RACI 2023

R&D of new molecules in diverse therapeutic areas

TECHNOPHAGE SA

Colégio de Especialidade Indústria Farmacêutica

RACI PENICHE 2023

Multiplatform biopharmaceutical company

Bacteriophages as Innovative Biopharmaceutics Medicines: Shaping the Future of Healthcare?

From science to innovative biopharmaceuticals

Helena Dordio

October 2023

TECHNOPHAGE SA

FROM SCIENCE TO INNOVATIVE BIOPHARMACEUTICALS

OVERVIEW

1. TechnoPhage
2. Bacteriophages
3. Phage Therapy
4. Phage's History
5. Manufacturing & Formulation
6. Future & Market

2005

Start-up invested in the discovery of phage-products

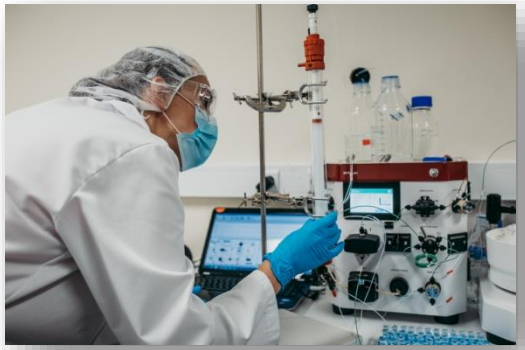
Clinical-stage biopharma with in house capacity for GMP manufacturing of biologics

