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RÉUNION INTERDISCIPLINAIRE DE
CHIMIOTHÉRAPIE ANTI-INFECTIEUSE

LUNDI 13 & MARDI 14
DÉCEMBRE 2021

PALAIS DES CONGRÈS • PARIS



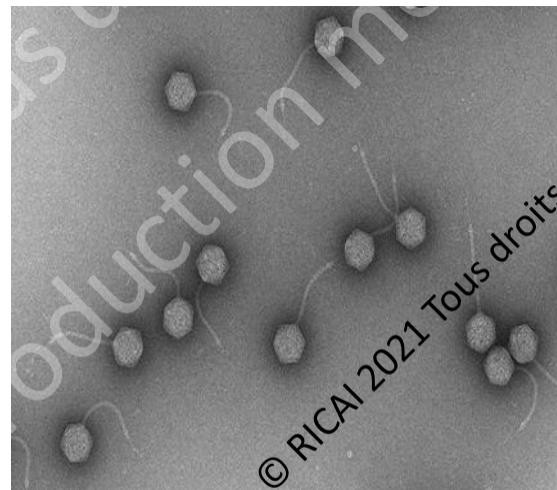
PHAGOTHÉRAPIE QUE NOUS APPORTENT LES MODÈLES ANIMAUX?

Dr. GRÉGORY RESCH, PhD

LABORATOIRE DES BACTÉRIOPHAGES



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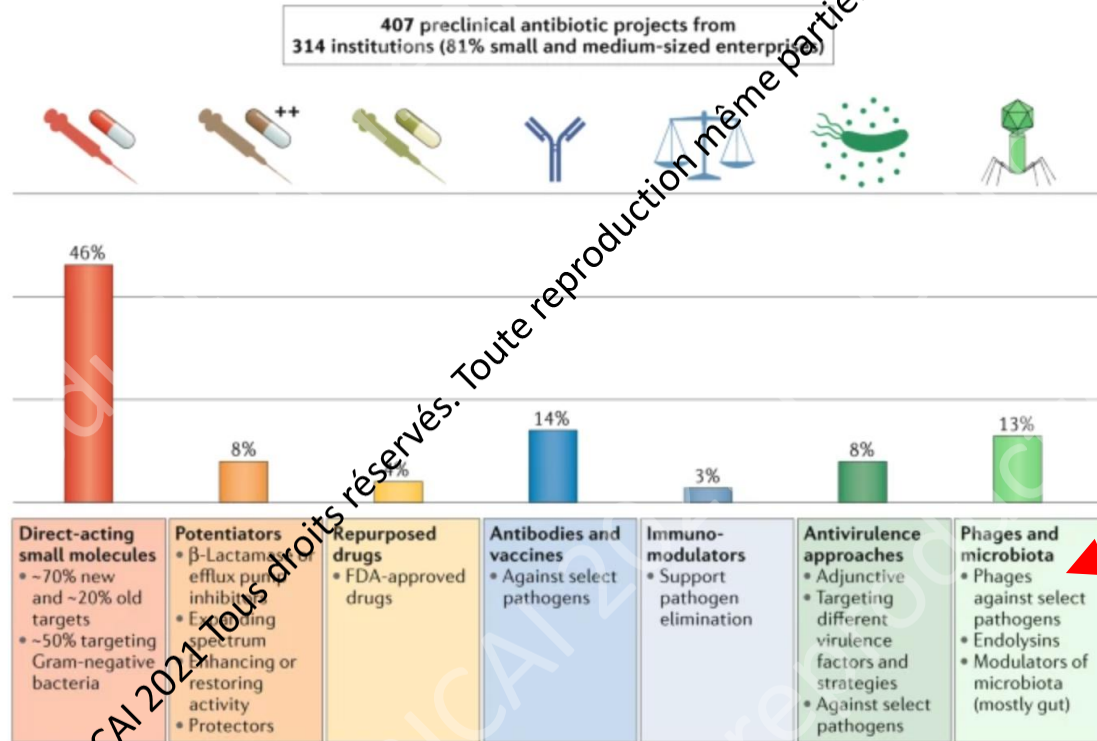
DISCLOSURES

- CO-INVESTIGATOR FOR PHAGOBURN
- SCIENTIFIC ADVISORY BOARD MEMBER
BIONTECH R&D AUSTRIA, VIENNA, AUSTRIA

INTRODUCTION

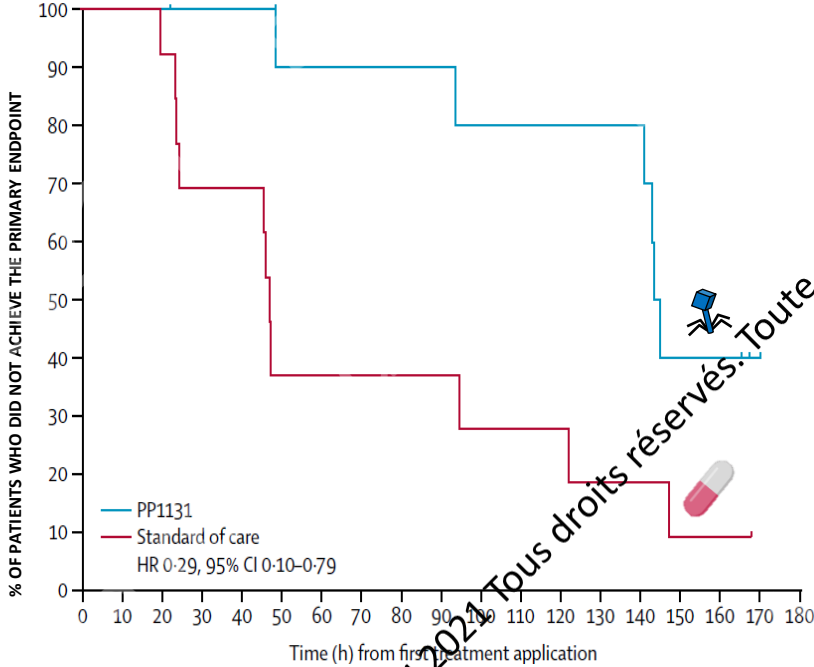
INNOVATIVE ANTIBACTERIAL STRATEGIES

Fig. 1: Overview of the preclinical antibacterial pipeline.



PHAGE THERAPY

WHY DID THE LAST PHAGE THERAPY RCT FAILED?



PHAGE COCKTAIL STABILITY ISSUES

10³ PFU/mL (10⁶ PFU/mL)

| | Number of colonies | Resistant | Intermediatly susceptible | Susceptible |
|---|--------------------|-----------|---------------------------|-------------|
| Participants who reached primary endpoint by day 7 | | | | |
| 1 | 5 | 0 | 0 | 5 |
| 2 | 5 | 0 | 0 | 5 |
| | | | | 4 |
| | | | | 6 |
| | | | | 5 |
| Total | 28 | 0 | 3 | 25 |
| Participants who did not reach primary endpoint by day 7 | | | | |
| 1 | 13 | 1 | 12 | 0 |
| 2 | 5 | 5 | 0 | |
| 3 | 11 | 0 | 11 | |
| 4 | 11 | 1 | 4 | |
| 5 | 5 | 0 | 0 | |
| Total | 45 | 7 | 27 | 11 |



RCT, RANDOMIZED CLINICAL TRIAL

WHY DID THE LAST PHAGE THERAPY RCT FAILED?

