infections. The great problem in medicine today is that we are becoming defenceless against the bacteria that cause them," says Professor Andrzej Górski.
Kablar/TFN



The Institute is supported by the Bacteriophage Laboratory, which stores over 600 different phages.
Kablar/TFN



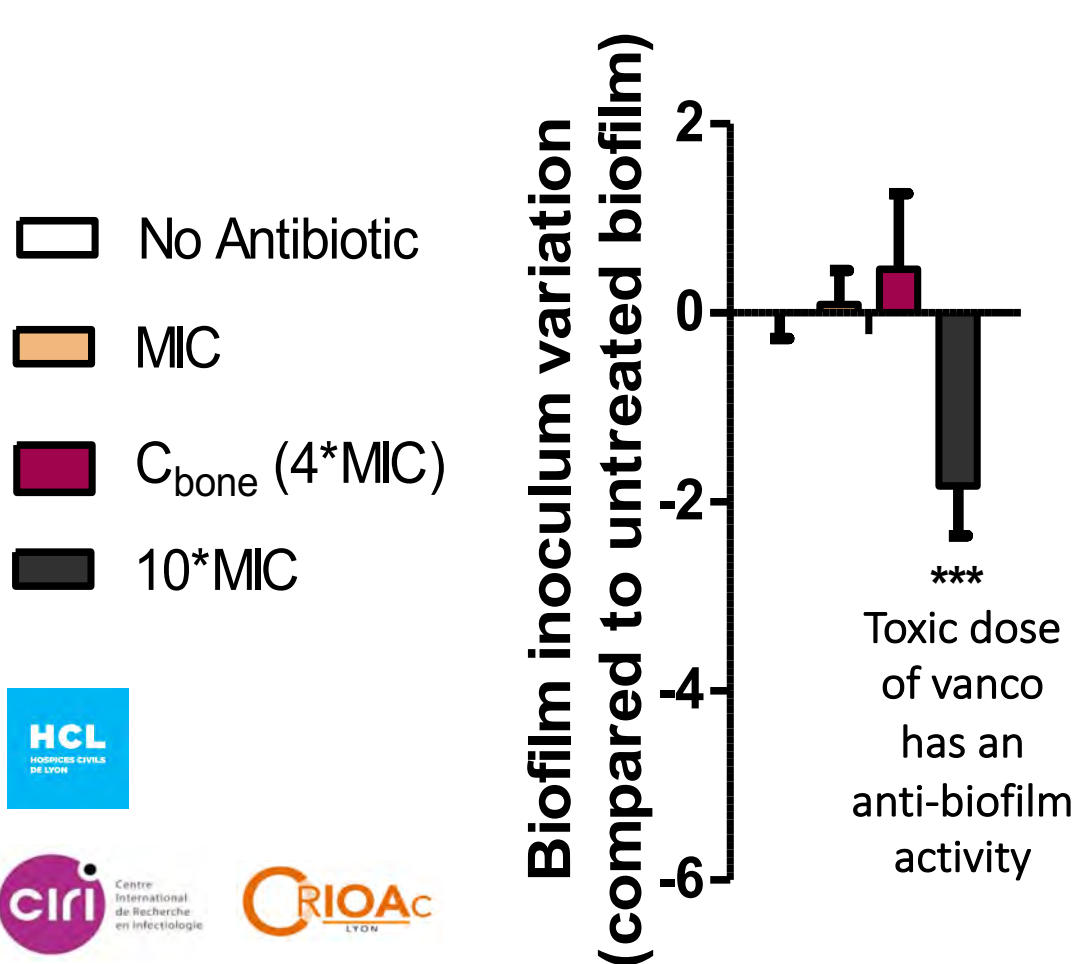
We carry phages in our bodies says Doctor Beata Weber-Dąbrowska.
Kablar/TFN

THEfirstNEWS

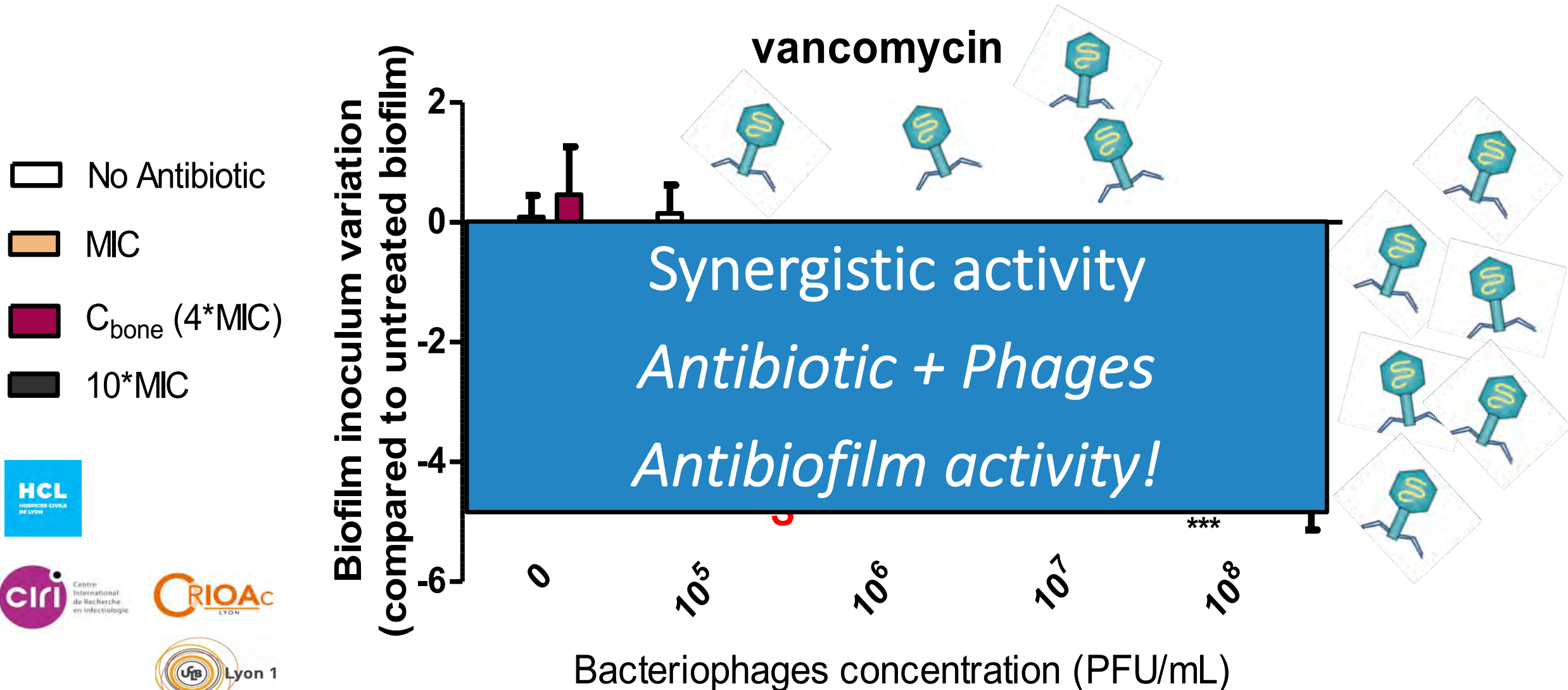
Wrocław clinic uses 'super viruses' to battle rebellious bacteria