2023

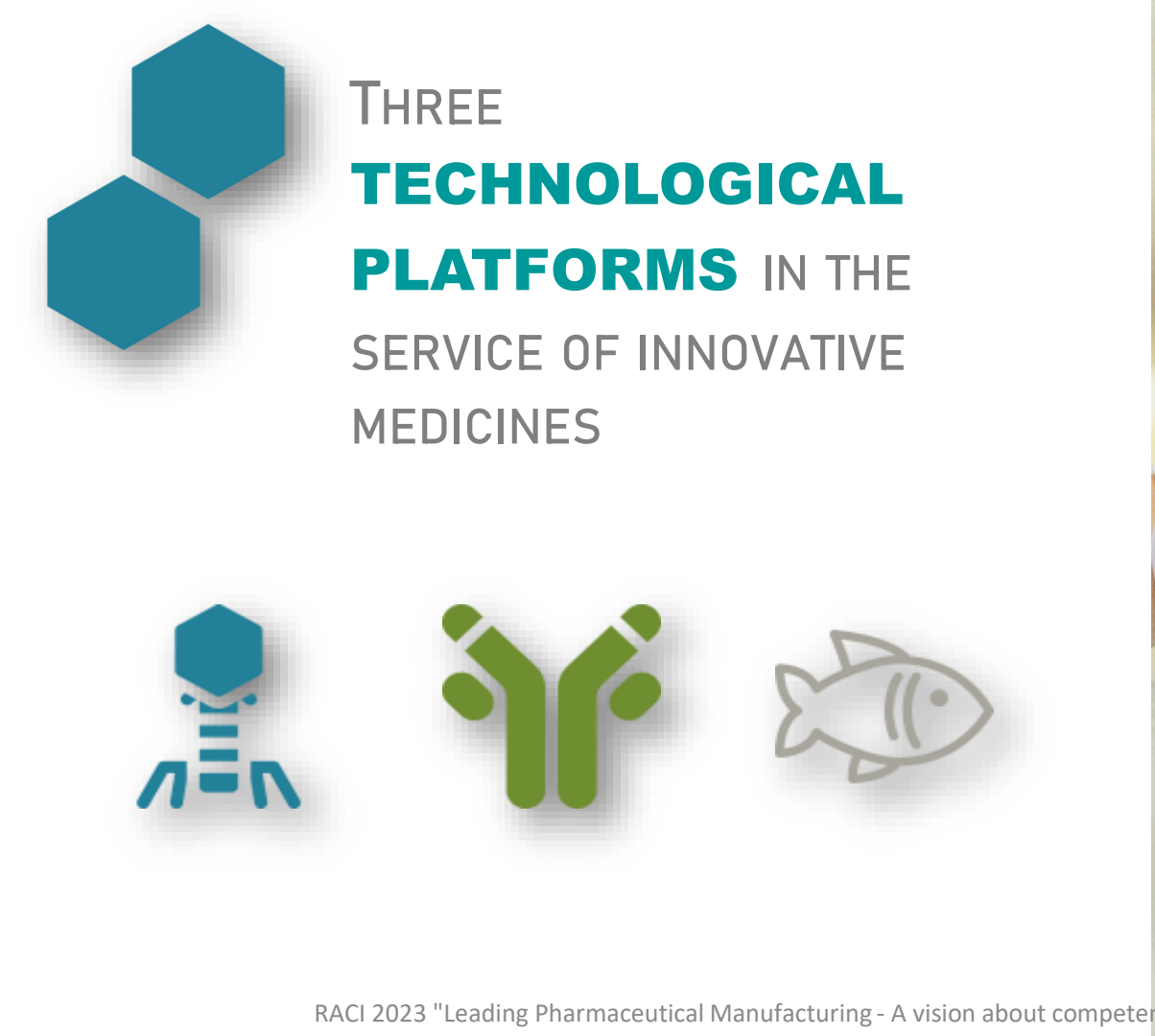
TECHNOPHAGE

18 YEARS OF EXCELLENCE IN BIOPHARMACEUTICALS

Development of biologics from early discovery into clinical trials, for unmet medical needs.




THREE **TECHNOLOGICAL PLATFORMS** IN THE SERVICE OF INNOVATIVE MEDICINES



>technology

OUR CORE THERAPEUTIC
PIPELINE

INFECTION

TP-102
TP-122
TP-164

NEUROSCIENCES

TA-111
TA-191
TZ-161
TZ-113

OPHTHALMOLOGY

TA-182
Eysulin

>pipeline

NEW LINE OF

NON-THERAPEUTIC

PRODUCTS

BIOMARKERS

TA-111C
TA-211

OTHER PRODUCTS

C1

PROBLEM

Unmet medical need

Condition for which there exists no satisfactory method of diagnosis, prevention or treatment.

Serious conditions

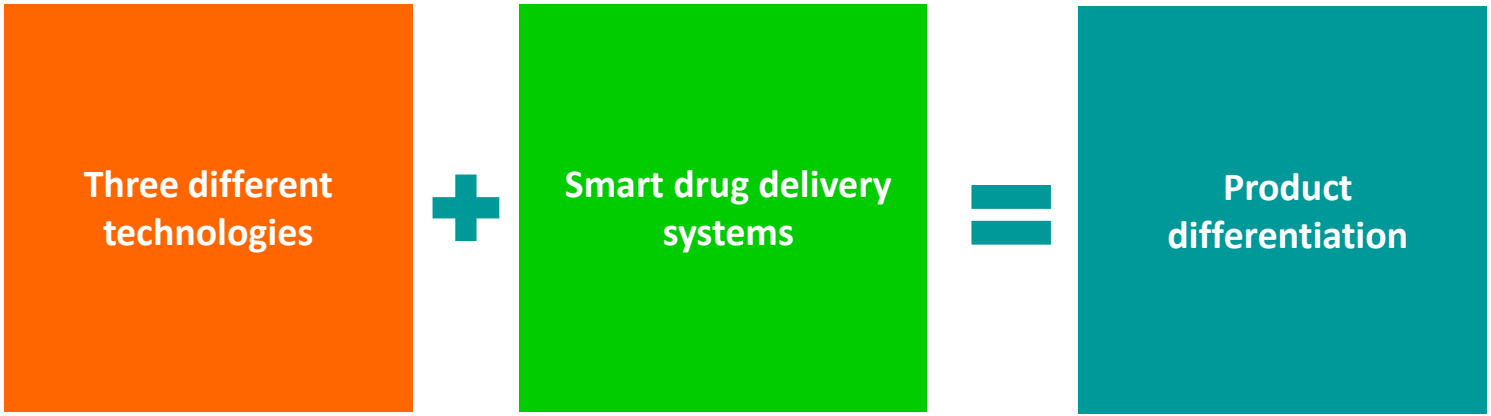
Disease or condition associated with morbidity that has substantial impact on day-to-day functioning.