SOME POTENTIAL ISSUES



Balgrist
Universitätsklinik

| SETTING | DIARRHEA (2016) | BURN (2019) | UTI (2020) |
|---|------------------------|-------------------|------------|
| TRIAL DESIGN | X | X | X |
| PRODUCT STABILITY | X (GAYTRIC ACIDITY) | X (SHELF-LIFE) | ✓ |
| PHAGOGRAM BEFORE INCLUSION (INNATE PHAGE RESISTANCE) | ✓ | X | ✓ |
| ACQUIRED PHAGE RESISTANCE | ✓ | N/A | N/A |
| PHAGE PK/PD | X | X | N/A |

N/A, NOT ADDRESSSED; UTI, URINARY TRACT INFECTION
PK/PD, PHARMACOKINETICS & PHARMACODYNAMICS

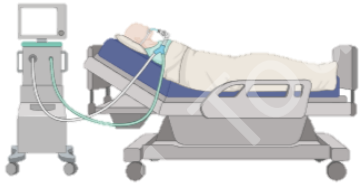
**WE NEED TO BETTER UNDERSTAND
AND
ADDRESS IDENTIFIED ISSUES
TO MAKE THE NEXT RCT A SUCCESS**

HOW?

TRANSLATIONAL PROCESS IN PHAGE THERAPY

KEY FEATURES

THE PROBLEM



CLINICAL RESEARCH



REGULATION



CLINICAL
TRIALS



TREATMENT

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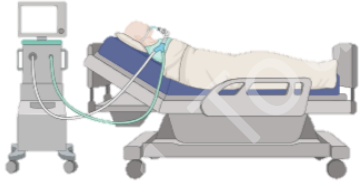
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TRANSLATIONAL PROCESS IN PHAGE THERAPY

KEY FEATURES

FUNDAMENTAL RESEARCH

THE PROBLEM



SCREENING

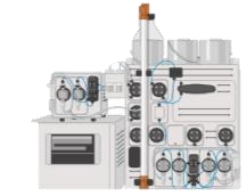
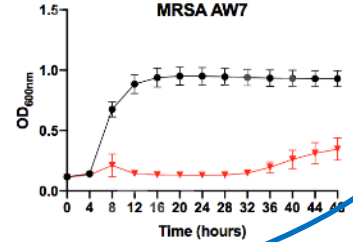


PHAGE BANK



>300 ESKAPE PHAGES

LEAD



GMP PRODUCTION



IN VITRO



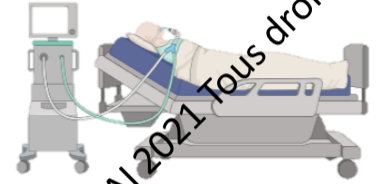
IN VIVO



REGULATION



CLINICAL TRIALS



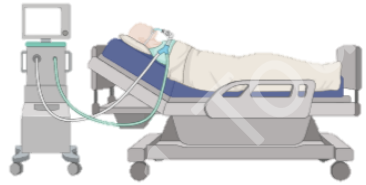
TREATMENT

GMP; GOOD MANUFACTURING PRACTICES

TRANSLATIONAL PROCESS IN PHAGE THERAPY

KEY FEATURES

THE PROBLEM



SCREENING

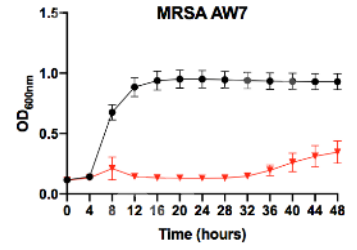


PHAGE BANK



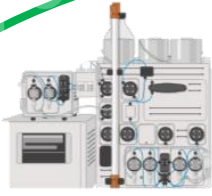
>300 ESKAPE PHAGES

LEAD



TRANSLATIONAL RESEARCH

GMP PRODUCTION



IN VITRO



IN VIVO



REGULATION



CLINICAL TRIALS



TREATMENT



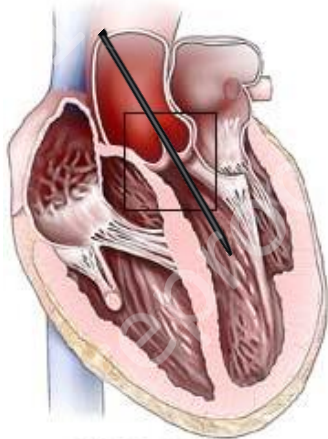
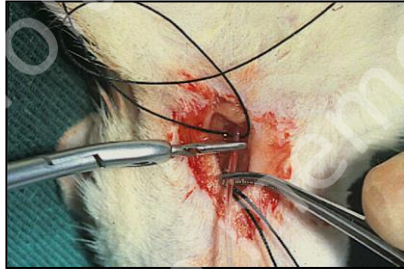
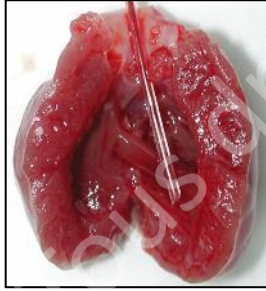
GMP; GOOD MANUFACTURING PRACTICES

PART I

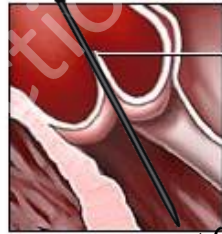
TRANSLATIONAL RESEARCH ALLOWS STUDYING ACQUIRED PHAGE RESISTANCE

THE MODEL OF INFECTIVE ENDOCARDITIS (IE)

IN VIVO



Cross section of the heart



Normal aortic valve



Area of infection on the aortic valve

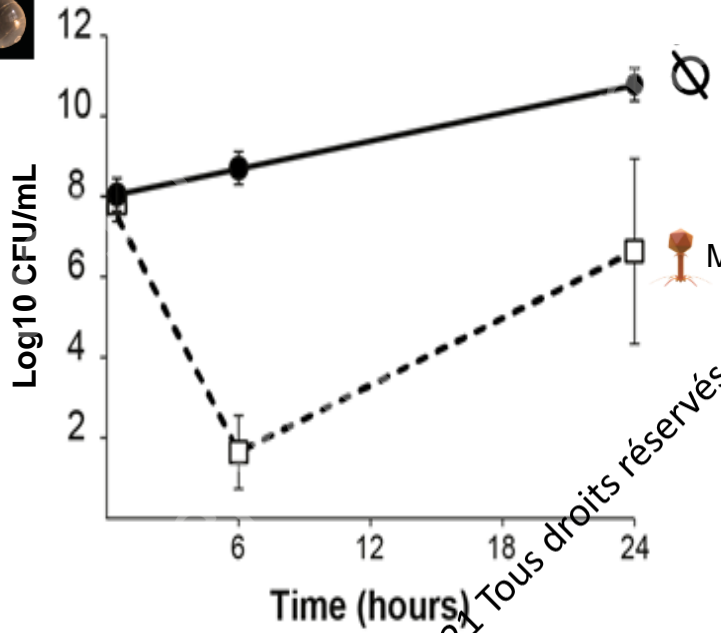
IN VITRO



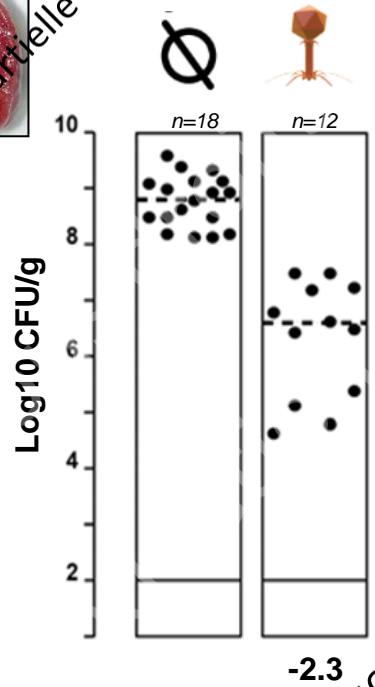
FIBRIN CLOT

INFECTED VEGETATION

PHAGE THERAPY AND *P. AERUGINOSA* IE IN VITRO/IN VIVO COMPARISON



Fibrin clot (*in vitro*)