JOANNA JASIŃSKA MARCH 22, 2020

Phages have antibiofilm activity



Phages have antibiofilm activity



T. FERRY



KEEP
CALM
AND USE

PHARMACEUTICAL
GRADE
PHAGES

PHAGE
2.0
THERAPY

ESCMID MANAGING INFECTIONS
PROMOTING SCIENCE



ESGNTA

European Society of Clinical Microbiology and Infectious Diseases

ESCMID STUDY GROUP
FOR NON-TRADITIONAL
ANTIBACTERIAL THERAPY

Elected Executive Committee:

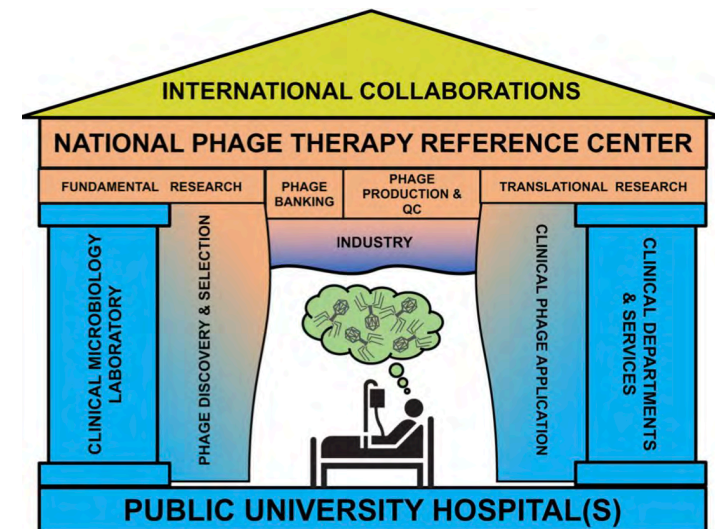
Jean-Paul Pirnay, Belgium

Ran Nir-Paz, Israël

Tristan Ferry, France

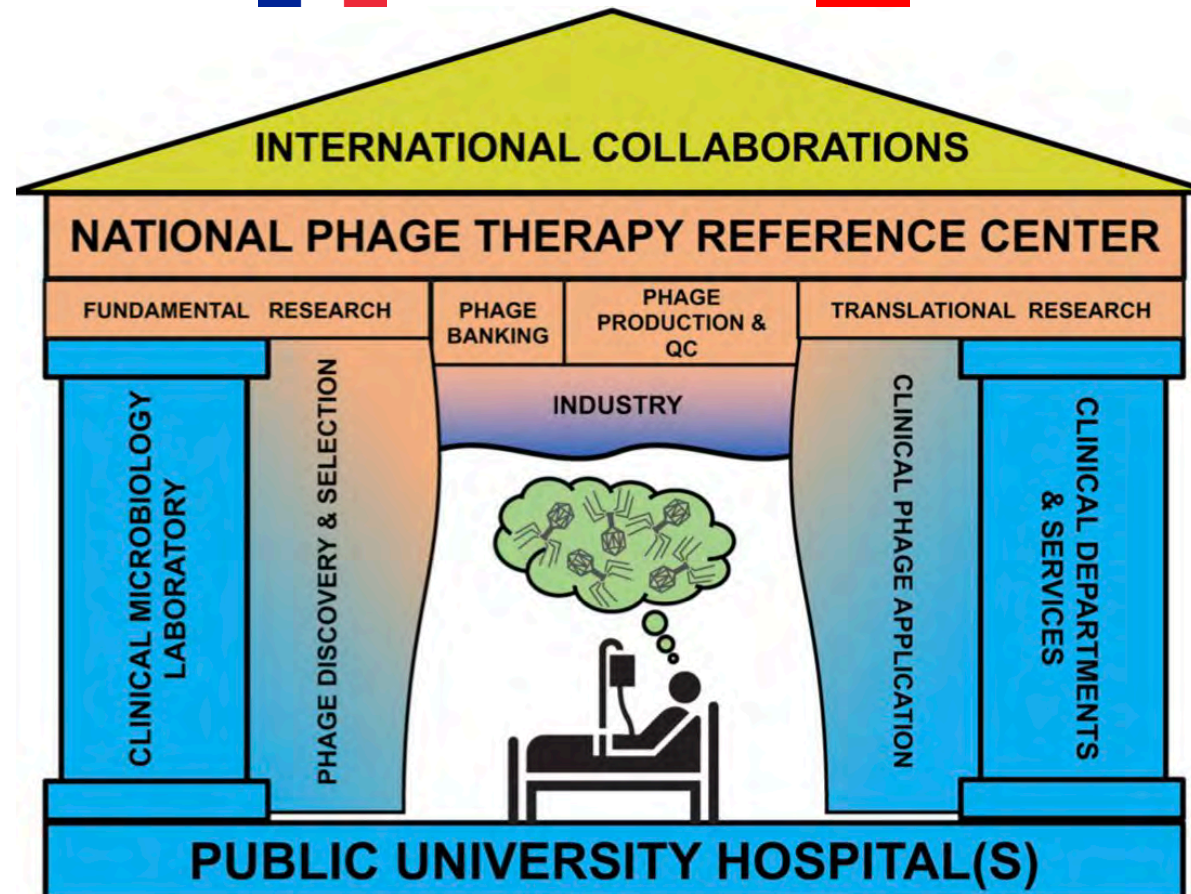
Shawna Mc Callin, Switzerland

Zuzanna Drulis-kawa, Poland



Recent progress toward the implementation of phage therapy in Western medicine

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



**THE MYTHOLOGY
OF PHAGE THERAPY**



T. FERRY

VS.