Drug delivery

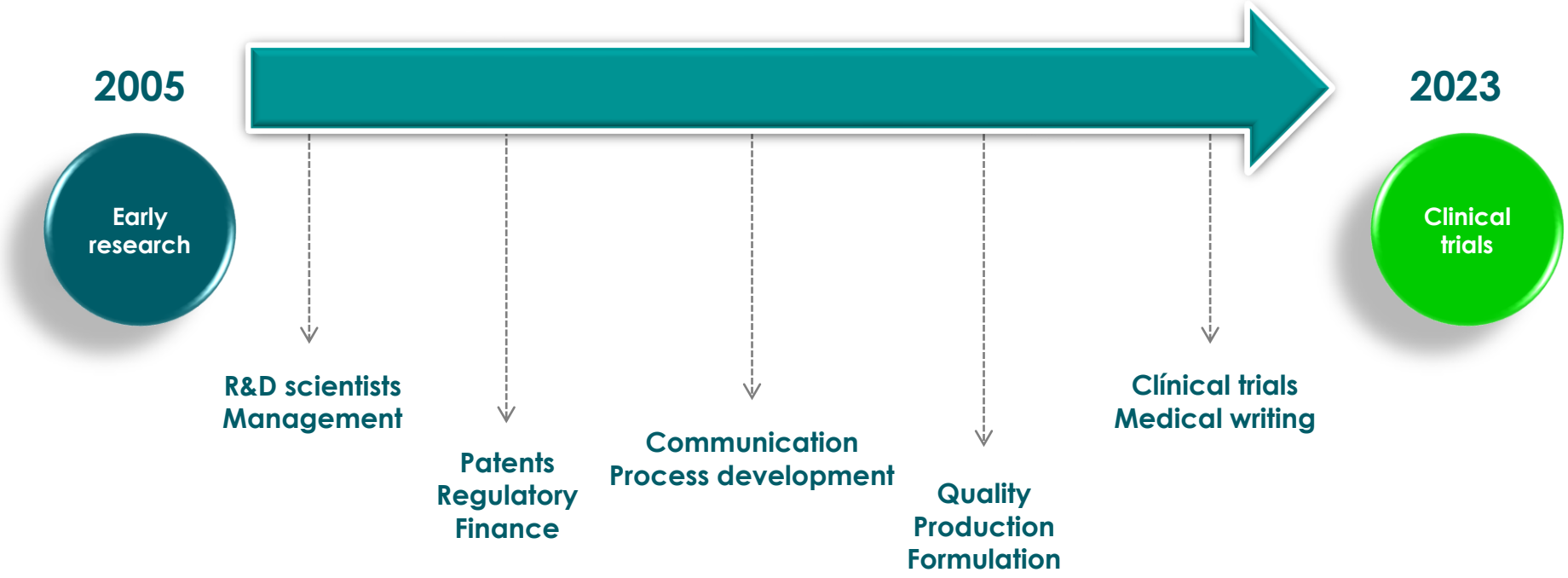
Technology to carry a drug inside the human body until it reaches its target.

SOLUTION

Creation of a pipeline of differentiated products based on different technologies, for unmet needs and using smart deliveries.



INTERNAL CAPACITY



>internal capacity

RACI 2023 "Leading Pharmaceutical Manufacturing - A vision about competences, quality and competitiveness"

PATENT PORTFOLIO

patent families, corresponding to 9 proprietary projects, developed *in-house*

215 live patents

133 granted in more than **10** countries

Fast Track Designation

Granted by **FDA** to TP-102 for the treatment of diabetic foot ulcers infected by *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Staphylococcus aureus*

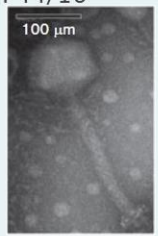
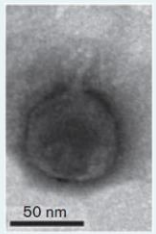
ROLLING REVIEW

EXPEDITE DEVELOPMENT

TP-102

Product features

Technophage has developed a bacteriophage cocktail, targeting three of the predominant bacteria in chronic wound infections, ***Staphylococcus aureus***, ***Pseudomonas aeruginosa*** and ***Acinetobacter baumannii***

	Staphylococcus aureus	*Pseudomonas aeruginosa*	*Acinetobacter baumannii*
TP-102 Bacteriophages:	F44/10  F125/10 	F770/05  F510/08 	F1245/05 

Source: *Mendes et al. J Med Microbiol, 2014*

TP-102

REVERSE study - outline

A Double-Blind and Randomized Study to Determine the Safety and Tolerability of Multiple Doses of TP-102 in Subjects with Non-Infected and Infected Diabetic Foot Ulcers

PRIMARY OBJECTIVE	The primary objective of this study is to evaluate the safety and tolerability following topical administration of multiple doses of TP-102 in diabetic subjects with non-infected diabetic foot ulcers (Part A, Cohort 1) and in diabetic subjects with DFU with infection grade 2 or 3 as per PEDIS classification (Part B, Cohort 2).
PRIMARY ENDPOINT	Emergent solicited and unsolicited local and systemic AEs and relationship to IP from first administration until 1 week after EOT

Non-INFECTED DFU

Cohort 1
(N = 8; TP-102: placebo 6:2 3x weekly up to 1 week IP q.d.

