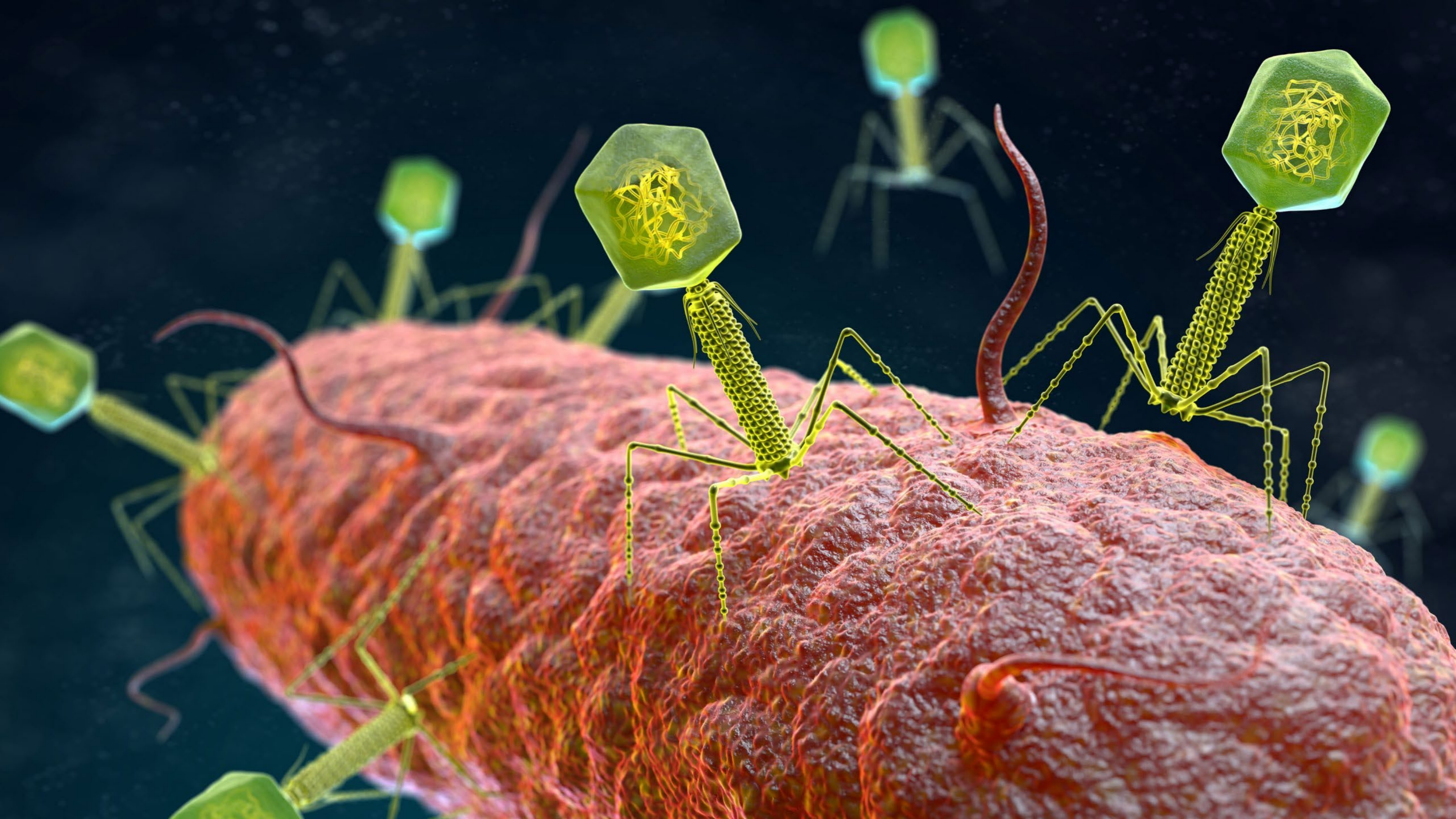


IABS WEBMEETING

PHAGES AND PHAGE PROTEINS IN BACTERIAL INFECTION TREATMENT

Prof. dr. ir. Yves Briers – November 19, 2024

*President and co-founder Belgian Society for Viruses of Microbes
CSO and co-founder Obulytix*



What is a (bacterio)phage?