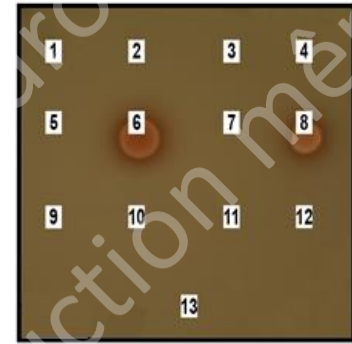
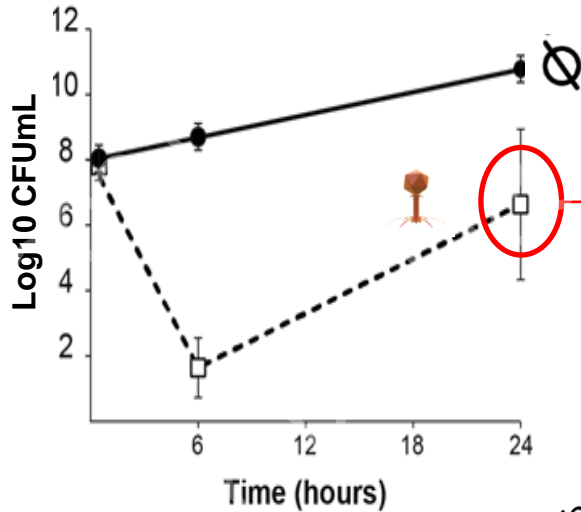


IE (*in vivo*), 6h post-treatment

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INVESTIGATING RESISTANCE – *IN VITRO*

IE – FIBRIN CLOT (*P. aeruginosa*)



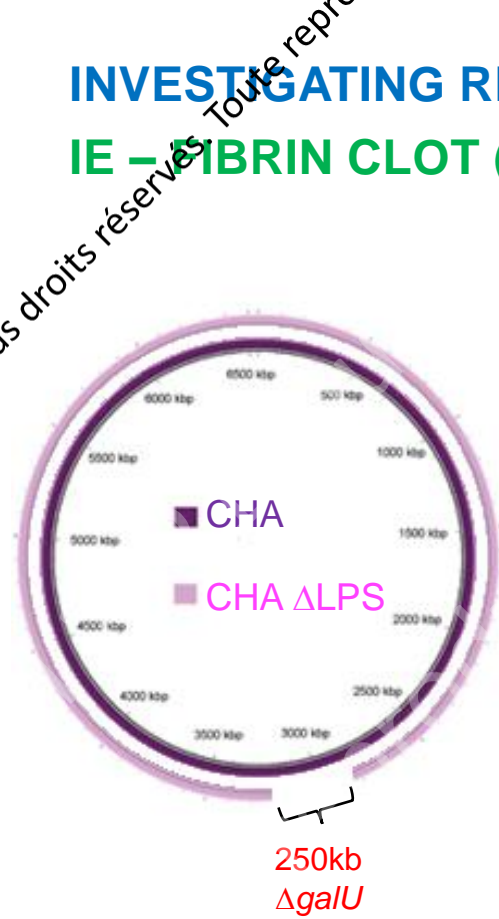
NEVER OBSERVED *IN VIVO!*

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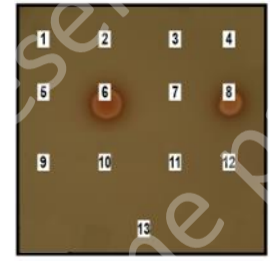
INVESTIGATING RESISTANCE - *IN VITRO*

IE – FIBRIN CLOT (*P. aeruginosa*)



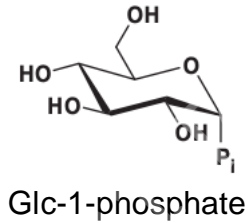
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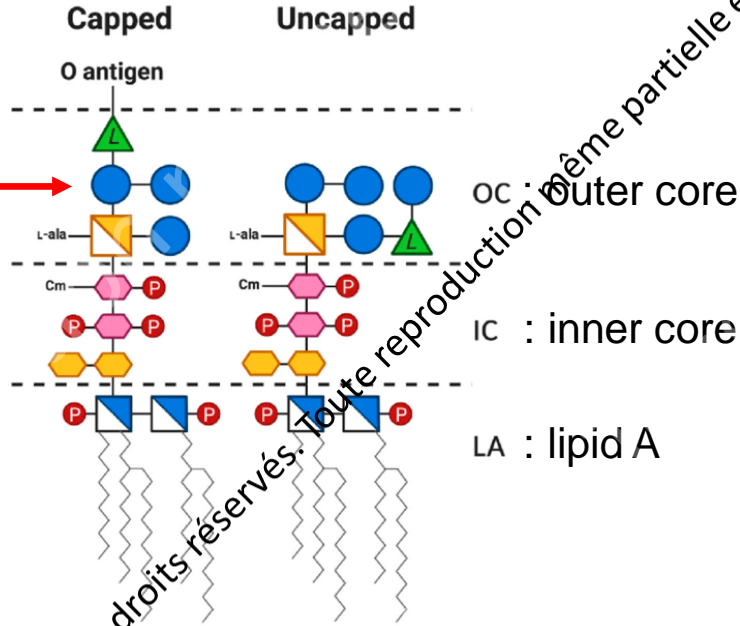


LPS STRUCTURE

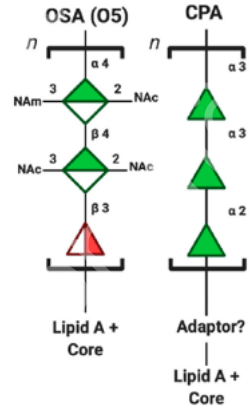
P. aeruginosa



GalU
+ UTP



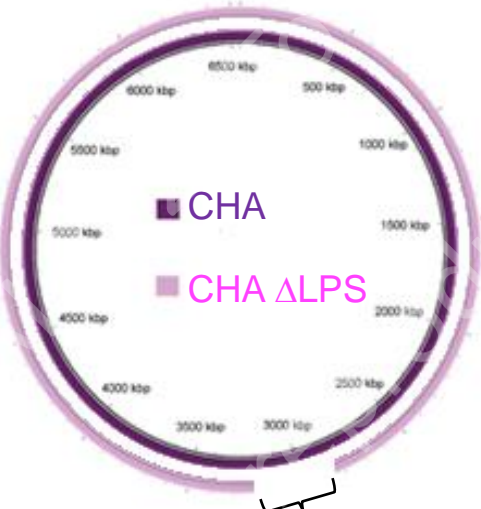
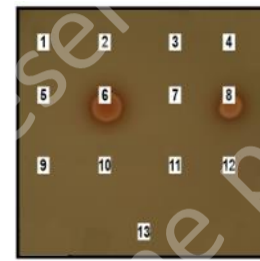
O antigen