CEC*

INFECTED DFU

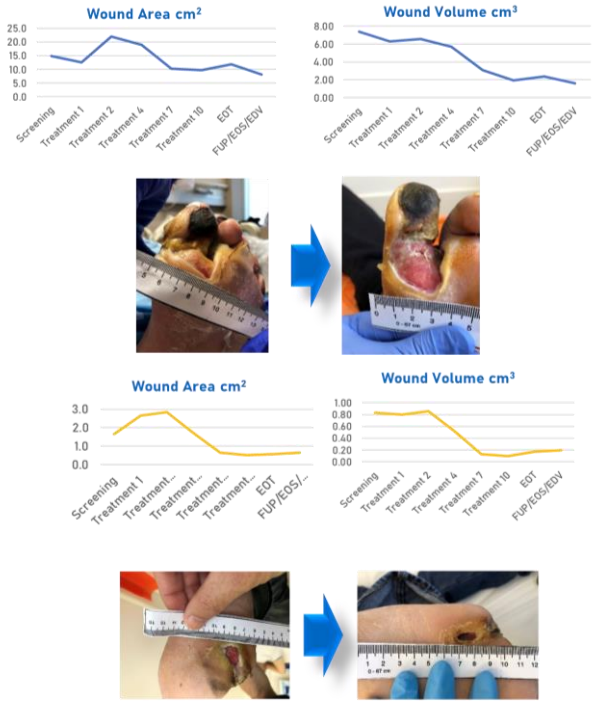
Cohort 2
(N = 18; TP-102: placebo 12:6) 3x weekly up to four weeks IP q.d.

*CEC (Cohort Escalation Committee) will make a recomendation to the sponsor to proceed or not to the next cohort based on data review

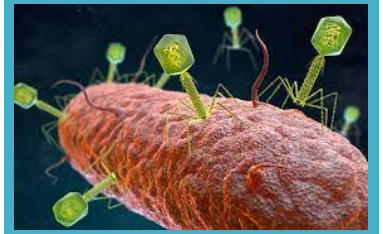
TP-102

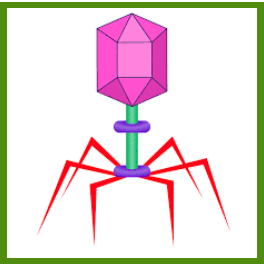
REVERSE study – conclusions

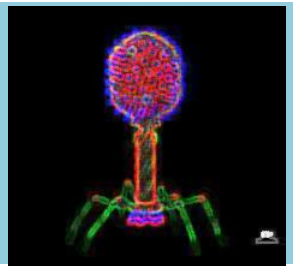
- NO TREATMENT RELATED ADVERSE EVENTS ASSOCIATED TO TP-102 OR PLACEBO REPORTED DURING THE TRIAL.
- PRELIMINARY DATA SUGGESTS THAT TP-102 MAY BE **EFFECTIVE IN REDUCTION OF DIABETIC FOOT ULCERS VOLUME.**
- *S. AUREUS* STRAINS ISOLATED FROM THE PATIENTS' WOUNDS WERE HIGHLY SUSCEPTIBLE TO THE INVESTIGATIONAL PRODUCT.
- THE **PHASE IIB STUDY** IS PLANNED TO START IN THE SECOND SEMESTER.



Bacteriophages





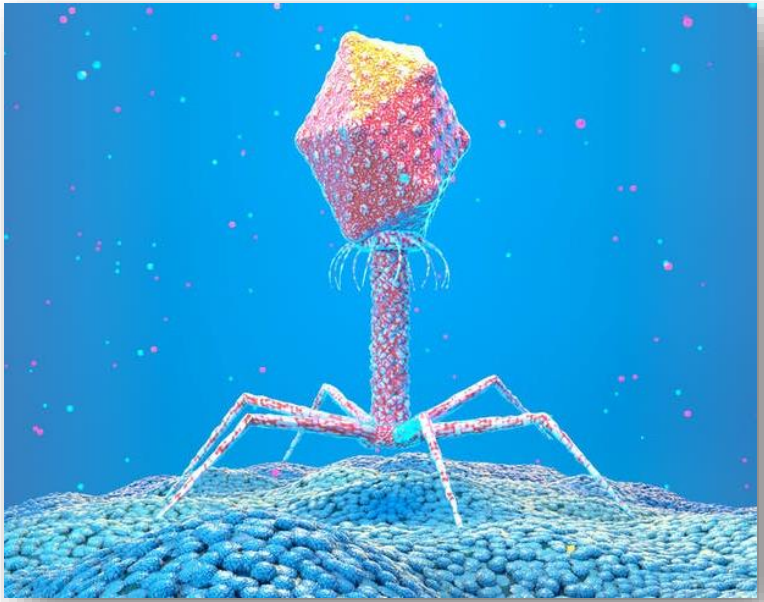


Bacteriophages

What is a Bacteriophage?