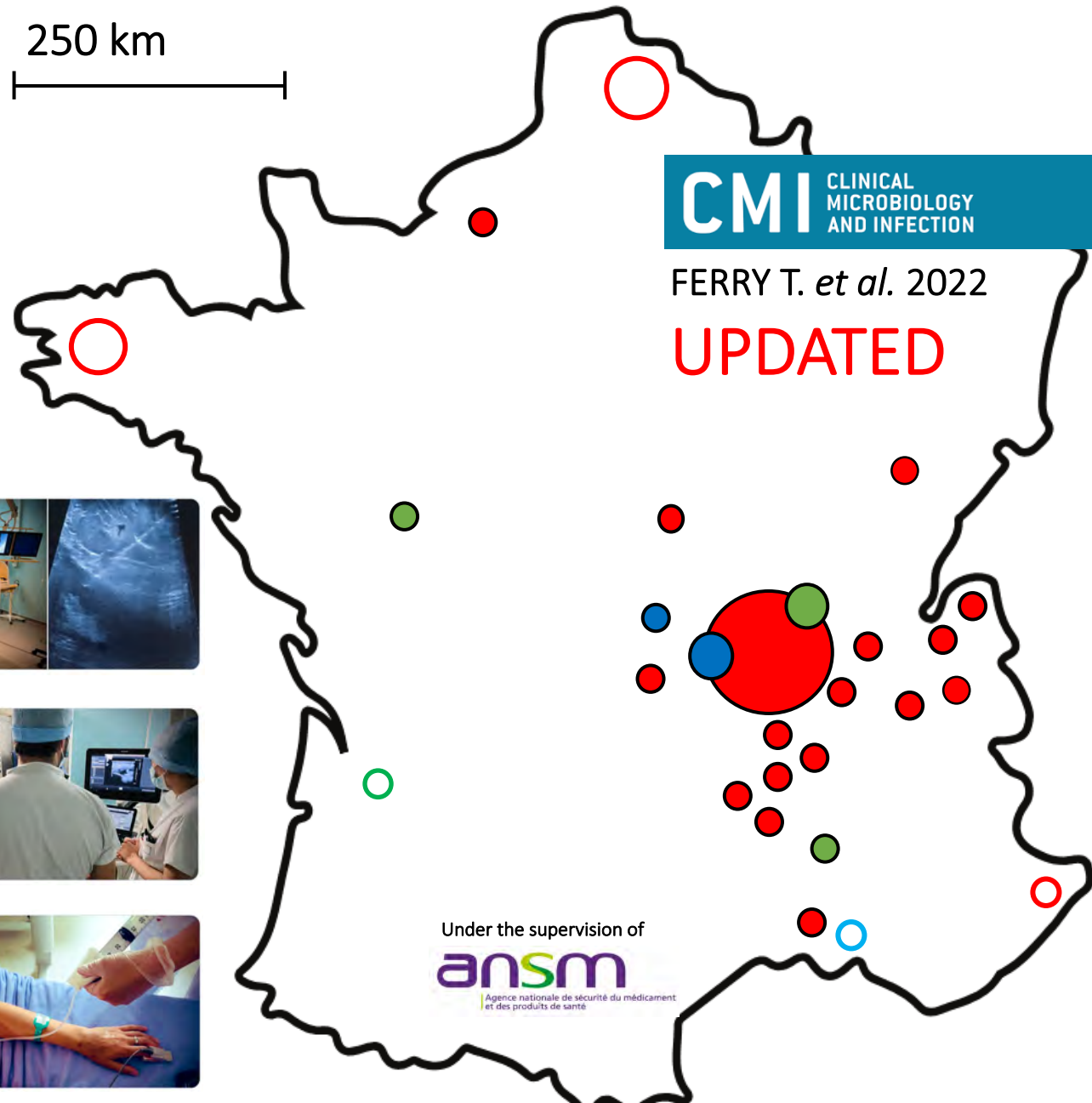
EBM

Clinical
Trials



T. FERRY

Implementation of a Phage Therapy Center in a CRIOAc



PHAGE*in***LYON**



41 patients in Lyon since 2017

75% of of whole treated patients in France



• 38 with phages from **PHERECYDES PHARMA**

• 3 with phages from



- 34 **BJI** (inclusion 30 **PJI**)
- 4 **endocarditis/vascular graft**
- 3 **lung infections** (VAP + bacteremia, pneumonia in lung graft bronchiectasia, cystic fibrosis exacerbation)