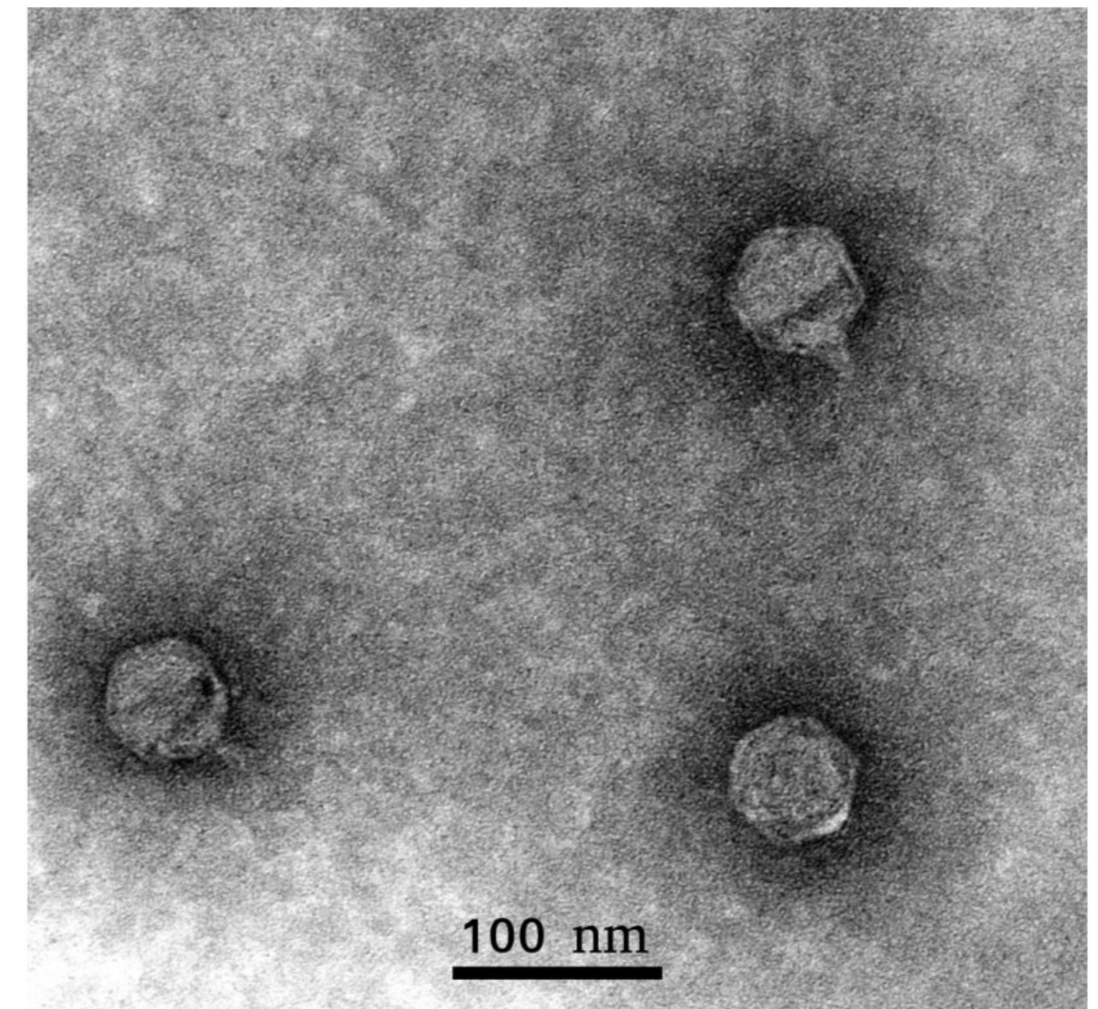
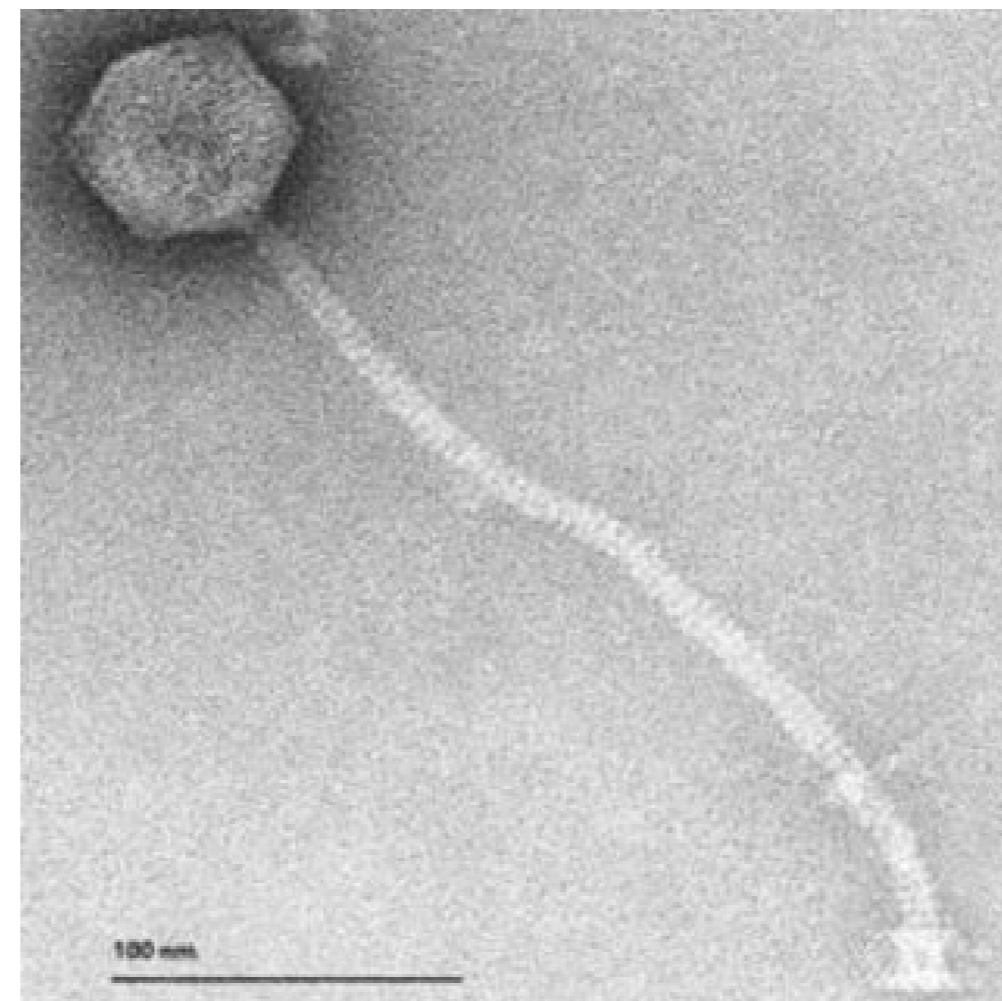
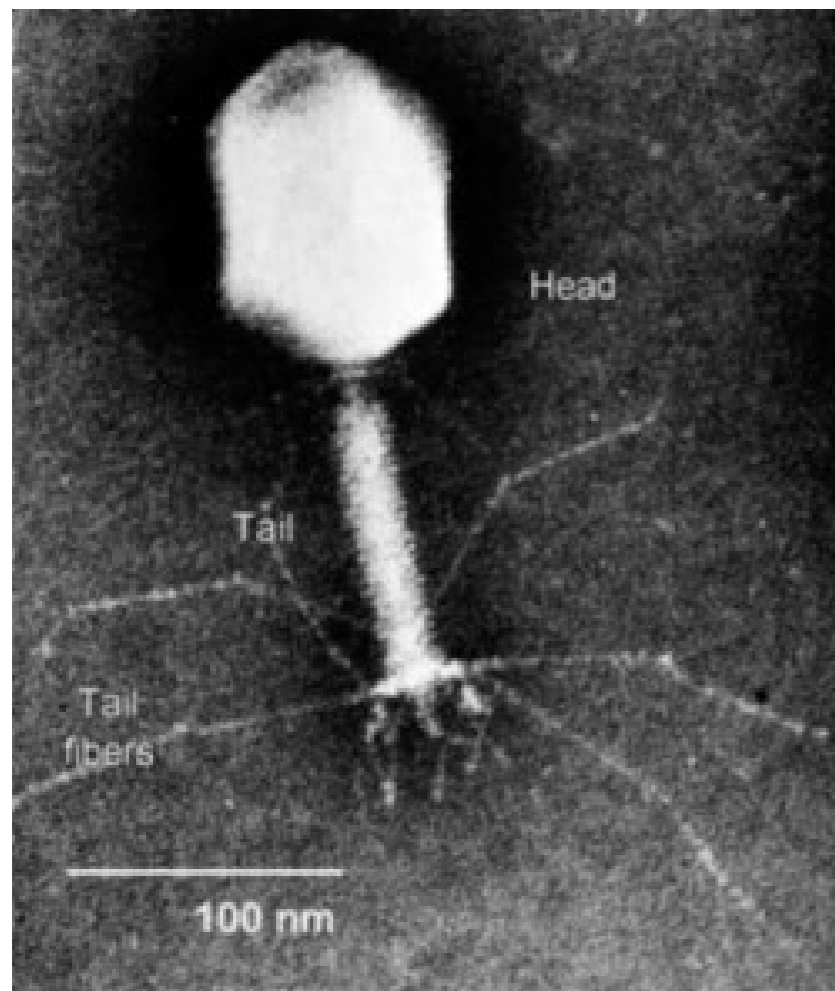
- A virus that infects a bacterium, followed by replication
- Essential in balanced ecosystems: phages keep the bacterial number under control and promote bacterial diversity
- A staggering number of $\sim 10^{31}$ bacteriophages, making them the most abundant biological entity on earth