Confidential

- **Viruses that infect exclusively bacteria and use them as hosts**
- High level of specificity – target a particular bacteria species or subgroup
- Harmless to other organisms, including humans



Source: https://theconversation.com/viruses-are-both-the-villains-and-heroes-of-life-as-we-know-it-169131

Bacteriophages

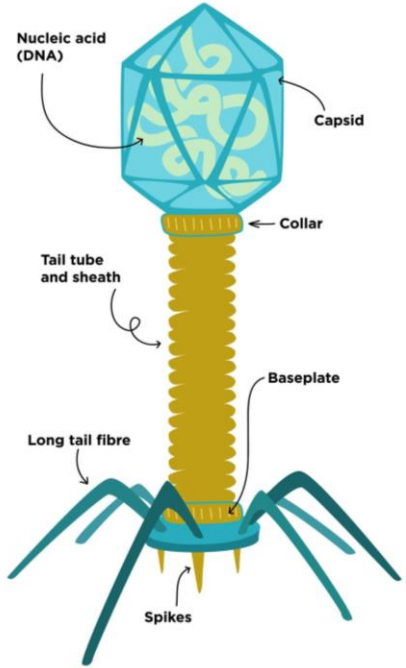
What is a Bacteriophage?

- Concerning genetic material:

  - ssDNA phages
  - dsDNA phages
  - ssRNA phages
  - dsRNA phages

Concerning structure and morphology:

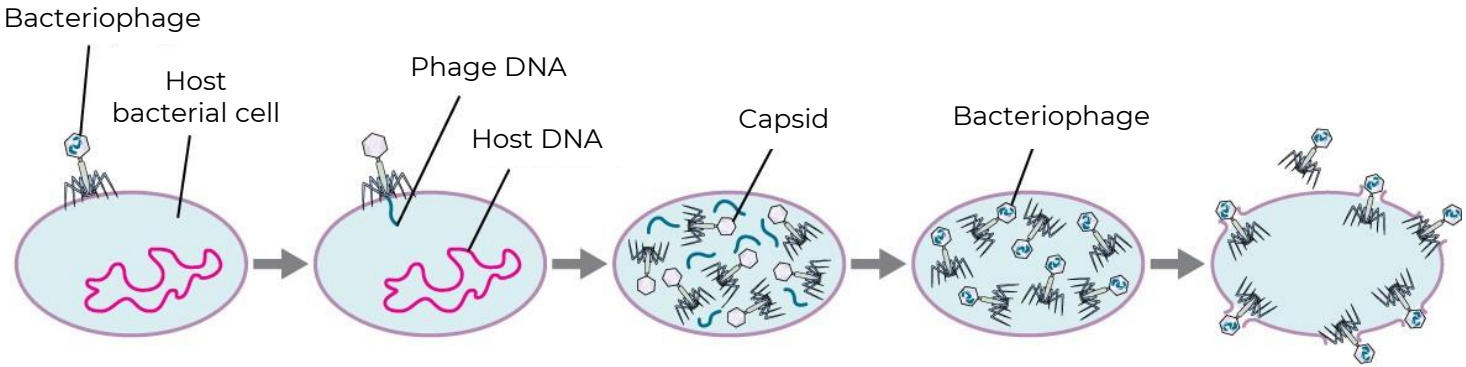
- Tailed phages → 96% *Caudovirales* order
- Filamentous phages
- Polyhedral phages
- Pleomorphic phages



Source: https://theconversation.com/viruses-are-both-the-villains-and-heroes-of-life-as-we-know-it-169131

Bacteriophages

Infection Mechanism



1 Adsorption

- The phage attaches to the surface of the host

2 Penetration

The viral DNA enters the host cell

3 Biosynthesis

Phage DNA replicates and phage proteins are made

4 Maturation

New phage particles are assembled.

5 Lysis

The cell lyses, releasing the newly made phages.