+ 8 patients managed outside Lyon ○

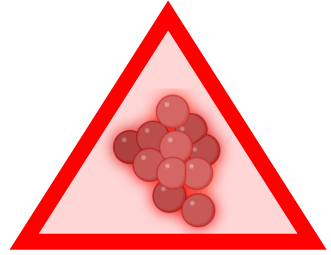
including 1 patient in Sweden

●○ **BJI**

●○ **Endocarditis**

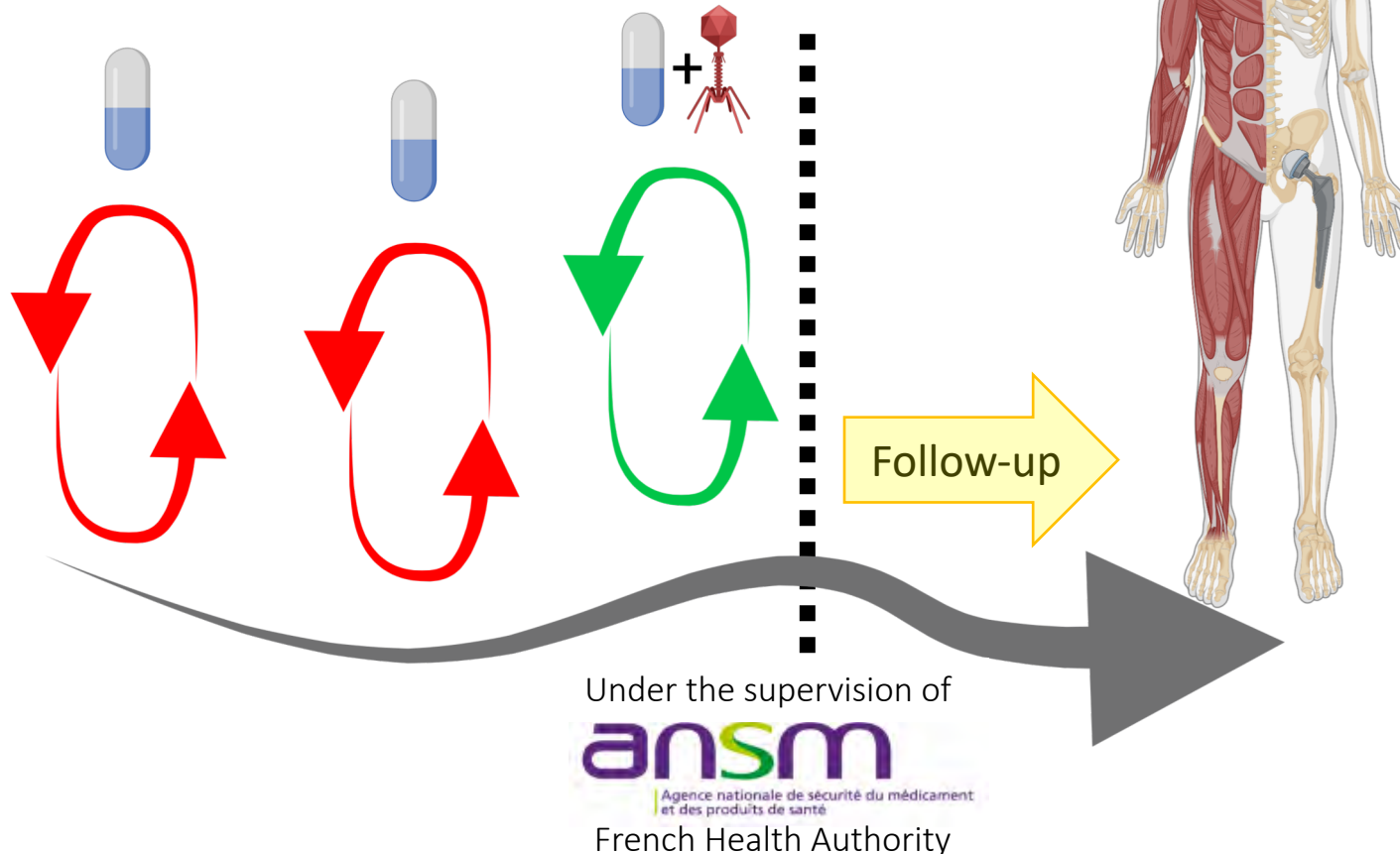
●○ **Pneumonia**

A large panel of severe bacterial infections



Some positive signals
in these infections

The patient is his “own control”



- Relevant clinical conditions based on the Helsinki declaration
- Especially in patients with:
 - life- or functional- threatening severe infections
 - infected with multidrug resistant pathogens

HOWEVER

- A case report has a low scientific evidence
- Only case reports with a positive outcome are published
- Huge challenge for the phages
Do not conclude that phages have no place if the outcome is negative



Review

Past and Future of Phage Therapy and Phage-Derived Proteins in Patients with Bone and Joint Infection

REVIEW ARTICLE

OPEN ACCESS

Tristan Ferry
Jérôme Josse
Frédéric Laurent
on behalf of

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

Tristan Ferry^{1,2,3,4,*}, Cécile Batailler^{2,3,5}, Sophie Brosset^{2,3,6}, Camille Kolenda^{2,3,4,7},
Sylvain Goutelle^{2,3,8,9}, Elliot Sappey-Marinier^{2,3,5}, Jérôme Josse^{2,3,4,7}, Frédéric Laurent^{2,3,4,7},
Sébastien Lustig^{2,3,5}, On Behalf of the Lyon BJI Study Group,^a

infection ostéoarticulaire : historique, fondements, faisabilité et perspectives en France

Phage therapy in bone and joint infection: history, rationale, feasibility and perspectives in France

Virologie

et une

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

3,743

TOTAL VIEWS



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^{2,3,4,5}, on behalf of the Lyon BJI Study Group

VIEWS

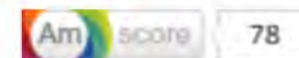
3,770

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

5,711

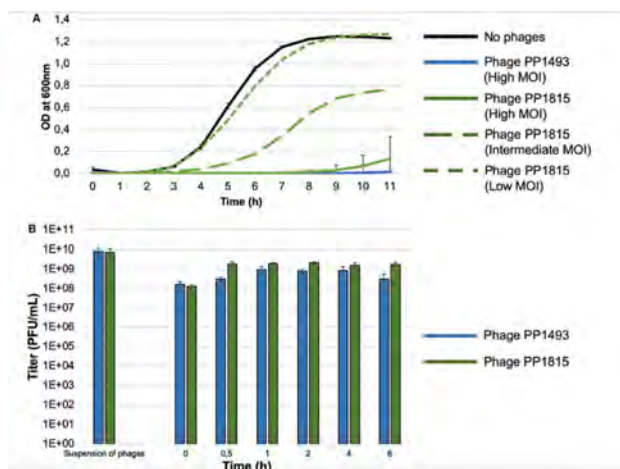
TOTAL VIEWS



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 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

4,970
TOTAL VIEWS



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 Ferry^{1–4*}, 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[†]

CITATIONS



VIEWS



ALTMETRIC



More metrics information

Série de cas procédure HCL « PhagoDAIR »

