infections osteoarticulaires, bactériophages et thérapie phagique : Histoire et perspectives

Pr. 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)













- Infections <u>hétérogènes</u>
- Epidémiologie bactérienne variable
- Incidence '<u>faible'</u>
- Différentes stratégies
- La stratégie et les comorbidités influencent le pronostic
- Pourcentage de succès faible
 - dans certaines situations cliniques
- <u>Coût considérable</u> (individuel et collectif)

Lew et al. NEJM 1997



- Infections <u>hétérogènes</u>
- Epidémiologie bactérienne variable
- Incidence '<u>faible'</u>
- Différentes stratégies
- La stratégie et les comorbidités influencent le pronostic
- Pourcentage de succès faible
- dans certaines situations cliniques
 <u>Coût considérable</u> (individuel et

collectif)

- Peu d'essai clinique
- Peu de molécules antiinfectieuses approuvée



NIH U.S. National Library of Medicine

ClinicalTrials.gov

- Osteomyelitis: 68
- Prosthetic-joint infection: 47
- Meningitis: 348
- Urinary tract infection: 492
- Tuberculosis: 915
- Influenza: 2'152



NIH U.S. National Library of Medicine

ClinicalTrials.gov

- Osteomyelitis: 68
- Prosthetic-joint infection: 47
- Meningitis: 348
- Urinary tract infection: 492
- Tuberculosis: 915
- Influenza: 2'152

Les IOA : Maladies infectieuses négligées des pays industrialisés

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: 10³¹ bacteriophages on the planet, more than every other organism
- Especially in marine environment, sea, lake, backwater, soil, animal and human stools, etc.







Marine viruses — major players in the global ecosystem

Curtis A. Suttle





Figure 1 | Relative biomass and abundances of prokaryotes, protists and viruses.

Probing this vast reservoir of genetic and biological diversity continues to yield exciting discoveries.

Nature Review Microbiology 2007

Self-limiting nature of seasonal cholera epidemics: Role of host-mediated amplification of phage

Shah M. Faruque**, M. Johirul Islam*, Qazi Shafi Ahmad*, A. S. G. Faruque*, David A. Sack*, G. Balakrish Nair*, and John J. Mekalanos[‡] Proc Natl Acad Sci U S A, 2005

> tion **Dhaka City** V. cholerae O1 Bacteria 30 V. cholerae O1-cholera 25 20 15 chol Airport 10 ę 5 W2 W3 W4 W1 W2 W3 W4 toll Bus Stand COOR B noura Bride 10



Month and Year

A 4000

patients 3500

3000



Fig. 1. Map of Dhaka showing the environmental sampling sites (•) and the location of the ICDDRB cholera hospital at the center of the city.

Bangladesh

10 to 100 fold smaller than a bacteria

Translucent tap water



X million of ≠ Bactériophage<u>S</u> !!! (targeting environmental bacteria)



preparation

10⁸ of THREE bacteriophages/mL (targeting *S. aureus*)





Ferry T.



Lysogenic cycle

Ferry T.



Lysogenic cycle

Ferry T.



Self-maintained bacterial lysis





Self-maintained bacterial lysis



Self-maintained bacterial lysis

A clear antibacterial activity!

S. aureus being lysed by the Sa2 phage



Bacterial DNA appeared in green

Courtesy Pascal Maguin Luciano Marraffini Lab THE ROCKEFELLER UNIVERSITY







- Felix d'Herelle
- Institut Pasteur, Paris







- Felix d'Herelle
- Institut Pasteur, Paris
- He treated <u>shigellosis</u> (diarrhea) in children with <u>oral intake</u> of specific "filtered" <u>bacteriophages</u> that he found in stools of patients who spontaneously healed from... shigellosis







- Felix d'Herelle
- Institut Pasteur, Paris
- He treated <u>shigellosis</u> (diarrhea) in children with <u>oral intake</u> of specific "filtered" <u>bacteriophages</u> that he found in stools of patients who spontaneously healed from... shigellosis
- He founded <u>Eliava institute in Georgia</u> and the <u>"Laboratoire Français des</u> <u>Bactériophages"</u> in Paris



Lessons to be learned of phage therapy of the 20th century





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.



Docteur André RAIGA

Ancien Interne lauréat des Hópitaux 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.