Enormous diversity of phages

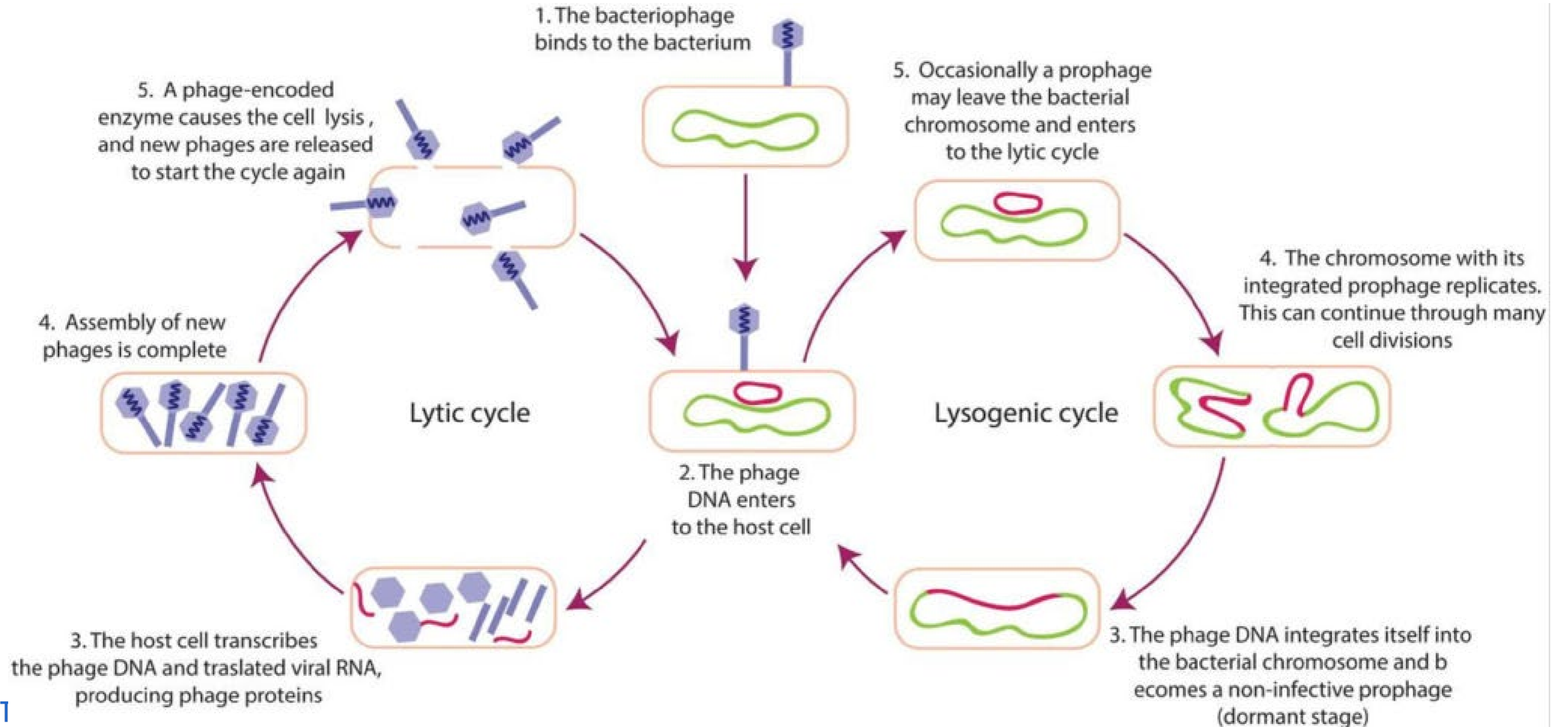
- Genetic code: DNA (abundant) versus RNA (rare), double-stranded (abundant) versus single-stranded (rare)
- Genome size: from a few thousand to >500 kbp
- Practically endless taxonomic diversity

