

31<sup>ST</sup> CHALLENGE IN INFECTIOUS DISEASES

# Phage therapy in bone infections

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### 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



SECOND YEAR) Copy Town Taxable THIRD YEAR



# Phage therapy is fascinating

• Viral therapy for bacterial infections



- Story of phage therapy is connected to worldwide geopolicital events
- Potential <u>incredible</u> preclinical <u>efficacy</u>
- 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



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



Merabishvili et al. PloS ONE 2009

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Institute	Structure	Events	PhD Studies	Projects	Contact	







#### Professor Andrzej Górski





their alments could disappear.





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



# THEfirstNEWS

#### Wrocław clinic uses 'super viruses' to battle rebellious bacteria

JOANNA JASIŃSKA MARCH 22, 2020

### **Russian Phages**





1 000 000 000 boxes produced each year







Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails 2017 **Development and Use of Personalized** To Treat a Patient with a Disseminated Resistant Acinetobacter baumannii Infection



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Applications and Therapeutics ion of Infectious Diseases & Global Public Health

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# United States



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Welcome to IPATH Center for Innovative Phage Applications and

We are the first dedicated phage therapy center in North America, bringing innovative research and clinical practice to the field of medicine. Join us on

our journey and witness a revolutionary wave of solutions to combat antibiotic resistance

DELVON







Europe 1



Accueil > Actualités > Des virus pour soigner des infections résistantes aux antibiotiques

### Contemporary

# Previous clinical trials have not « failed »

- Most of them were phase I/IIa/IIb and <u>not phase III</u>
- Phages are <u>particular anti-infective agents</u> (≠ antibiotics)
- Need a <u>specific</u> purification process
- Purified phages or phage cocktails are potentially not stable during time
- High specificity of phages
- Potential need for a phagogram (like antibiogram) before treatment

Don't forget the lessons of the past

Respect the experience of the East







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:** Jean-Paul Pirnay, **Belgium** Ran Nir-Paz, **Israël** 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<sup>1,†</sup>, Tristan Ferry<sup>2,3,†</sup> and Grégory Resch<sup>4,\*,†</sup>





2021



VS.









HCL HOSPICES CIVILS DE LYON

**IOA**C

LYON













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





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

Some **positive signals** in these infections

The patient is his "own control"



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

Some **positive signals** in these infections

The patient is his "own control"



- Relevant clinical conditions based on the <u>Helsinki declaration</u>
- Especially in patients with:
  - life- or functionnal- threathening severe infections
  - infected with multidrug resistant pathogens

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

Some **positive signals** in these infections

The patient is his "own control"



- Relevant clinical conditions based on the <u>Helsinki declaration</u>
- Especially in patients with:
  - life- or functionnal- threathening severe infections
  - infected with multidrug resistant pathogens

### HOWEVER

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

# Phages have antibiofilm activity



vancomycin

C. Kolenda et al. Antimicrob Agents Chemother 2019

# Phages have antibiofilm activity



### Premiers cas cliniques traités en 2017, publiés

**Open Forum Infectious Diseases** 

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?

> Ferry T. 2018 Open Forum Infectious Diseases



# Premiers cas cliniques traités en 2017, publiés

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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?



#### Under the supervision of

Agence nationale de securité du médicament et des produits de santé French Health Authority



Ferry T. 2018 Open FcInnovations for the treatment of a complex bone and jointInfectious Diseaseinfection due to XDR Pseudomonas aeruginosa including localapplication of a selected cocktail of bacteriophagesTristan Ferry 🕿, Fabien Boucher, Cindy Fevre, Thomas Perpoint, Joseph Chateau, Charlotte Petitjean,

Jérôme Josse, Christian Chidiac, Guillaume L'hostis, Gilles Leboucher, ... Show more

Journal of Antimicrobial Chemotherapy, Volume 73, Issue 10, 1 October 2018, Pages 2901–2903,



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 <sup>1,2,3,4\*</sup>, Camille Kolenda<sup>2,3,4,5</sup>, Cécile Batailler<sup>2,3,6</sup>, Romain Gaillard<sup>3,6</sup>, Claude-Alexandre Gustave<sup>2,3,4,5</sup>, Sébastien Lustig<sup>2,3,6</sup>, Cindy Fevre<sup>7</sup>, Charlotte Petitjean<sup>7</sup>, Gilles Leboucher<sup>8</sup>, Frédéric Laurent<sup>2,3,4,5</sup> 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,<sup>1,2,3,4</sup> Gilles Leboucher,<sup>5</sup> Cindy Fevre,<sup>6</sup> Yannick Herry,<sup>2,4,7</sup> Anne Conrad,<sup>1,2,3,4</sup> Jérôme Josse,<sup>2,3,4,8</sup> Cécile Batailler,<sup>2,4,7</sup> Christian Chidiac,<sup>1,2,3,4</sup> Mathieu Medina,<sup>6</sup> S. Lustig,<sup>7</sup> and Frédéric Laurent<sup>2,3,4,8</sup>; 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 <sup>1,2,3,4\*</sup>, Camille Kolenda<sup>2,3,4,5</sup>, Cécile Batailler<sup>2,3,6</sup>, Claude-Alexandre Gustave<sup>2,3,4,5</sup>, Sébastien Lustig<sup>2,3,6</sup>, Matthieu Malatray<sup>3,6</sup>, Cindy Fevre<sup>7</sup>, Jérôme Josse<sup>2,3,4,5</sup>, Charlotte Petitjean<sup>7</sup>, Christian Chidiac<sup>1,2,3,4</sup>, Gilles Leboucher<sup>8</sup> and Frédéric Laurent<sup>2,3,4,5</sup> on behalf of the Lyon BJI Study group





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>1,23,4\*</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