Partial bone necrosis requiring <u>surgery</u>

Skin and soft tissue damage requiring surgical coverage



MAJOR BIOLOGICAL LIMIT:

Bacteriophages <u>have not the</u> <u>capacity</u> to perform bone debridement nor to regenerate skin and sof tissue

Patient with a relapsing infection after Phage therapy in Tbilissi

Le Journal de Médecine de Lyon

After d'Herelle, the story continued in Lyon

Traitement des infections à bacilles pyocyaniques par des bactériophages adaptés par sélection.

Par MM. André BERTOVE et A.-I., COUBTIEU.





Clinique des Maladies Infectieuses, Hôpital de la Croix-Rousse Hospices Civils de Lyon 1958-1960





Bactériophages thérapeutiques préparés à l'Institut Pasteur de Lyon dans les années 1970

Academic collaboration 70 patients/year!

Pr. Bertoye

Pathogenic bacteria from the patient

978

Institut Pasteur Lyon Active and trained bacteriophages





Large production of antibiotics in 1970-1980 killed the phage therapy

- Industrial production
- Large spectrum
- Bactericidal activity
- Oral and IV
- <u>Systemic diffusion</u> to the infected site
- Numerous <u>different</u>
 <u>kinds of families</u>,

with different mechanism of action



Large production of antibiotics in 1970-1980 killed the phage therapy

- Industrial production
- Large spectrum
- Bactericidal activity
- Oral and IV
- <u>Systemic diffusion</u> to the infected site
- Numerous <u>different</u>
 <u>kinds of families</u>,

with different mechanism of action





<u>Complex virus</u>-based <u>personalized</u> treatment without clear industrial process, <u>not considered as a drug</u>

Large production of antibiotics in 1970-1980 killed the phage therapy

- Industrial production
- Large spectrum
- Bactericidal activity
- Oral and IV
- <u>Systemic diffusion</u> to the infected site
- Numerous <u>different</u>
 <u>kinds of families</u>,

with different mechanism of action





<u>Complex virus</u>-based <u>personalized</u> treatment without clear industrial process, <u>not considered as a drug</u>

Large production of antibiotics in 1970-1980 killed the phage therapy

- Industrial production
- Large spectrum Phages as the Phoenix?
- **Bactericidal** activity
- Oral and IV
- Systemic diffusion to the infected site
- Numerous different kinds of families,

with different mechanism of actions





<u>Complex</u> <u>virus</u>-based <u>personalized</u> treatment without clear industrial ss, not considered as a drug

Cocktails produced in 2020 by the Eliava Institute

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



Bacteriophage ISP (*Myoviridae*)



Merabishvili et al. PloS ONE 2009

T. Ferry. The story of Phage therapy

Not meeting Good Manufacturing Practices (GMP)



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









REFERENCE CENTERS FOR THE MANAGEMENT OF BONE AND JOINT INFECTION



Adapted from Ferry T, et al. Orthop Traumatol Surg Res. 2019;105(1):185-190

REFERENCE CENTERS FOR THE MANAGEMENT OF BONE AND JOINT INFECTION



Adapted from Ferry T, et al. Orthop Traumatol Surg Res. 2019;105(1):185-190
Comité scientifique des CRIOAc

Président : Pr. T. Ferry (Infectiologue, Lyon) Pr. E. Senneville (Infectiologue, Lille-Tourcoing) Pr. A. Stein (Infectiologue, Marseille)

Dr. S. Marmor (Orthopédiste, Paris)

- Pr. E. Steindel (Orthopédiste, Brest)
- Pr. D. Meynard (Orthopédiste, Strasbourg)

Dr. P. Bemer (Microbiologiste, Nantes) Pr. V. Dubois (Microbiologiste, Bordeaux) Centraliser les idées pour la réalisation de projets de recherche à l'échelle nationale

Expertise pluridisciplinaire



MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ DIRECTION GÉNÉRALE DE L'OFFRE DE SOINS

Promotion de la recherche et de l'innovation Utilisation du système d'information pour les études de faisabilité

"Bacterial cells that escape the effects of antibiotics without undergoing genetic change"



"Bacterial cells that escape the effects of antibiotics without undergoing genetic change"



"Bacterial cells that escape the effects of antibiotics without undergoing genetic change"



"Bacterial cells that escape the effects of antibiotics without undergoing genetic change"



"Bacterial cells that escape the effects of antibiotics without undergoing genetic change"





C. Kolenda et al.







vancomycin









Bacteriophages concentration (PFU/mL)