INVESTIGATING RESISTANCE - *IN VITRO*

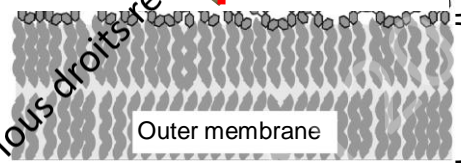
IE – FIBRIN CLOT (*P. aeruginosa*)

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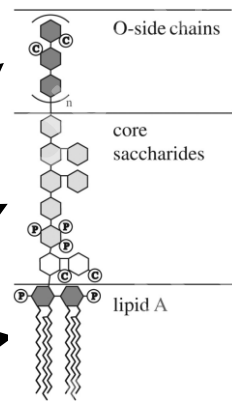


250kb
ΔgalU

CHA Δ LPS



Outer membrane

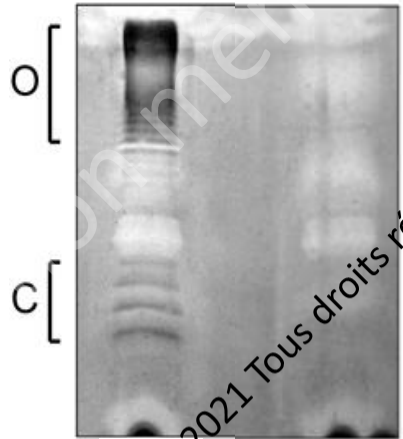


O-side chains

core saccharides

lipid A

adapted from Schneck et al. 2009. J. R. Soc. Interface. Oct. 6;6: Suppl. 5:S671-8.



CHA

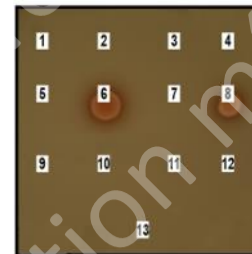
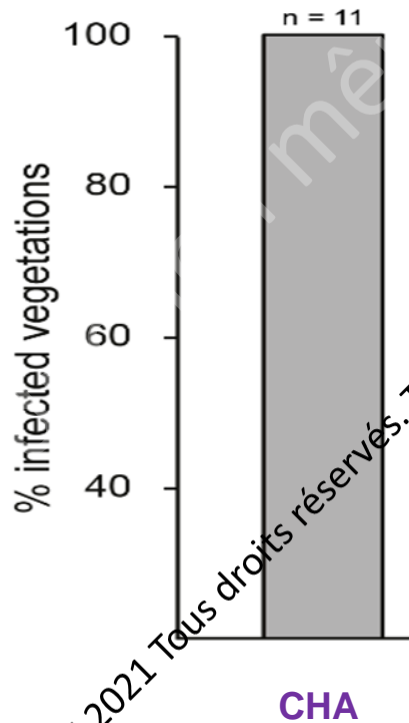
CHA Δ LPS

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INVESTIGATING RESISTANCE - *IN VIVO*

IE (*P. aeruginosa*)



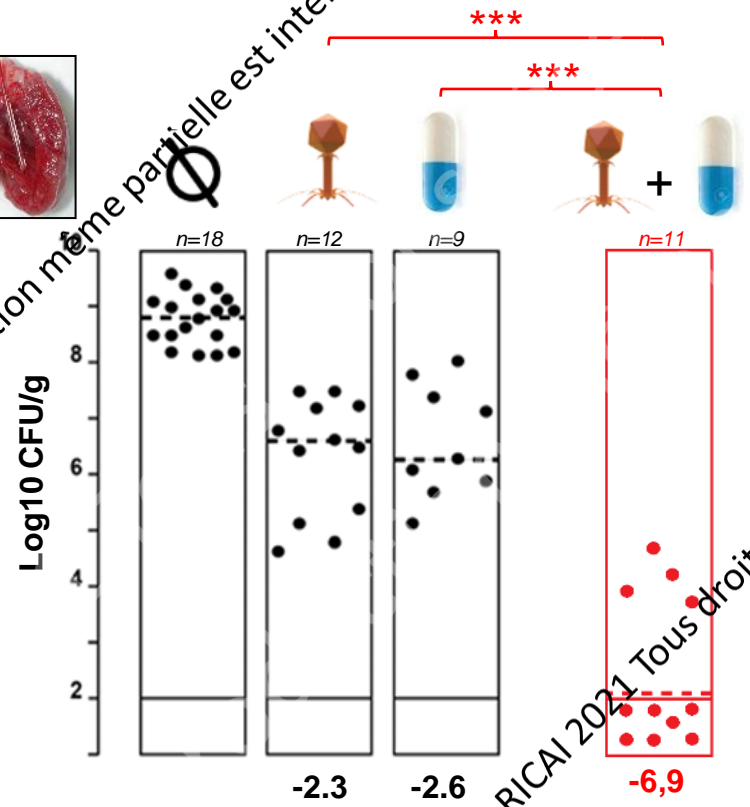
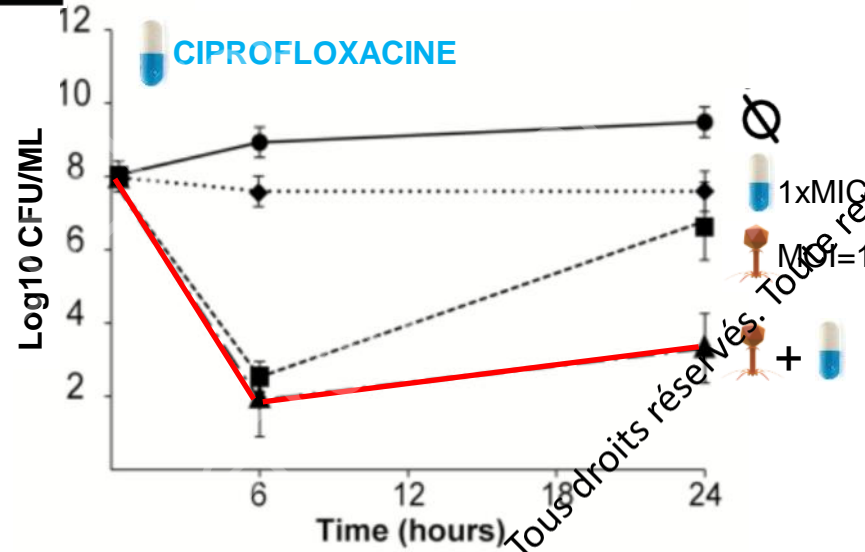
NEVER OBSERVED *IN VIVO*!