Enormous diversity of phages

Different morphotypes: myovirus, siphovirus and podovirus



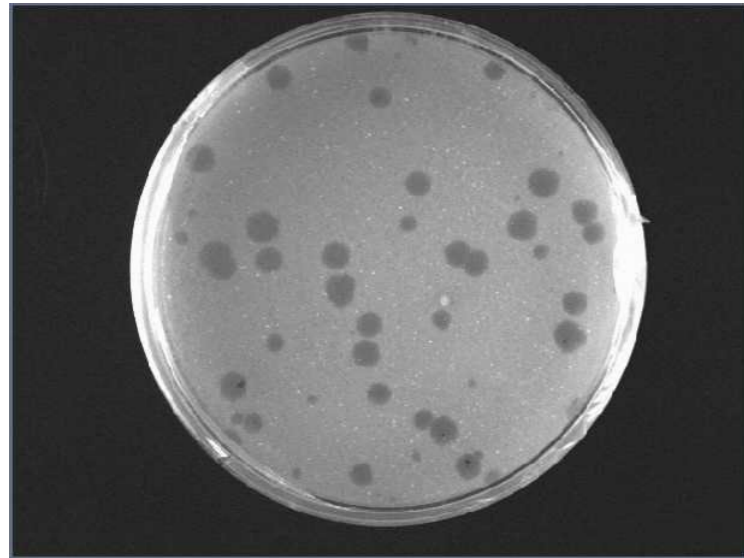
Different replication cycles



First observation of phages



First descriptions of bacteriophages



Plaques

Bacteria-eaters

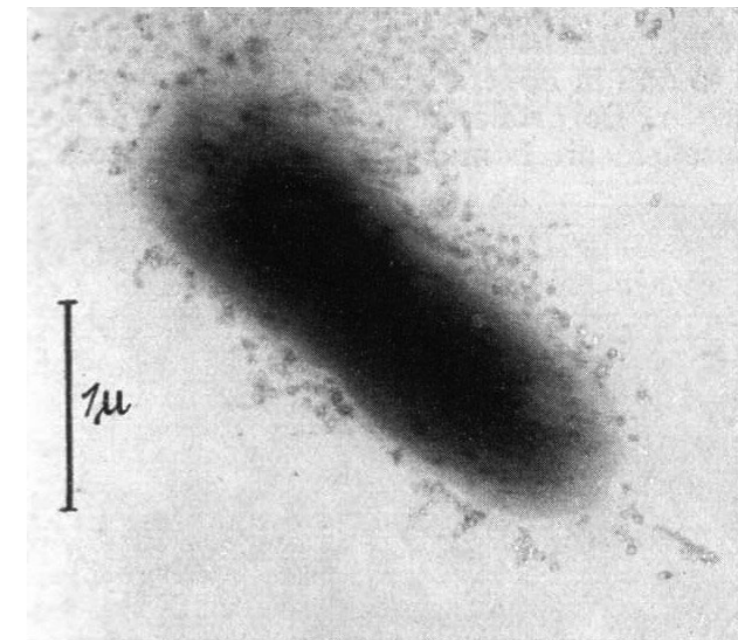
Greek 'phagein' = eating



Frederik Twort
1915

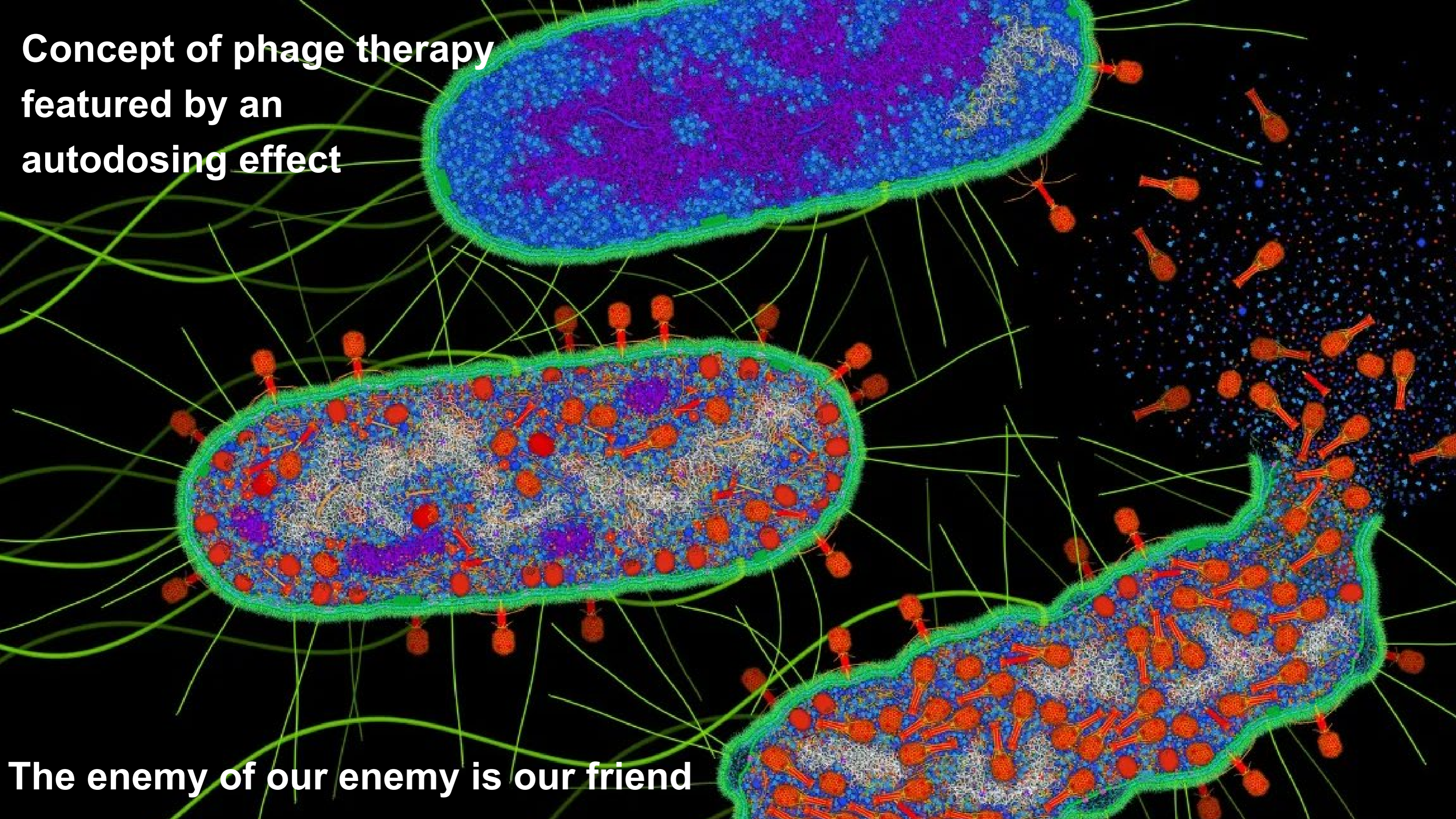


Felix D'Herelle
1917



Ackermann, 2011. First image of phage in 1940
by Ruska
doi: 10.4161/bact.1.4.17624

**Concept of phage therapy
featured by an
autodosing effect**



The enemy of our enemy is our friend

First phage therapy trials

- **Chicken typhoid:** Before moving to human trials, d'Hérelle successfully treated chicken typhoid using phages isolated from chicken feces
- **Dysentery treatment:** In August 1919, d'Hérelle administered phage therapy to a boy suffering from severe dysentery at the Hospital des Enfants-Malades in Paris

Emergence and decline of phage therapy

- **1920-1940:** Initial success for various bacterial infections and early studies in several countries including France, Belgium, US and the Soviet Union; commercializations by Eli Lilly, Abbott Laboratories, Bristol-Myers Squibb and L'Oréal
- **Inconsistent results:** a lack of understanding of phage biology and the highly specific nature resulted in inconsistent outcome