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

5,711

TOTAL VIEWS



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*



#PhagoDAIR

Debridement Antibiotics and Implant Retention

CASE REPORT

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

Clinical case

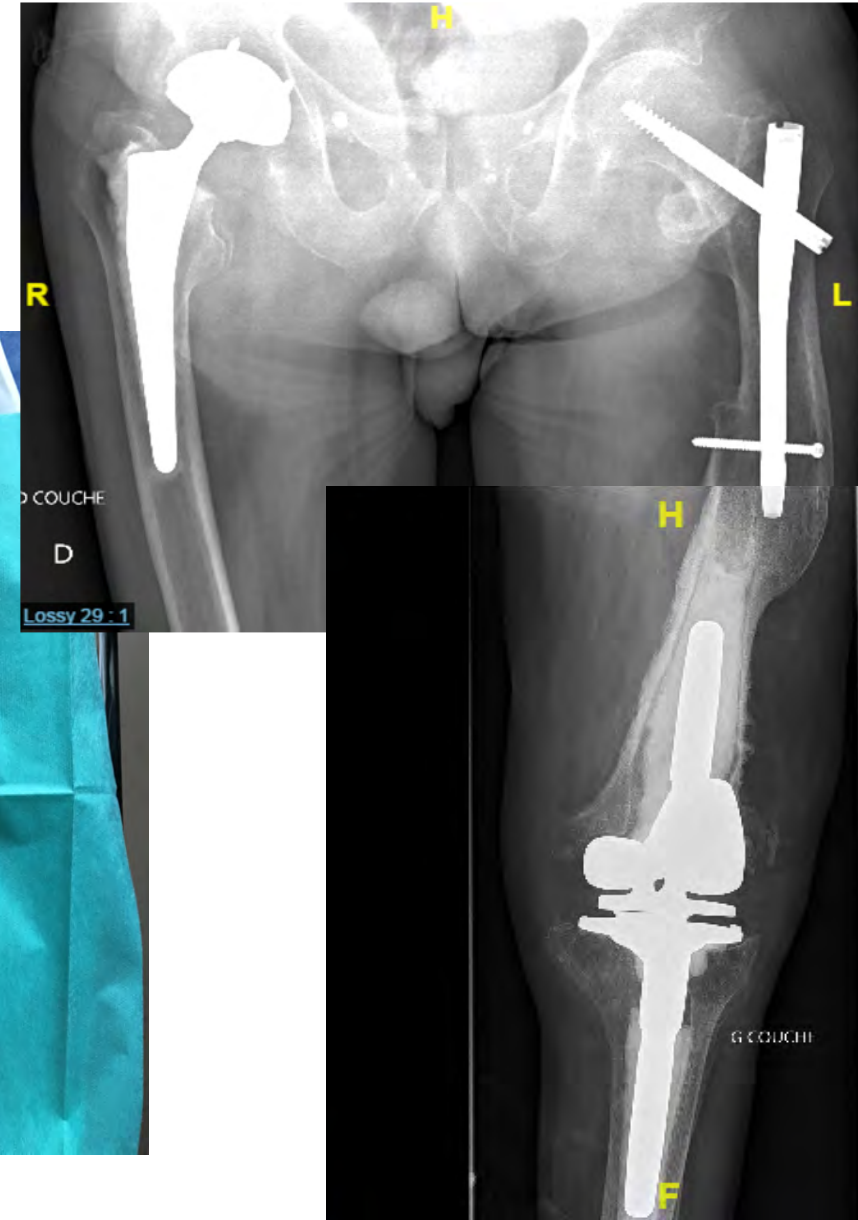
80-year-old man

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

Failure

Complex orthopaedic situation with past femoral fracture

Impossible to walk (painful knee)