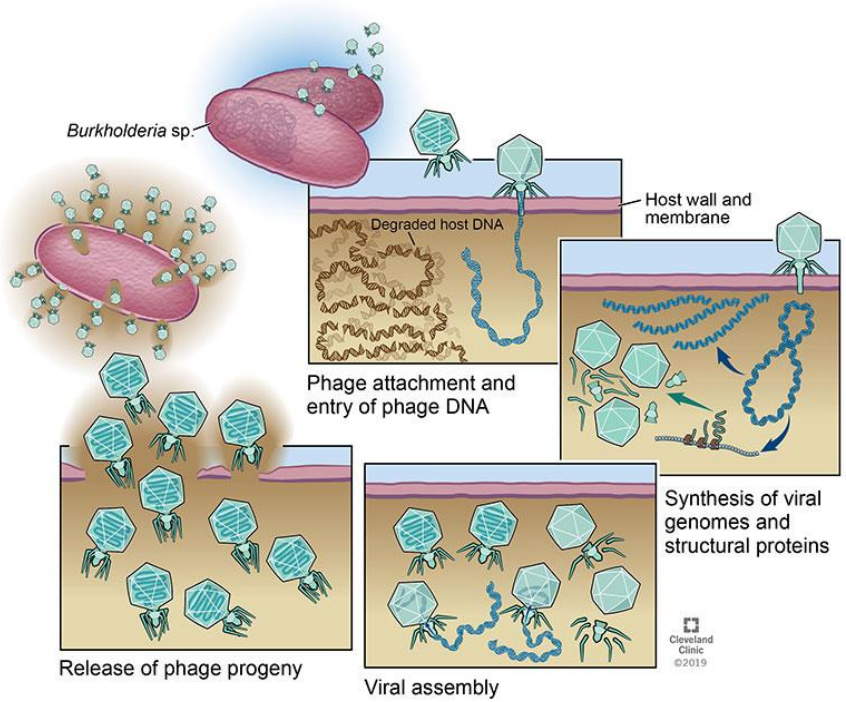
Adapted from https://courses.lumenlearning.com/microbiology/chapter/the-viral-life-cycle/

Bacteriophages

Phage Therapy

Confidential

- Clinical use of natural/modified phages as antimicrobials for the treatment of human infections.
- Administration of naturally isolated virulent phages directly to the patient with the purpose of lysing a bacterial pathogen that is responsible for a chronic or acute infection.
- **Expected to reach $3.6 billion by 2031.**



Source: https://consultqd.clevelandclinic.org/phage-therapy-for-multidrug-resistant-bacterial-infections/

Bacteriophages history

Discovery

1890 - First description of bacteriophages by **Hankin** noted something not filterable in the waters of Ganges and Jumna rivers in India with antibacterial activity

1915 - British bacteriologist **Frederick Twort** isolated filterable entities that destroy bacteria

1917 - Felix D' Herelle found parasitic viruses of bacteria. Called them bacteriophages "eaters of bacteria"

- **Giorgi Eliava** Georgian microbiologist observed the same phenomena

Bacteriophages history

Therapeutic use of specific bacteriophage formulations to treat bacterial infections

Félix d' Herelle

1st therapeutic application:

1919 Hôpital des Enfants-Malades, Paris

7 children with dysentery

Bacteriophages history

- Discovery of antibiotics (beginning of XX Century)
- Lack of knowledge of the bacteriophage's biology
- Lack of controls in the therapeutic formulations and treatments
- Changes in drug regulation in Europe and USA

Abandonment of phage therapy in the Western world, continuing in the eastern countries, where the application of bacteriophages remains to the present day

Bacteriophages history

Increasing incidence of antibiotic resistant bacteria

Deficit in the development of new classes of antibiotics

Renewed interest on phage therapy as alternative to halt the progression of the bacterial 'resistome'

The Food and Drug Administration (FDA) continues to look into ways to regulate it. The first clinical trial for intravenous (IV) phage therapy gained FDA approval in 2019.