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PHAGE THERAPY AND *P. AERUGINOSA* IE IN VITRO/IN VIVO COMPARISON



Fibrin clot (*in vitro*)

IE (*in vivo*), 6h post-treatment

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ACQUIRED PHAGE RESISTANCE

IMPORTANT CONCLUSIONS FOR DESIGNING RCT

- **NEED TO BE SYSTEMATICALLY STUDIED *IN VIVO***
 - *IN VITRO* ≠ *IN VIVO*
- **CAN LEAD TO LOSS OF VIRULENCE**
 - *NOT UNIVERSAL*
- **CAN INCREASE SUSCEPTIBILITY TO SoC ANTIBIOTIC**
 - *NOT UNIVERSAL*

PHAGE COCKTAILS NEED TO BE ASSEMBLED ACCORDINGLY

SoC; STANDARD OF CARE

PART II

TRANSLATIONAL RESEARCH ALLOWS STUDYING PHAGE PK/PD

PK, PHARMACOKINETICS; PD, PHARMACODYNAMICS

PK/PD IN PHAGE THERAPY

DEFINITIONS

- PRIMARY PD = PHAGE EFFICACY
- SECONDARY PD = NEGATIVE EFFECTS OF PHAGES (TOXICITY)
- PK = DISTRIBUTION OF PHAGES IN THE BODY

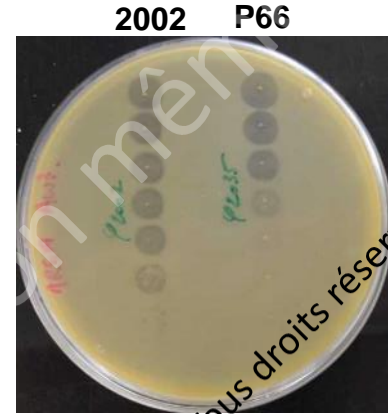
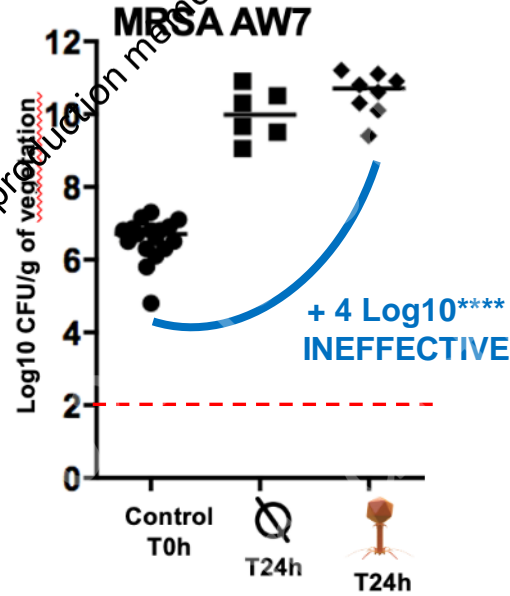
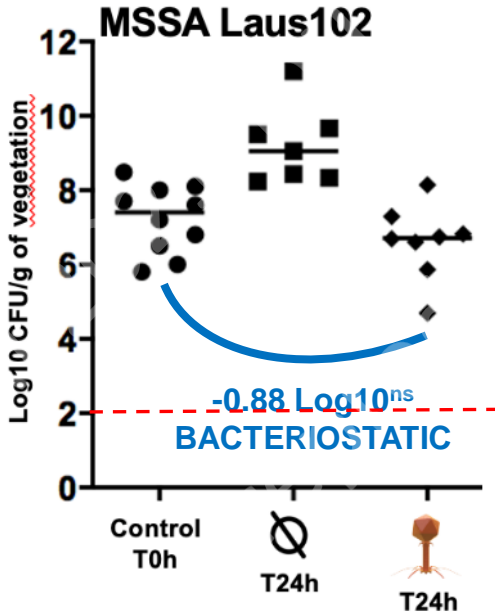
ALLOWS DEFINING

- ROUTE
- FREQUENCY
- DOSING
- INFLUENCE OF ASSOCIATED DRUGS

PHAGE PRIMARY PD – *IN VIVO*

IE (*S. aureus*)

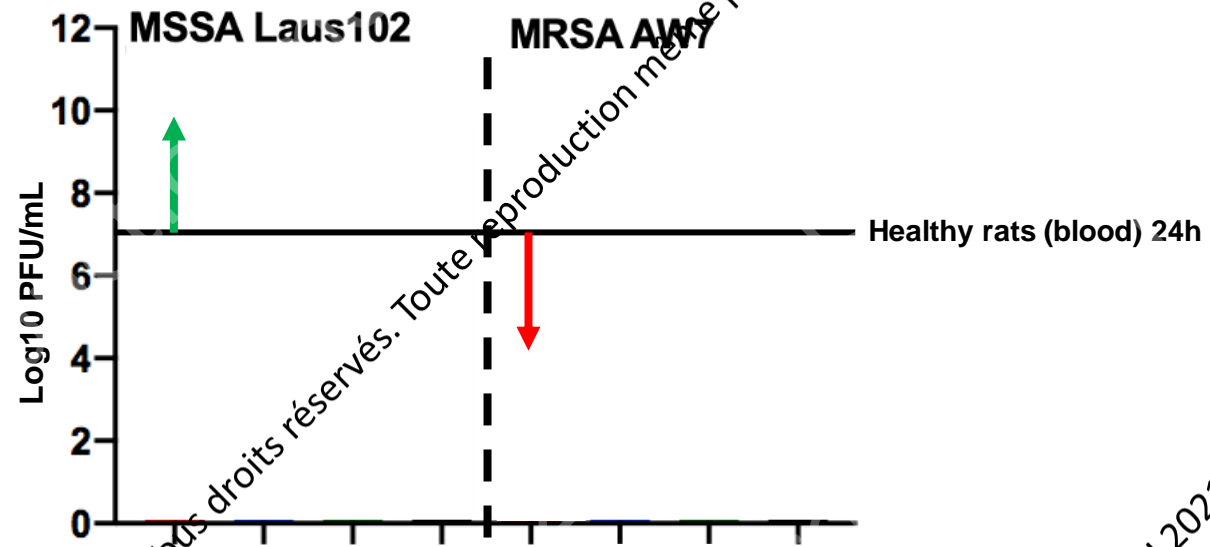
PHAGES ALONE 24h



PRIMARY PD DEPENDS ON THE INFECTING STRAIN (# SUSCEPTIBILITY)

PHAGE PK IE (*S. aureus*)

PHAGES ALONE 24h

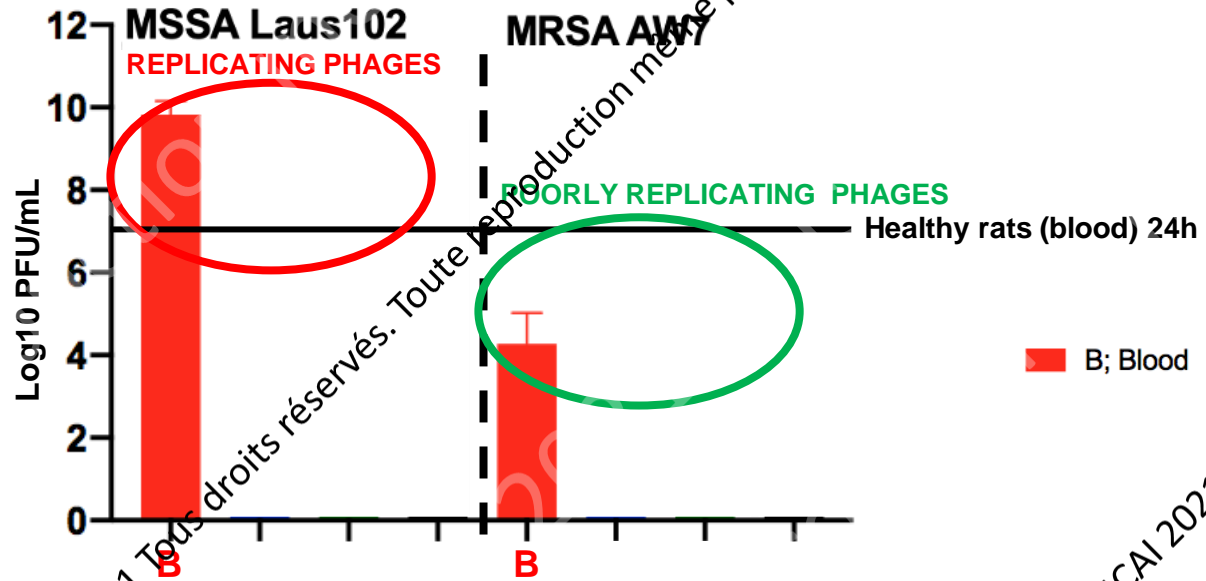


PK DEPENDS ON THE INFECTING STRAIN (AUTO-DOSING)