- **Production and regulatory issues:** standardizing phage preparations proved to be challenging and phages are incompatible with standard regulatory framework for therapeutics

Emergence and decline of phage therapy

- **From 1940:** Discovery and widespread use of antibiotics that were easier to produce
- **1950-1960:** Golden era of antibiotic discovery
- **Outcome:** In the West, phage therapy was abandoned, while it was continued in the Soviet Union and Eastern Europe

Phage therapy in Georgia



Eliava institute
Tbilisi

Phage therapy in Georgia



Phage therapy in Western medicine

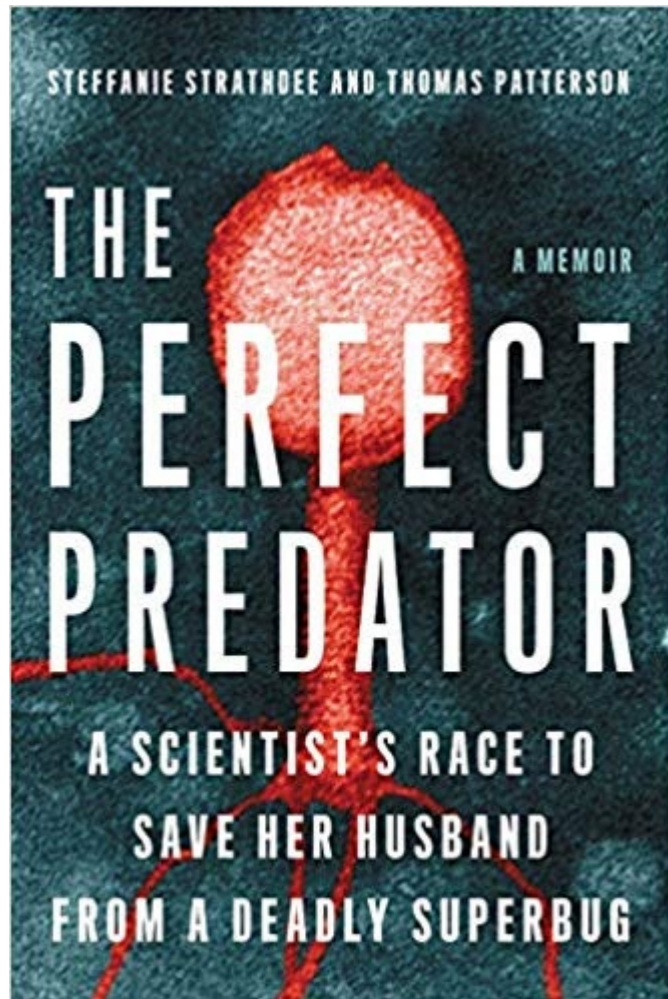
- The rise of antibiotic resistance has renewed the interest in phage therapy in the West
- Rapidly growing academic community and increasing number of SMEs in the field
- Accumulating understanding of phage biology and production methods
- High level political discussions on regulatory framework for phage therapy

Phage therapy in Western medicine

- **Declaration of Helsinki:** compassionate use -> many successful case studies, especially with patients having chronic, antibiotic-resistant infections

Declaration of Helsinki artikel 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, may use an unproven intervention if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.”