Bacteriophages

Bacteriophages history

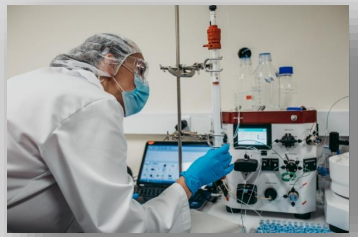
Confidential

2023



Bacteriophages Manufacturing & Formulation





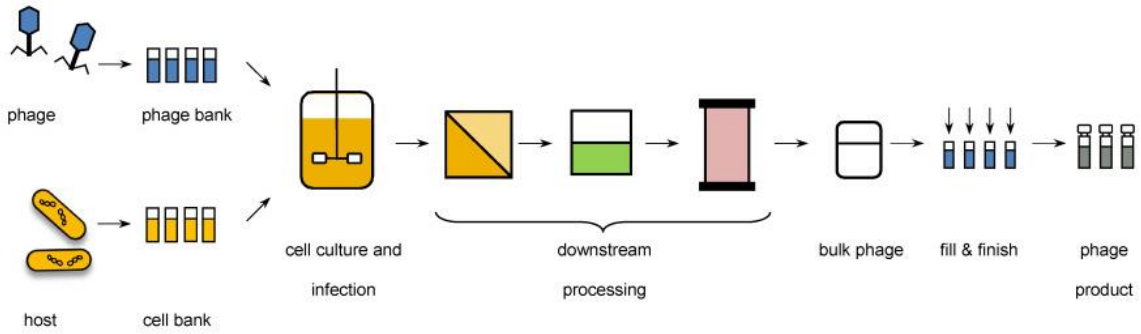

Bacteriophages

Manufacturing process

Phages are classified as medicinal products → Products must be manufactured in compliance with GMP and follow the evaluation through clinical trials

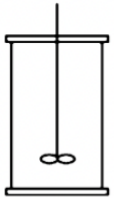
Good Manufacturing Practices:
"Minimum requirements for the methods, facilities and controls used in manufacturing, processing and packaging of a drug product. The regulations make sure that a product is safe for use, and that is has the ingredients and strengths it claims to have" – **FDA**

The manufacturing process of a given phage involves several activities that are designed with the objective of producing a certain number of biologically active particles with specific qualities.



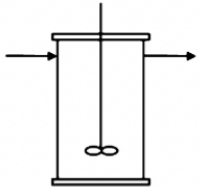
Manufacturing process

Upstream Processing



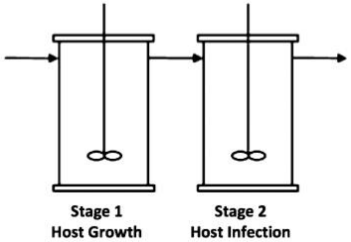
Batch operation

Most common



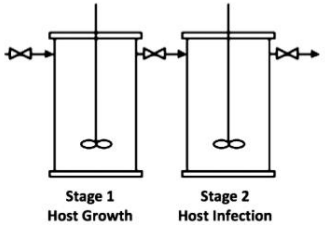
Continuous operation

Better quality and consistency of the product



Two-stage continuous operation

Control over the physiological state of the host



Semi-continuous operation (self-cycling process)

Combined advantages

Manufacturing process

Dowstream Processing

1 Clarification

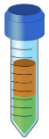
- Microfiltration

- Low speed centrifugation

2 Capture

- Tangential flow filtration (TFF)

- Precipitation



3 Polishing

Sources: https://www.lenntech.com/products/Pentair-X-Flow/2451RB452NG/2451RB452NG-S-14-Microfiltration-membrane-element/index.html ; https://www.indiamart.com/proddetail/lc-8-low-speed-centrifuge-22679598262.html;

Sources: https://www.meissner.com/products/tangential-flow-filters-seprapor/tangential-flow-cartridges; Mastiani, M. *et al.* (2019).

Manufacturing process

Dowstream Processing

1 Clarification

2 Capture

3 Polishing

Chromatography

Ion-Exchange (IEC)

Affinity

Monolithic

Multimodal

Size-exclusion (SEC)

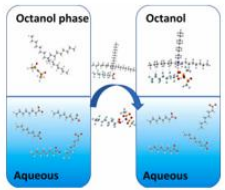
Sources: https://microbenotes.com/ion-exchange-chromatography/ ; http://technologyinscience.blogspot.com/2011/09/gel-filtration-chromatography-gf-size.html#.YeqF21jP2Lo ;

Manufacturing process

Dowstream Processing

1. Clarification
2. Capture
3. Polishing

- Affinity chromatography
- Octanol liquid-liquid extraction (LLE)
- TFF

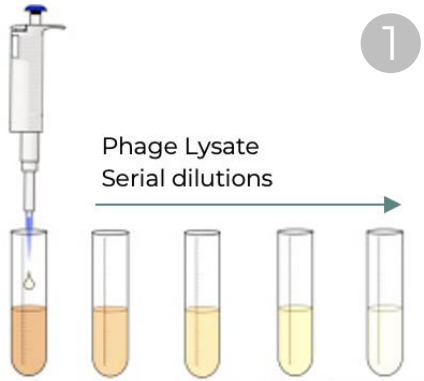


Source: Zhang, K., *et al.* (2020).