PHAGE PK IE (*S. aureus*)

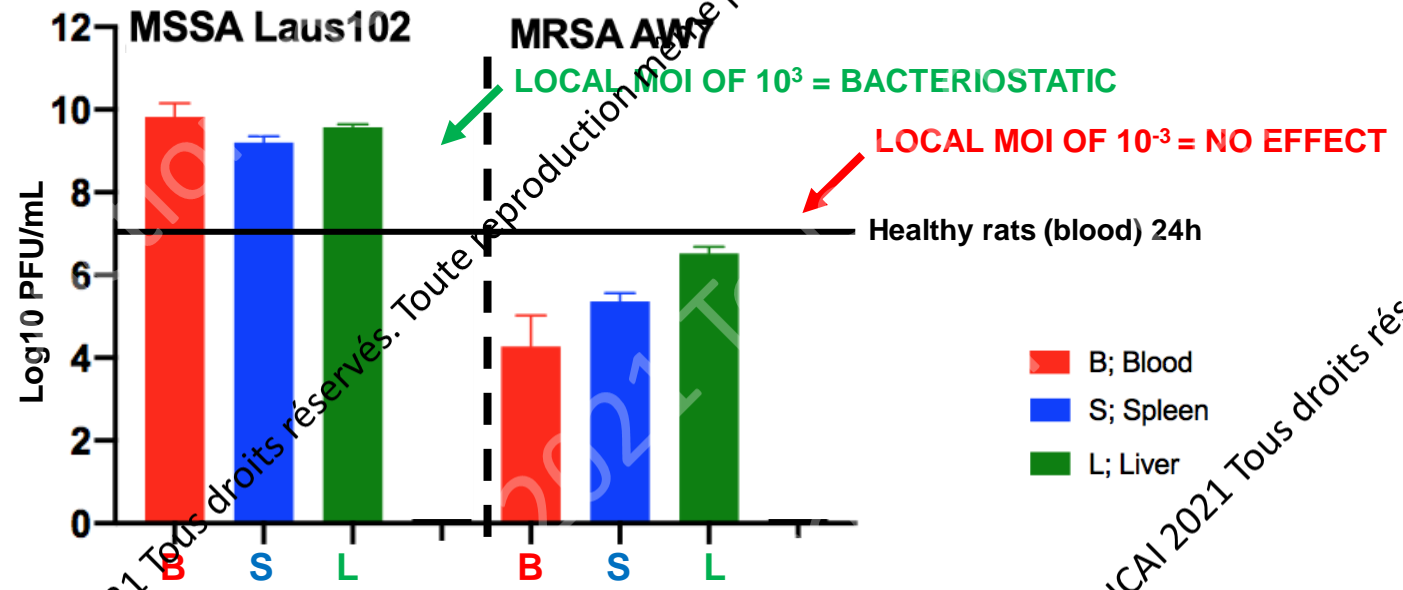
PHAGES ALONE 24h



PK IS A BALANCE BETWEEN REPLICATION AND ELIMINATION

PHAGE PK IE (*S. aureus*)

PHAGES ALONE 24h

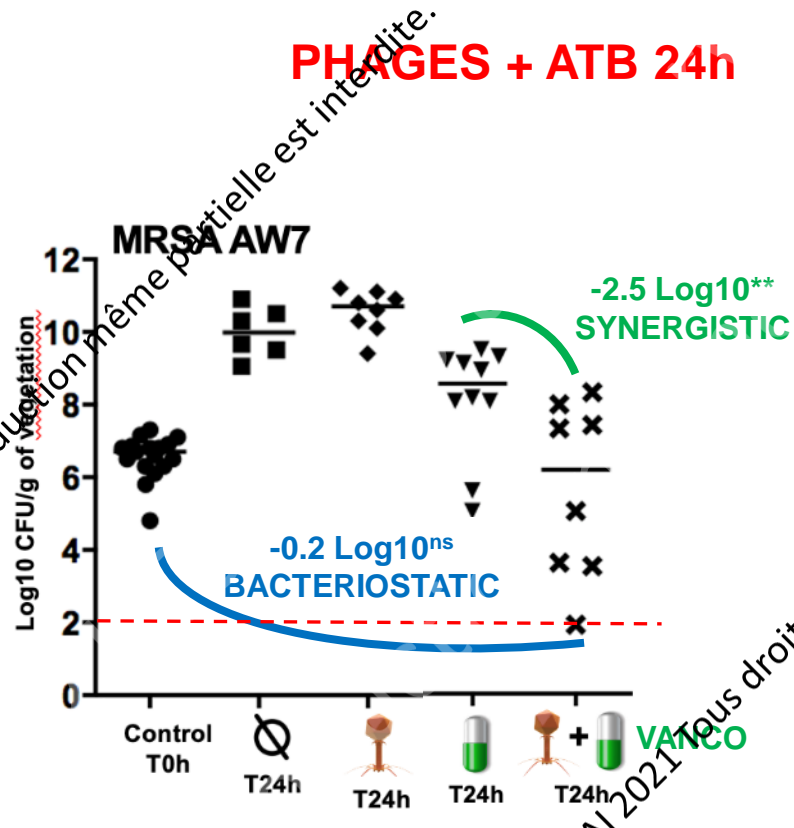
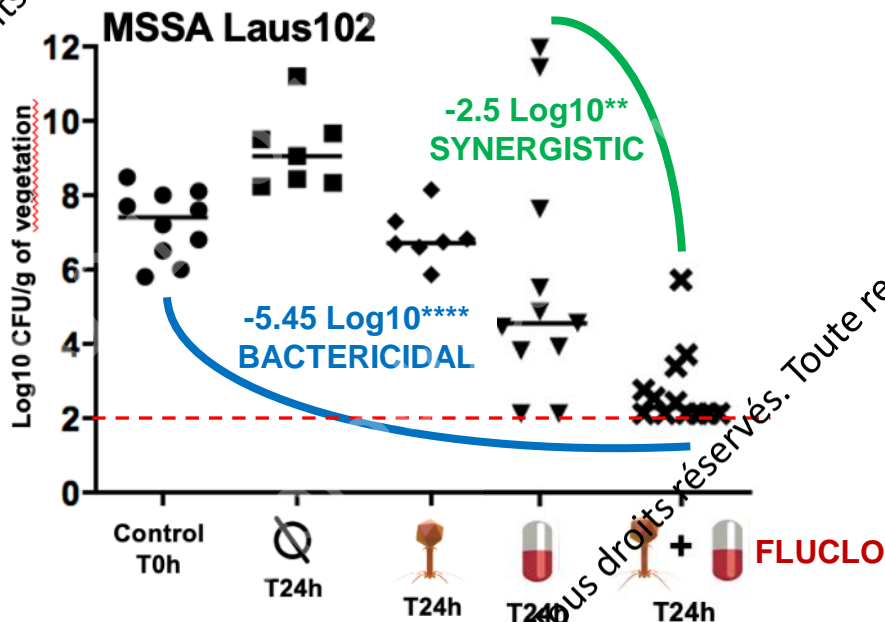