Phage therapy in Western medicine

- 1. Declaration of Helsinki:** compassionate use -> many successful case studies, especially with patients having chronic, antibiotic-resistant infections
- 2. The magistral phage** (pioneered in Belgium)

Communication

The Magistral Phage

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Charlotte Ameloot ⁴ and Alan Fauconnier ^{4,5}

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⁵ Culture In Vivo ASBL, rue du Progrès, 4, boîte 7, 1400 Nivelles, Belgium

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Abstract: Since time immemorial, phages—the viral parasites of bacteria—have been protecting Earth’s biosphere against bacterial overgrowth. Today, phages could help address the antibiotic resistance crisis that affects all of society. The greatest hurdle to the introduction of phage therapy in Western medicine is the lack of an appropriate legal and regulatory framework. Belgium is now implementing a pragmatic phage therapy framework that centers on the magistral preparation (compounding pharmacy in the US) of tailor-made phage medicines.

Keywords: antibiotic; antimicrobial resistance; magistral preparation; compounding pharmacy; phage therapy; regulatory framework; personalized medicine



Belgian hub for the world's phage-based solutions

Nestled in the heart of Europe, the Belgian Phage Valley is a hotbed of innovation and cutting-edge research that is transforming the way we approach human and animal health, food and crop protection.

DISCOVER MORE

CONNECT

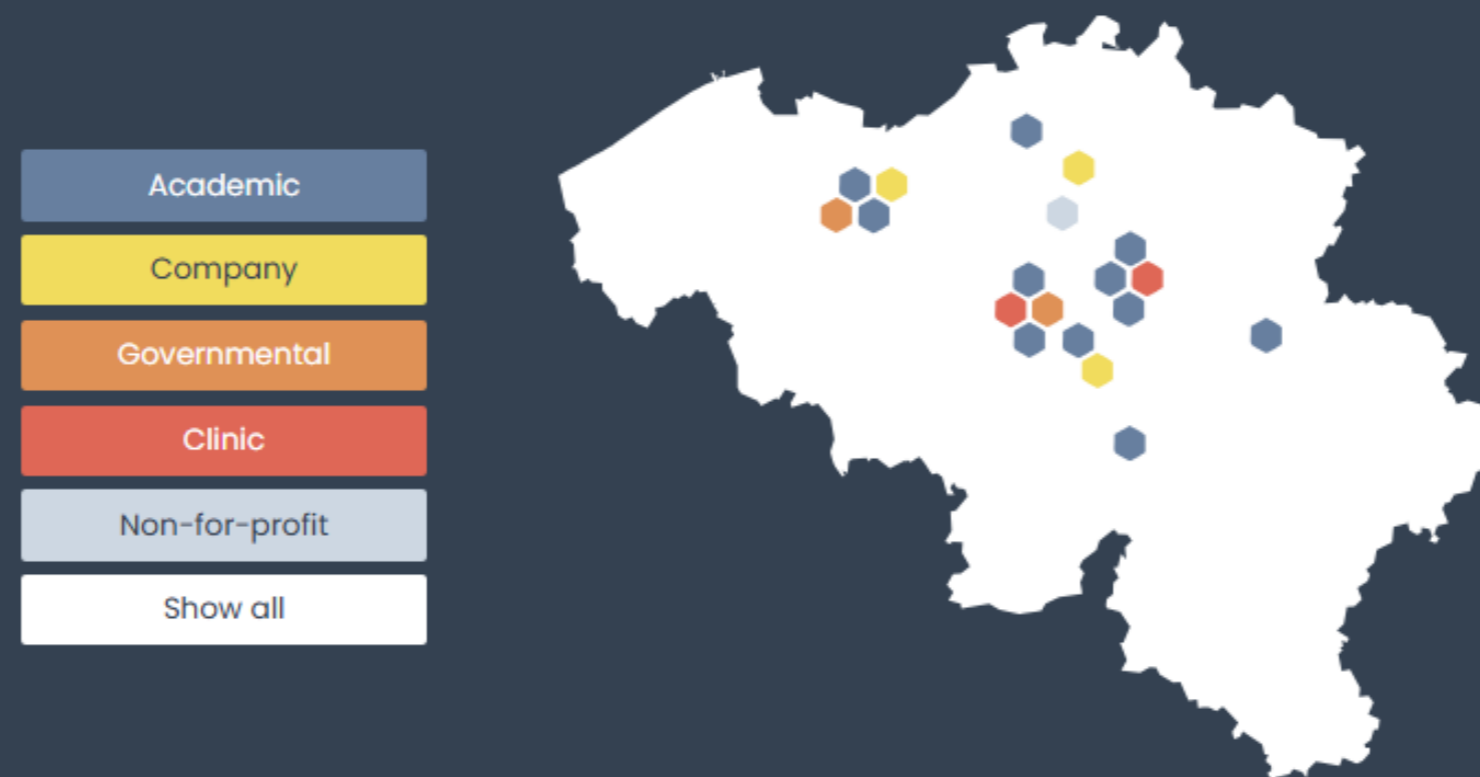


The Belgian Triple Helix

The **Belgian Phage Valley** is a vibrant hub of phage expertise, bringing together a diverse array of academic groups, companies, clinics, research institutes, and a supportive Belgian government. This unique ecosystem covers the full spectrum of phage research. From fundamental studies to innovative product development and clinical practice. a supporting Belgian government, covering phage expertise in the broadest sense of the word. From fundamental research to deepen our understanding of bacteriophages over applied research to develop innovative phage-based products to clinical practice in hospitals. Ranging from human therapy, animal health, food conservation to crop protection. From full virion phage therapy to phage lysins as enzyme-based antibiotics. From the discovery of the new phage defence systems to phage-inspired synthetic biology. From bacterial viruses to archaeal viruses. From wetlab to computational research. From individual researchers to multidisciplinary teams.