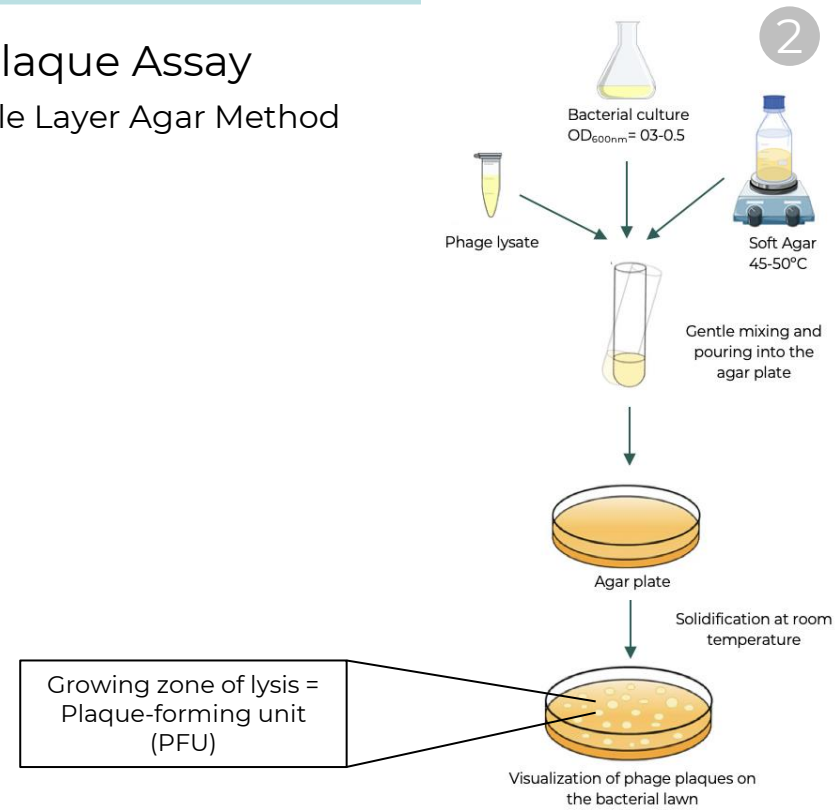
Quality Control – Phage titer

Plaque Assay

Double Layer Agar Method



Adapted from: Cotton, G. C. (2018)



Adapted from: Stachurska, X., *et al.* (2021).

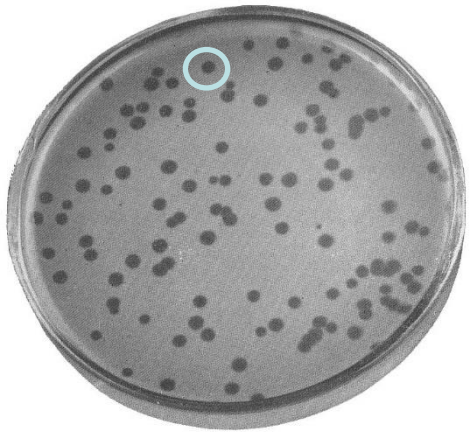
Quality Control – Phage titer

Plaque forming units (PFUs) can be described as both free phages and phage-infected bacteria.

- Serial dilutions necessary to enumerate a large number of phage particles.
- Assay should always be done in duplicates or triplicates.
- Plate needs to have sufficient plaque numbers for enumeration, but not so many that is not possible to distinguish one from another

↓

Issue of statistical importance referred to as Too Few to Count (TFTC) or Too Numerous to Count (TNTC)



Bacteriophages
Future & Market

Market forecast & Future

- Growth of biological medicines estimated at >10%/year (growth in dollars; data from ICI meeting 2015), with a global growth rate of **5.3% for phages** (2022-2032);
- Biological medicines market grew 70% (in USD) between 2011-2016;
- Big Pharma willing to invest in biological medicines;

- Market not ready (yet) to receive biological medicines;
- Medicines with phages not authorized by Health Authorities, yet;
- Regulatory path to be defined (ongoing);
- Complex manufacturing and analysis processes (some still in development, e.g., HCPs);

Success is no accident.
It is hard work, perseverance,
learning, studying, *sacrifice*,
and MOST of all,
love *of what you are doing.*
-Pele

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