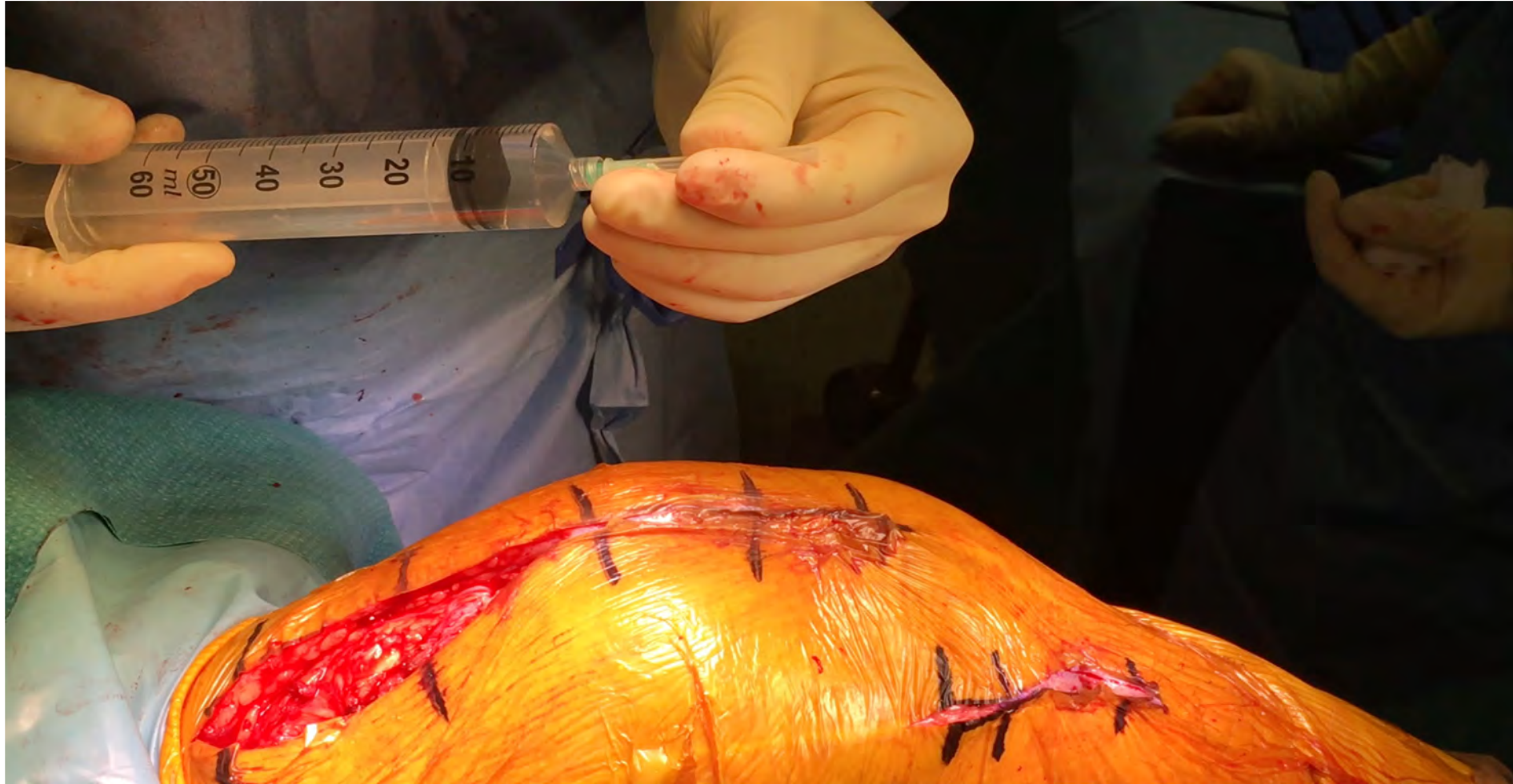
PHAGEinLYON



Fistula and
purulent discharge



“PhagoDAIR”



One shot peroperative phage
application after “DAIR”



PHAGEⁱⁿLYON



Post-operative antibiotics:

Daptomycin + Rifampin

At day 4 (only MSSA in all intraoperative samples):

Levofloxacin + Rifampin

Then:

Cefalexin as suppressive antimicrobial therapy



PHAGEⁱⁿLYON





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.



PHAGEⁱⁿLYON



A link between phage exposition and clinical success?

30 months after the PhagoDAIR procedure
Under cefalexin as suppressive therapy



	<i>Staphylococcus aureus</i> CMI (mg/l)
Pénicilline G	R
Oxacilline	S
Kanamycine	S
Gentamicine	S
Tobramycine	S
Erythromycine	S
Lincomycine	S
Pristinamycine	S
Tétracycline	S
Ofloxacine	S
Cotrimoxazole	S
Nitrofurantoïne	S
Rifampicine	S
Fosfomycine	S
Acide Fusidique	S
Vancomycine	S
Teicoplanine	S
Linézolide	S

A link between phage exposition and clinical success?



A link between phage

clinical success?



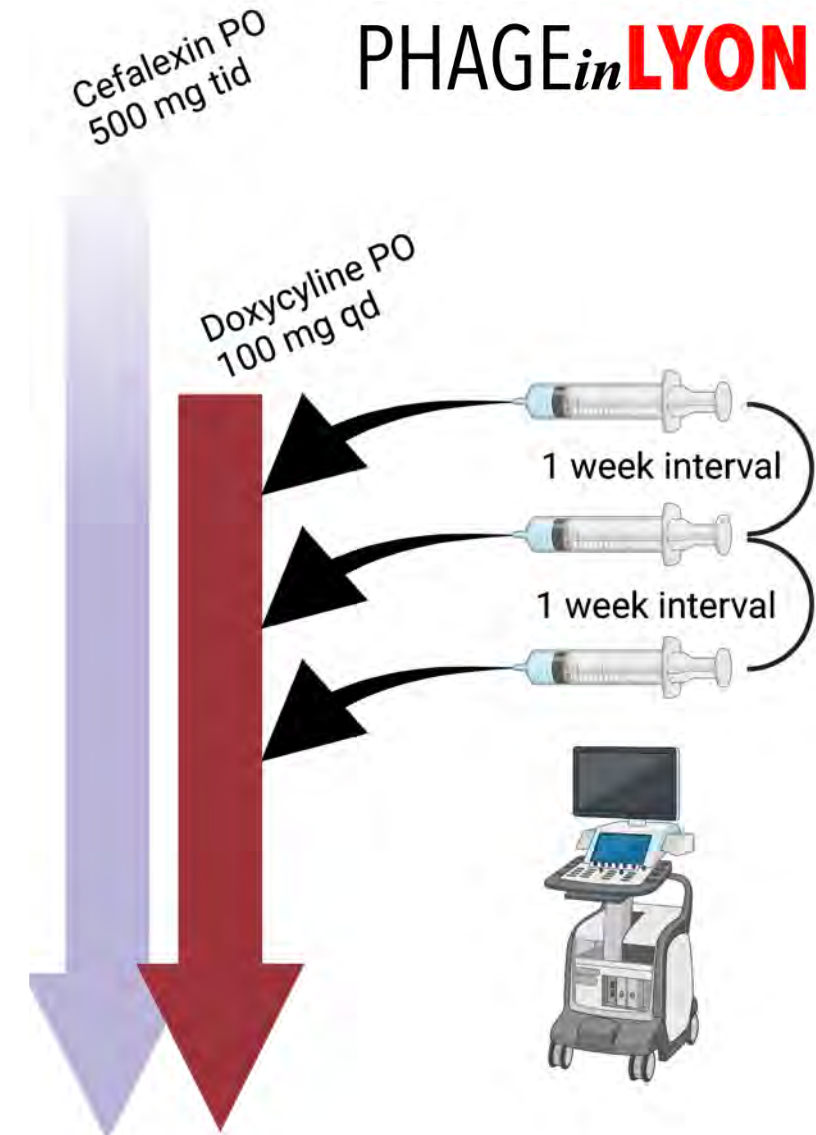
Cefalexin PO
500 mg tid

PHAGE_{in}LYON

Doxycycline PO
100 mg qd



A link between phage exposition and clinical success?