The Belgian Phage Valley exemplifies a successful triple helix collaboration between academia, industry, and government. This partnership has led to the creation of the most advanced legislation for phage therapy (**'magistral phage therapy'**), significantly increasing the number of patients treated. Our high concentration of phage researchers works closely together to achieve remarkable results.

Looking for the right expertise? Hover over the map or check the table below to contact the different Phage Valley members.



The Belgian Phage Valley

At the forefront of bacteriophage research

Phages, also known as bacteriophages, are viruses that infect bacteria and can kill harmful bacterial strains without harming human or animal cells. They offer a promising solution to the global **antimicrobial resistance crisis**, which poses a significant threat to human health. In addition, phages have the potential to enhance **food security** and promote **sustainable agriculture** by protecting crops from harmful bacteria and reducing foodborne illnesses. Moreover, phages play a crucial role in promoting the concept of **“one health”**, recognizing that human, animal, and environmental health are interconnected.

Phage-based solutions have the potential to benefit all three areas by reducing the use of harmful chemical pesticides and antibiotics, promoting healthy ecosystems, and preventing the spread of antibiotic-resistant bacteria. The Phage Valley is at the forefront of research, with scientists and innovators working to develop novel phage-based and phage-derived therapies, diagnostic tools, and biocontrol agents. As the demand for sustainable and effective antimicrobial solutions grows, the Phage Valley is well-positioned to lead the way in addressing some of the world’s most pressing health and food security challenges.