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<sup>1-4</sup>\*, Fabien Boucher<sup>1,4,5</sup>, Cindy Fevre<sup>6</sup>, Thomas Perpoint<sup>1,4</sup>, Joseph Chateau<sup>1,2,4,5</sup>, Charlotte Petitjean<sup>6</sup>, Jérôme Josse<sup>2-4,7</sup>, Christian Chidiac<sup>1,2-4</sup>, Guillaume L'hostis<sup>6</sup>, Gilles Leboucher<sup>8</sup> and Frédéric Laurent<sup>2-4,7</sup> on behalf of the Lyon Bone and Joint Infection Study Group<sup>†</sup>



# 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





Lyon 1

Tristan Ferry <sup>1,2,3,4\*</sup>, Camille Kolenda <sup>2,3,4,5</sup>, Cécile Batailler <sup>2,3,6</sup>, Claude-Alexandre Gustave <sup>2,3,4,5</sup>, Sébastien Lustig <sup>2,3,6</sup>, Matthieu Malatray <sup>3,6</sup>, Cindy Fevre <sup>7</sup>, Jérôme Josse <sup>2,3,4,5</sup>, Charlotte Petitjean <sup>7</sup>, Christian Chidiac <sup>1,2,3,4</sup>, Gilles Leboucher<sup>8</sup> and Frédéric Laurent <sup>2,3,4,5</sup> on behalf of the Lyon BJI Study group







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

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

### 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**

- 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  $12\pm 2$  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 Infectious Diseases

MAJOR ARTICLE





#### Phage Therapy for Limb-threatening Prosthetic Knee *Klebsiella pneumoniae* Infection: Case Report and In Vitro Characterization of Anti-biofilm Activity

Edison J. Cano,<sup>1,2</sup> Katherine M. Caflisch,<sup>2,3</sup> Paul L. Bollyky,<sup>4</sup> Jonas D. Van Belleghem,<sup>4</sup> Robin Patel,<sup>1,2,5</sup> Joseph Fackler,<sup>6</sup> Michael J. Brownstein,<sup>6</sup> Bri'Anna Horne,<sup>5</sup> Biswajit Biswas,<sup>7</sup> Matthew Henry,<sup>7,8</sup> Francisco Malagon,<sup>7</sup> David G. Lewallen,<sup>9</sup> and Gina A. Suh<sup>1</sup>

<sup>1</sup>Division of Infectious Diseases, Mayo Clinic, Rochester, Minnesota, USA, <sup>2</sup>Infectious Diseases Research Laboratory, Mayo Clinic, Rochester, Minnesota, USA, <sup>3</sup>Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, Minnesota, USA, <sup>4</sup>Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA, <sup>5</sup>Division of Clinical Microbiology, Mayo Clinic, Rochester, Minnesota, USA, <sup>5</sup>Adaptive Phage Therapeutics, Gaithersburg, Maryland, USA, <sup>7</sup>Genomics and Bioinformatics Department, Biological Defense Research Directorate, Naval Medical Research Center-Frederick, Fort Detrick, Maryland, USA, <sup>8</sup>Geneva Foundation, Tacoma, Washington, USA, and <sup>9</sup>Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota, USA.



Figure 3. Phage therapy resulted in reduced erythema and swelling. Images are shown of the patient's lower extremities (A) before and (B) after completion of phage therapy.

NO SURGERY! 40 doses of exclusive <u>INTRAVENOUS</u> phages (1 injection each weekday)

PHXGOMED

PHAGE-BASED THERAPIES





2021



#### Case Report

Successful Treatment of a Recalcitrant *Staphylococcus epidermidis* Prosthetic Knee Infection with Intraoperative Bacteriophage Therapy

James B. Doub<sup>1,\*</sup>, Vincent Y. Ng<sup>2</sup>, Eleanor Wilson<sup>1</sup>, Lorenzo Corsini<sup>3</sup> and Benjamin K. Chan<sup>4</sup>

Single LOCAL injection during DAIR





### ClinicalTrials.gov

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Phage Therapy Versus Placebo in Conjunction With DAIR in Patients With Chronic Prosthetic Joint Infection Who Previously Failed Surgery for PJI

An Open-Label Multicenter Study to Evaluate the Safety and Efficacy of PhageBank<sup>™</sup> Phage Therapy in Conjunction With Debridement, Antibiotics, and Implant Retention (DAIR) for Patients With First Time Culture Proven Chronic Prosthetic Joint Infection

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











# **Oral antibiotics**

# Local therapy Surgery

No surgery Arthroscopic DAIR **Open DAIR (SoC) Prosthesis exchange (SoC)** 



# **Oral antibiotics**

# Local therapy Surgery

No surgery Arthroscopic DAIR **Open DAIR (SoC) Prosthesis exchange (SoC)** 

# Local phages





### Unique European academic collaboration





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

T. FERRY



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





Phage therapy center



**Referral center complex BJI** 

Dedicated referral activity Significant number of patients Relevant clinical situations

Phages from the industry Phages from academic Lysins from the industry



RIOAC



EUROPEAN MEDICINES AGENC

**Disruptive approach** 

**Sucess** 

Individual patient benefit







ഗ്ള) Lyon 1

RIOAC

### Conclusion

- Use only <u>pharmacological-grade therapeutic phages</u>, under the supervision of health-care authorities
- <u>Some</u> severe bacterial infections seem to be <u>relevant indications</u>
- Create <u>referral centers</u> where phages <u>from the industry</u> and/or <u>from</u> <u>academic structures</u> could be used as <u>compassionate therapy</u>
- **<u>Treating patients</u>** 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
- FONDATION HCL HOSPICES CIVILS DE LYON
- 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 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 – Frederic 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

# 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, Benjamine Lapras, Gilles Leboucher, Thomas Briot























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