PHAGE AUTO-DOSING INFLUENCES LOCAL MOI

MOI; MULTIPLICITY OF INFECTION



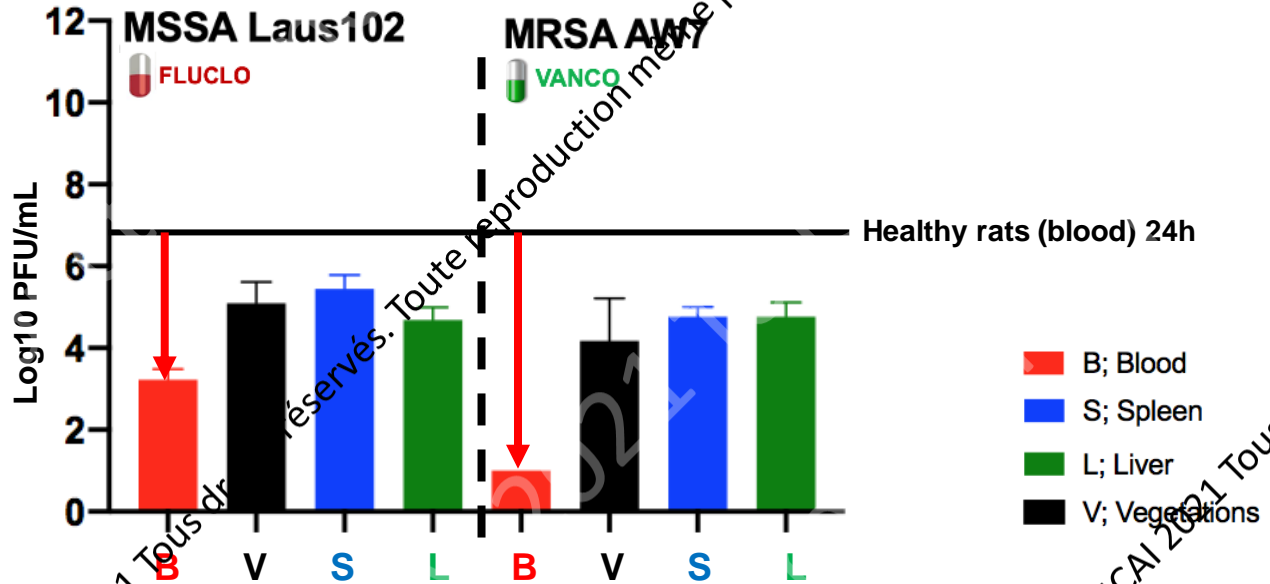
PHAGE PK IE (*S. aureus*)



PRIMARY PD DEPENDS ON THE PRESENCE OF ATB

PHAGE PK IE (*S. aureus*)

PHAGES + ATB 24h



PK DEPENDS ON THE PRESENCE OF ATB (DECREASE AUTO-DOSING)

PHAGE PK/PD

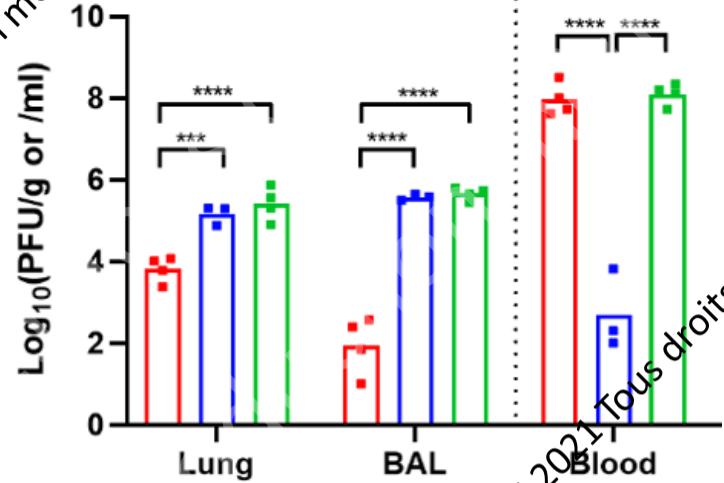
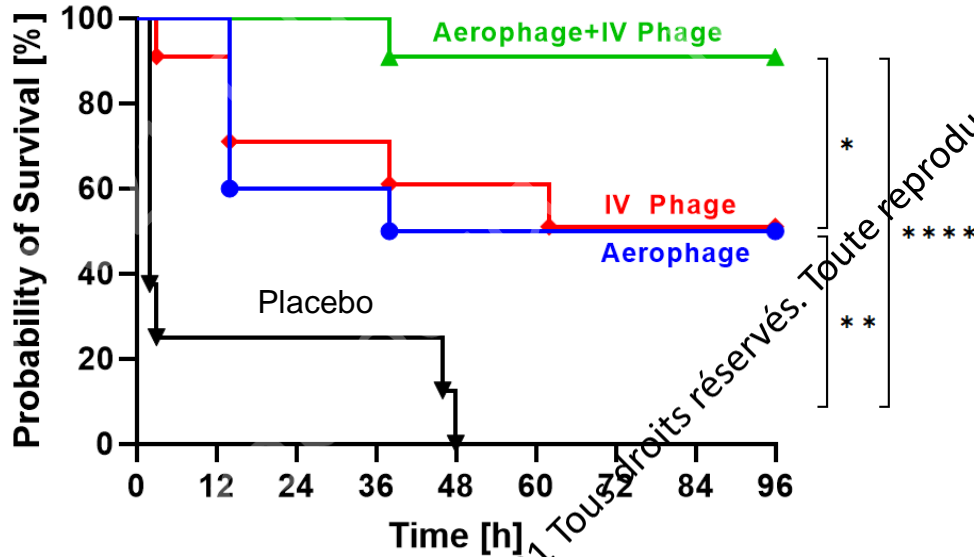
IMPORTANT CONCLUSIONS FOR DESIGNING S. AUREUS IE RCT

- **HIGHLY REPLICATING PHAGES LIKELY BETTER**
- **PHAGES ALONE NOT A GOOD STRATEGY**
- **PHAGE/ATB COMBINATION APPLYING**
 - REDUCE TREATMENT DURATION?
 - REDUCE UNDESIRE SIDE-EFFECTS?
- **QUID OF TREATMENT SEQUENCE**
 - PHAGES FIRST?