PhagoDAIR I

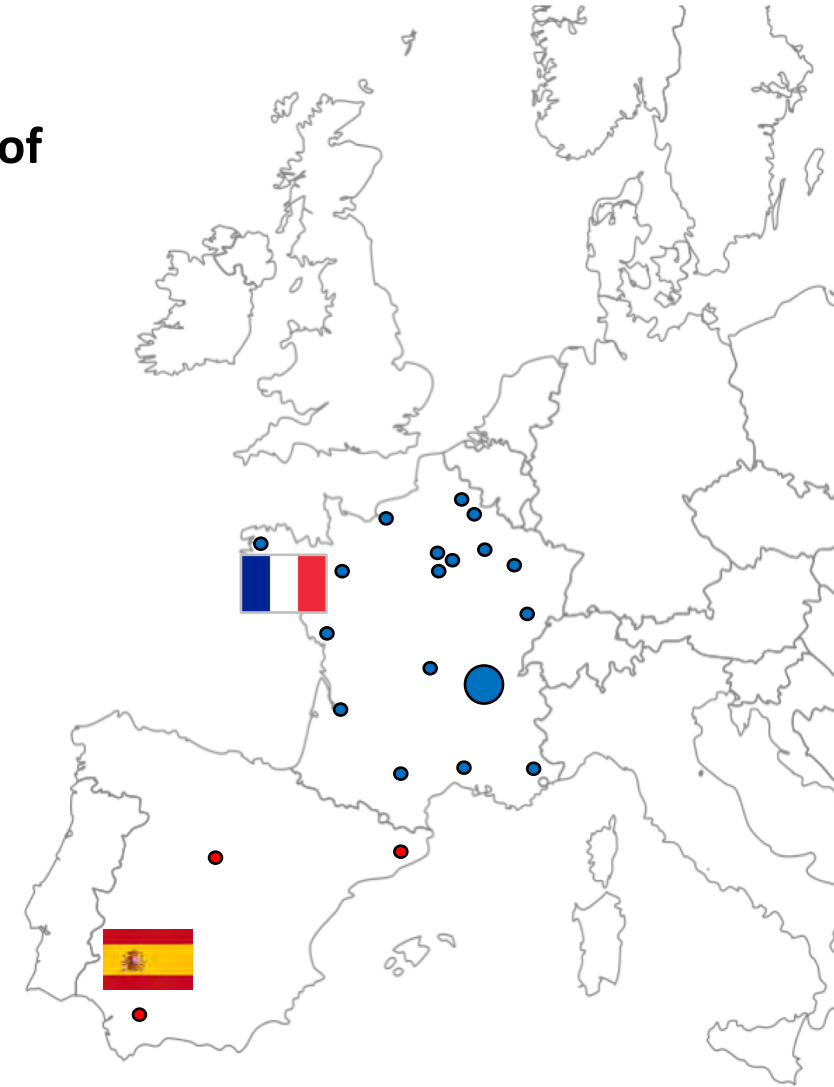
A Pilot, Multicenter, Randomized, Non-Comparative, Double-Blind Study of Phage Therapy in Patients with Hip or Knee PJI due to *S. aureus* Treated with DAIR and Antibiotic Therapy

Inclusion Criteria

1. *S. aureus* monomicrobial knee or hip PJI >3 months after prosthesis implantation 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

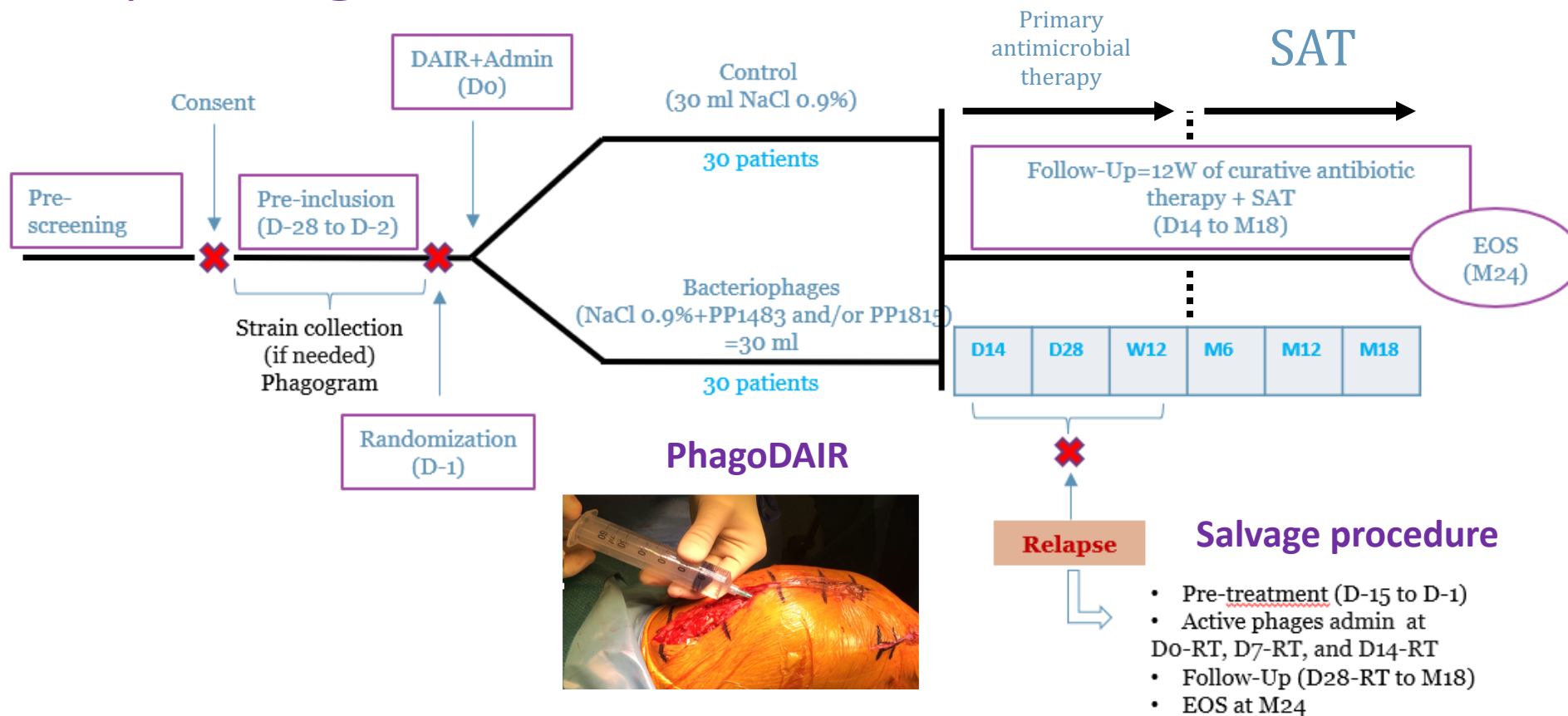
To estimate the rate of clinical control of infection at Week 12±2 which will allow to calculate the sample size for future comparative studies.