Declaration of Helsinki



Medical Research Involving Human Subjects VVVA ASSOCIATION

Special Communication

World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects



Wori d

MEDICAL

World Medical Association

- Unproven Interventions in Clinical Practice
- 37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, <u>May use an Unproven intervention</u> if in the physician's judgement it offers hope of <u>saving life</u>, <u>re-establishing health</u> or alleviating suffering. In France: <u>compassionate</u> use, magistral preparation by the hospital pharmacist



A clear antibacterial activity! Phagogram

PFU/mL

S. aureus culture on a gelosis



Clinical case #4

80-year-old man

<u>**Relapsing MSSA</u>** prosthetic left knee infection (past revision)</u>

Failure under suppressive oral antimicrobial therapy

Complex orthopaedic situation with past femoral fracture

Impossible to walk (painful knee)









Clinical case #4

Amputation (but not feasible !) ?



Doing nothing, but poor clinical situation with <u>risk of</u> complication and death

Conservative surgery

"Debridement And Implant Retention" (DAIR) + <u>innovative approach to</u> <u>disrupt biofilm</u> + suppressive antimicrobial therapy ?



Lyon Phage team

















"Debridement And Implant Retention" (DAIR)





"PhagoDAIR"



One shot peroperative phage application after "DAIR"





Clinical case #4

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. <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.

<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.

Clinical case #5

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 #5

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!

	Pseudomonas aeruginosa 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)
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)	B-test∶1 → R
Ceftolozane-tazobactam (Etest)	R E-test : > 256

R

E-test: 64

The strain was also spontaneously

Ceftazidime-Avibactam (Etest)

resistant to GMP bacteriophages !!!

PHERECYDES

Potential European academic collaborations



Potential European academic collaborations ansm



Potential European academic collaborations ansm





Potential European academic collaborations answ



Potential European academic collaborations ansm


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.**

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





Under the supervision of Agence nationale de sécurité du médicament Agence hationale de sécurité du médicament French Health Authority

niversité de Lausanne



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.**



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





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





Combo

CF-301

VAN

Buffer

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



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.

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



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.

Potential anti-Persisters





 Crucial need for (alternatives) <u>additional therapies</u> <u>to antibiotics</u> to maximize clinical success in complex bacterial infections





- Crucial need for (alternatives) <u>additional therapies</u> to antibiotics to maximize clinical success in complex bacterial infections
- Phage therapy is a <u>Phoenix</u>
- Don't forget <u>Lessons from 20th century</u>







- Crucial need for (alternatives) <u>additional therapies</u> <u>to antibiotics</u> to maximize clinical success in complex bacterial infections
- Phage therapy is a <u>Phoenix</u>
- Don't forget <u>Lessons from 20th century</u>
- Develop and use <u>GMP bacteriophages</u> (phages 2.0) ▶ <u>18 patients treated in 2 years</u>
- Industry / health authority / academic <u>collaborations</u>









- Crucial need for (alternatives) <u>additional therapies</u> to antibiotics to maximize clinical success in complex bacterial infections
- Phage therapy is a <u>Phoenix</u>
- Don't forget <u>Lessons from 20th century</u>
- Develop and use <u>GMP bacteriophages</u> (phages 2.0) ▶ <u>18 patients treated in 2 years</u>
- Industry / health authority / academic <u>collaborations</u>
- Reference (regional or national) clinical centers to determine relevant indications
- Need for <u>Phage</u> <u>discovery</u>, <u>banking</u>, <u>susceptibility</u>, to personalize the therapy







- Crucial need for (alternatives) <u>additional therapies</u> to antibiotics to maximize clinical success in complex bacterial infections
- Phage therapy is a <u>Phoenix</u>
- Don't forget <u>Lessons from 20th century</u>
- Develop and use <u>GMP bacteriophages</u> (phages 2.0) ▶ <u>18 patients treated in 2 years</u>
- Industry / health authority / academic <u>collaborations</u>
- Reference (regional or national) clinical centers to determine relevant indications
- Need for <u>Phage discovery</u>, <u>banking</u>, <u>susceptibility</u>, to personalize the therapy
- Need for national phage therapy center(s)





t des produits de santé

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, Eliott 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







Centre International de Recherche en Infectiologie











Centre International de Recherche en Infectiologie





http://www.crioac-lyon.fr





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





🕨 YouTube

@CrioacLyon





Centre International de Recherche en Infectiologie