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PHAGE PK/PD PNEUMONIA (*S. aureus*)

PHAGES ALONE



THERAPEUTIC SUCCESS = LOCAL AND SYSTEMIC PHAGES

PHAGE PK/PD

IMPORTANT CONCLUSIONS FOR DESIGNING S. AUREUS PNEUMONIAE RCT

- **PRESENCE OF THE ALVEOLAR-CAPILLARY BARRIER**
 - BIODISPONIBILITY OF PHAGES IS POOR AFTER INHALATION
 - VERY LOW PASSAGE OF PHAGES FROM BLOOD TO LUNG

- **STILL PHAGES ALONE COULD BE A GOOD STRATEGY**
 - **NEBULIZATION (LUNG INFECTION)**

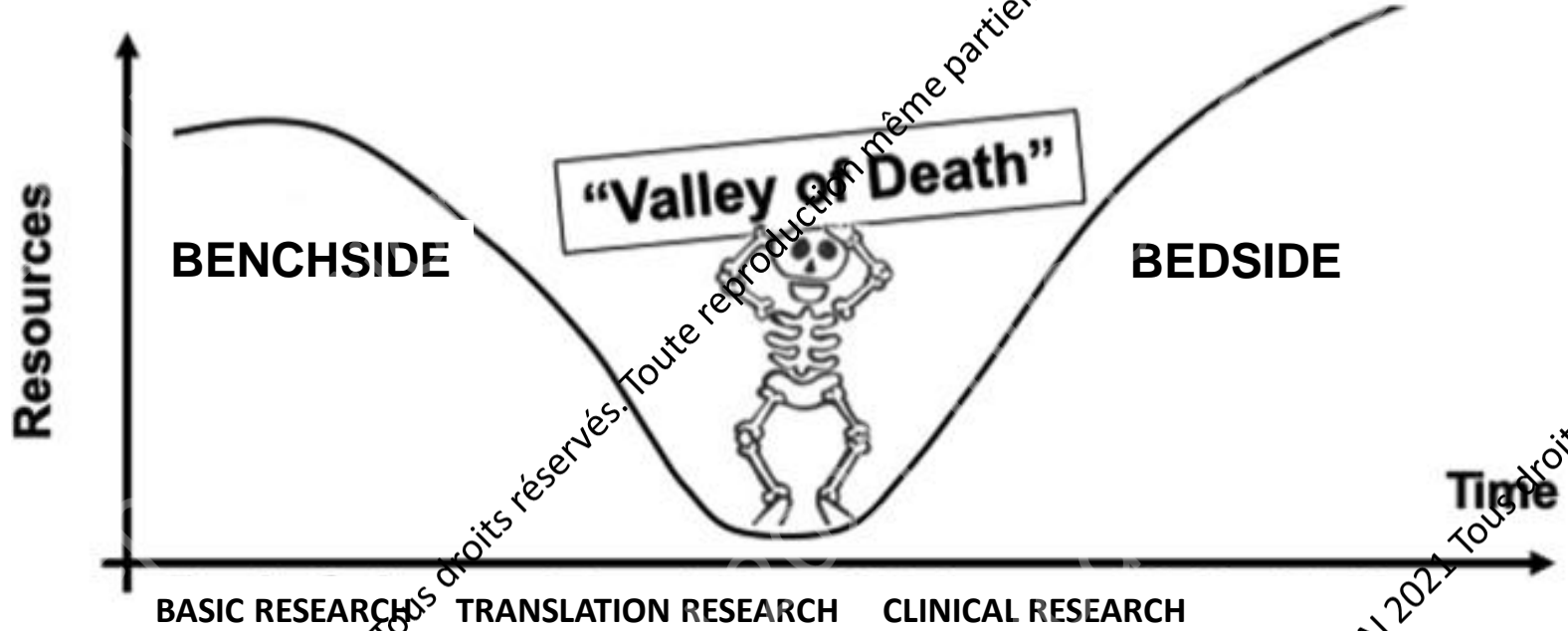
AND

 - **IV (ASSOCIATED BACTEREMIA)**

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THE FACT

TRANSLATIONAL RESEARCH

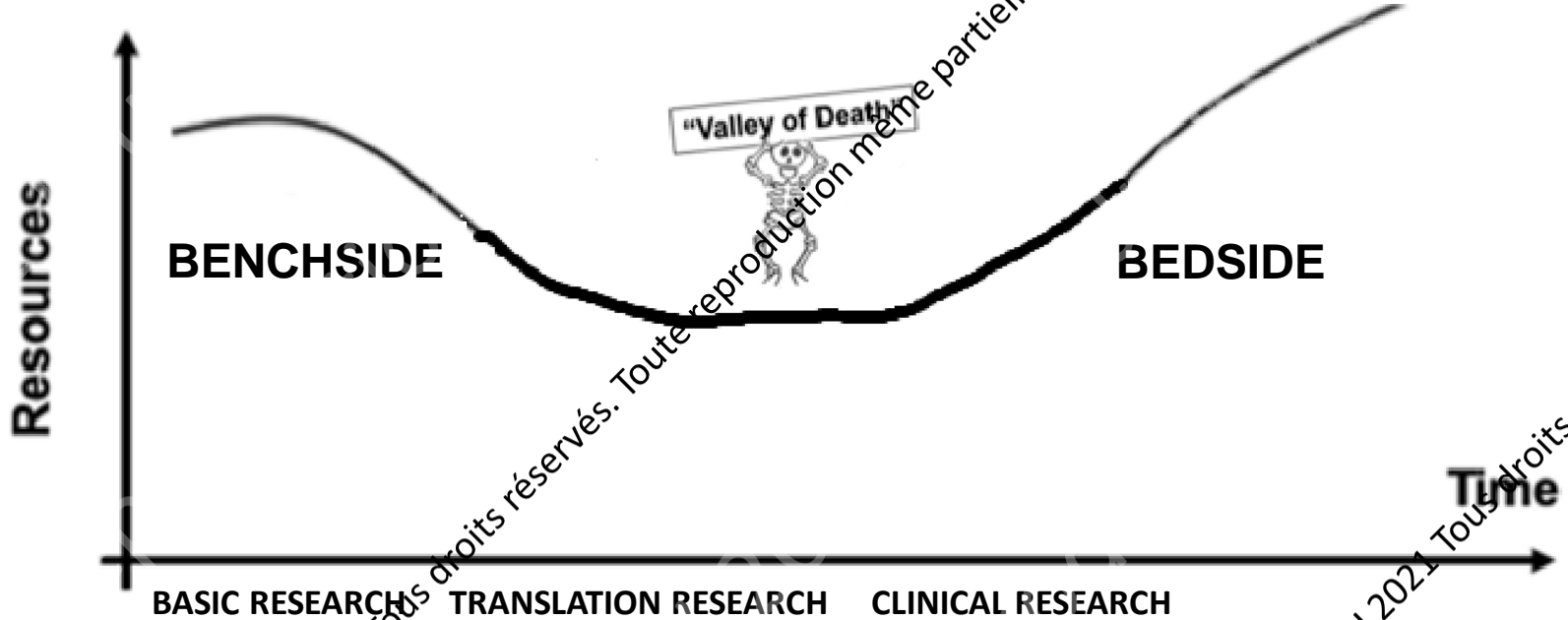


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THE HOPE

TRANSLATIONAL RESEARCH IN PHAGE THERAPY



THANKS!



Aurélie Marchet



Jonathan Saveb



José Entenza



Frank Oechslin



Yok-Ai Que



Josef Prazak

FUNDING

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PALAIS DES CONGRÈS • PARIS



THANK YOU
FOR YOUR ATTENTION!



STANDARD OF CARE

MSSA IE ON NATIVE VALVES

CHUV

| 1er choix |
|---|
| A. Endocardite sur valve native |
| amoxicilline/ac. clavulanique iv 2.2 g 6x/j + gentamicine iv 3 mg/kg 1x/j |

European Society of Cardiology

Flucloxacillin

12g/day i.v. in 4-6 doses