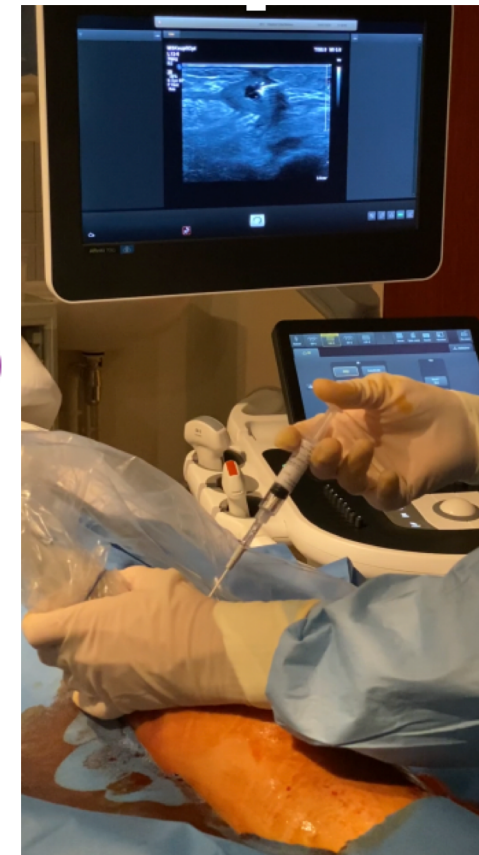
PhagoDAIR I

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

Study design



Salvage procedure



**THE MYTHOLOGY
OF PHAGE THERAPY**



**Phage therapy is fascinating
But it is not relevant
for all bacterial infections**

T. FERRY

EBM
Clinical
Trials

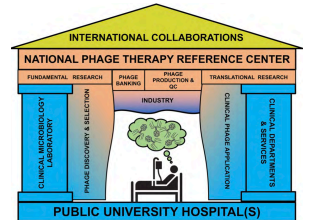


**Medical care
could not be exclusively based
on clinical trials**

T. FERRY

Conclusion

- Phages are not candidates to replace antibiotics
- As adjuvant therapy, the use only pharmacological-grade therapeutic phages, under the supervision of health-care authorities, could bring some benefit
- Create referral centers where phages from the industry and/or from academic structures could be used as compassionate therapy
- Treating patients with phages in these centers helps to:
 - Treat individual patients with relapsing infections in dead-end clinical situation
 - Better understand the phage pharmacokinetic in the context of infection
 - Evaluate the best ways of administration and the optimal exposition to phages
 - Design relevant clinical trials in less severe clinical conditions
- The phage therapy 2.0 era is just open
- From the mythology to reality



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

Imaging – Fabien Craighero, Loic Bousel, 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

Some figures
were created with

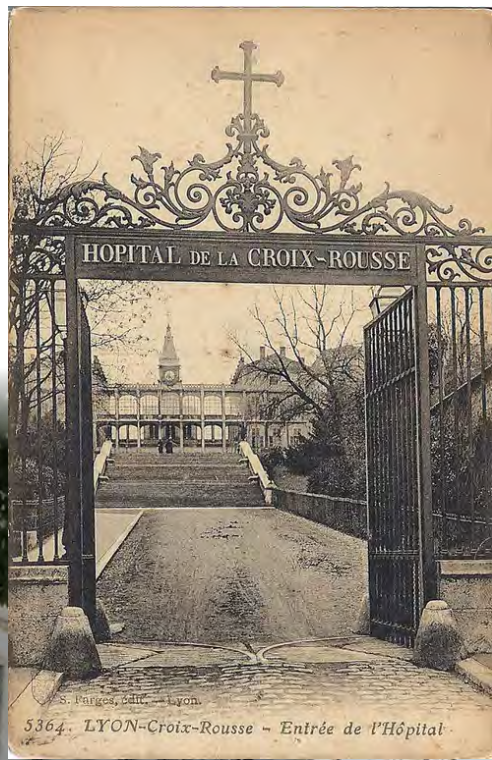


Coordinator: Tristan Ferry and Frederic Laurent

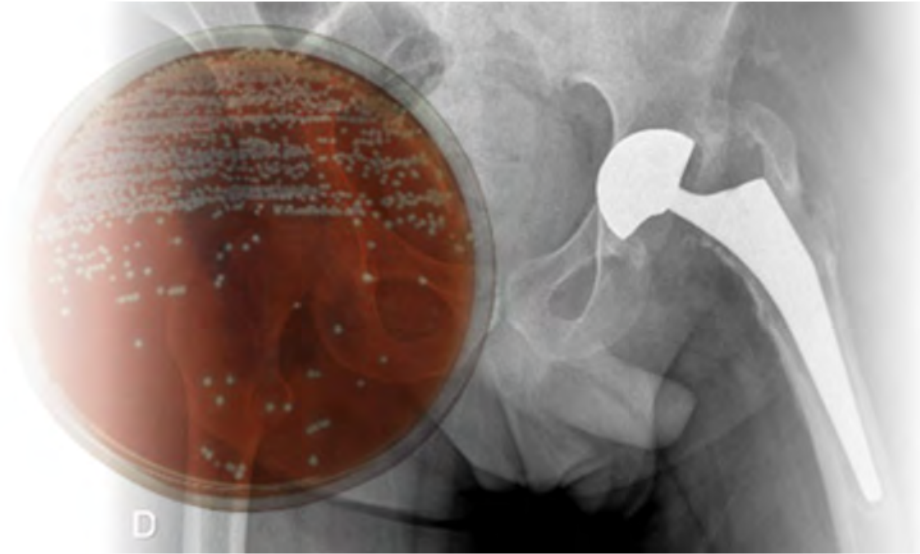
Mathieu Medina, Camille Kolenda, Floriane Laumay, Melanie Bonhomme, Leslie Blazere, Tiphaine Legendre, Eline Terrazzoni, Fabrice Pirot, Camille Merienne, Samira Filali, Benamine Lapras, Gilles Leboucher, Thomas Briot



Croix-Rousse Hospital



<http://www.crioac-lyon.fr>



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