ANTIMICROBIAL
RESISTANCE



CROP
PROTECTION



FOOD
SAFETY

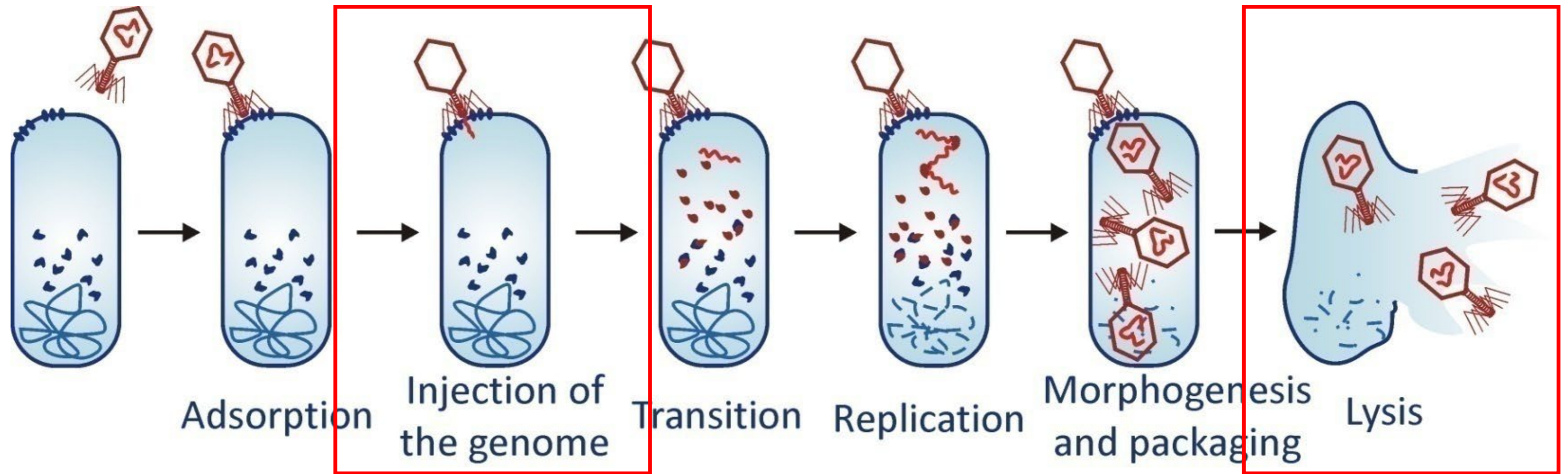


VETERINARY
HEALTH

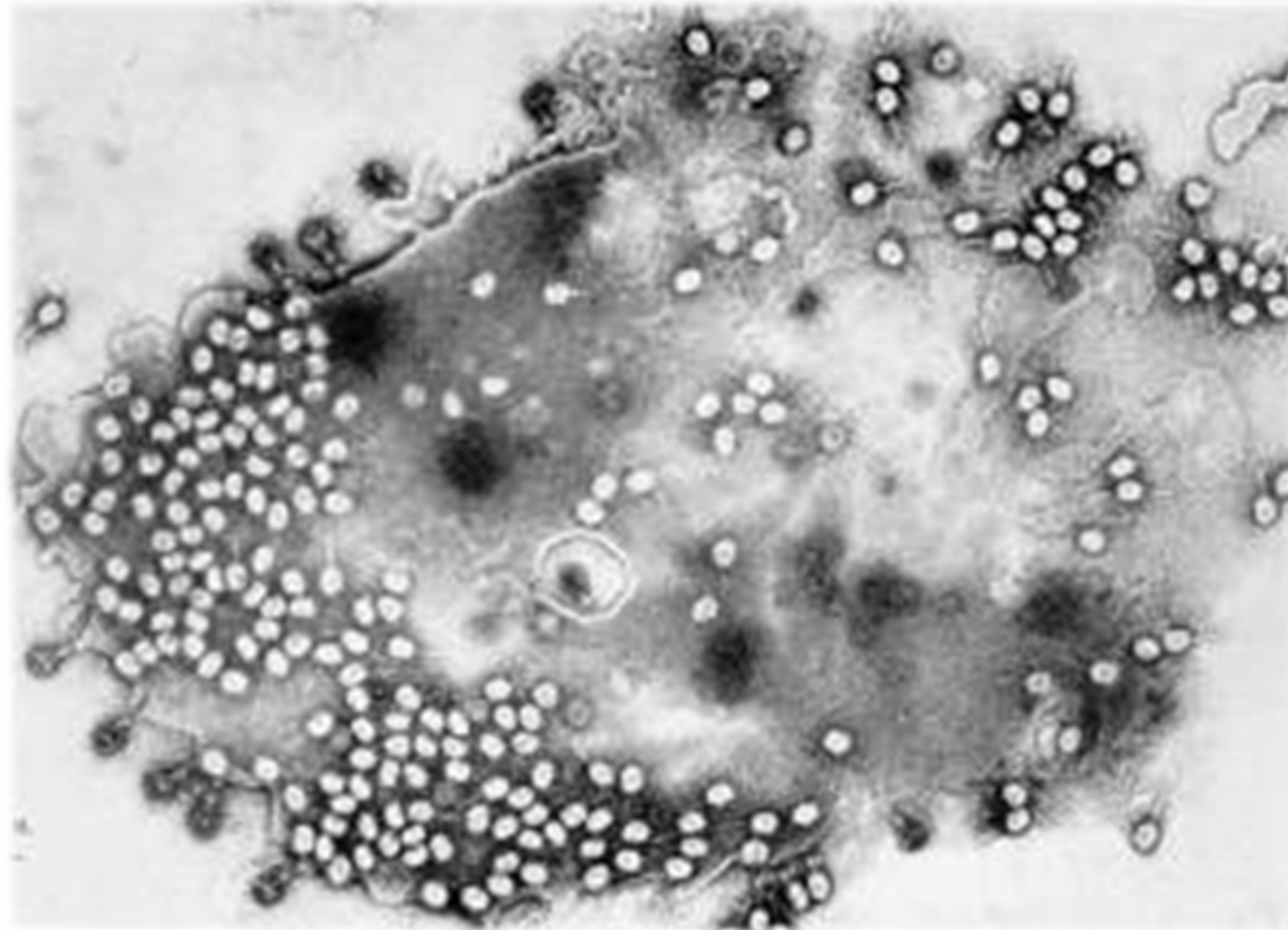
Phage-inspired antibacterials

- 1. Phage lysins**
- 2. Phage depolymerases**
- 3. Tailocins**

Phage lysis

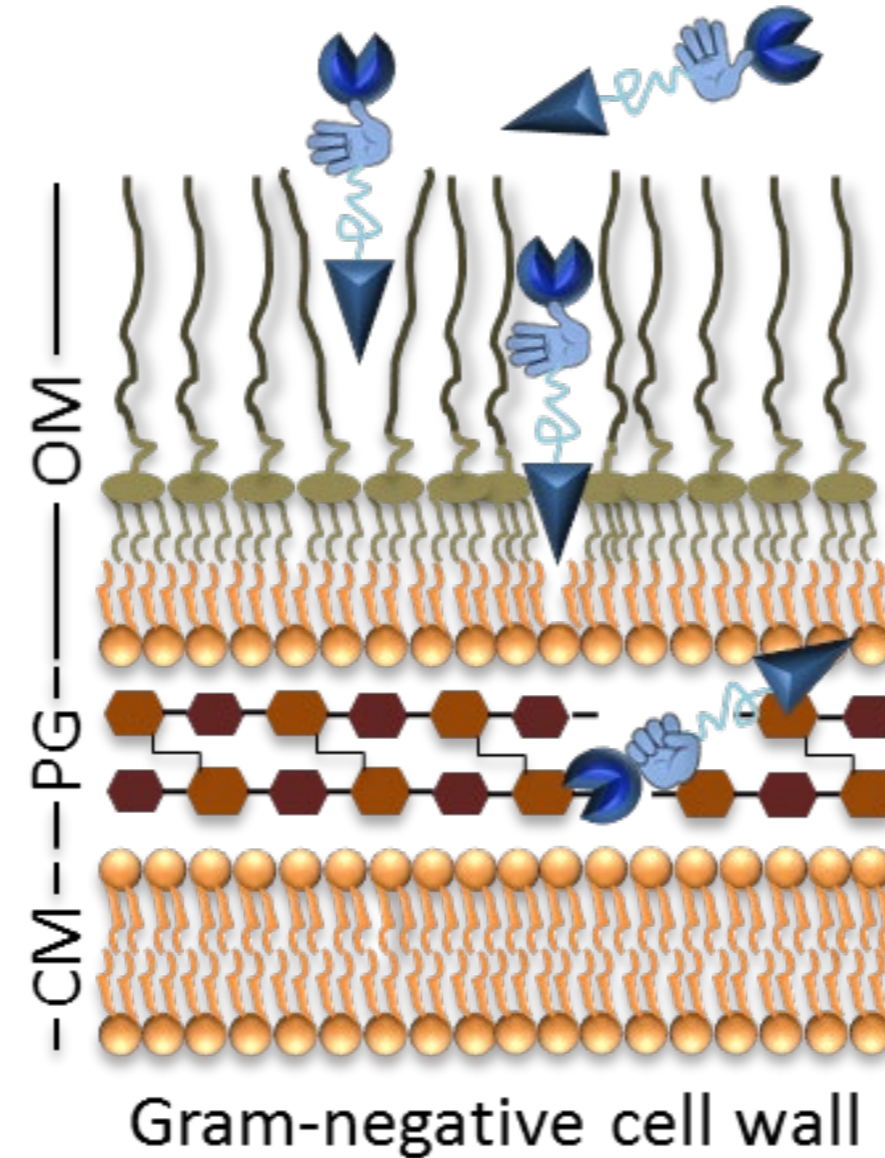
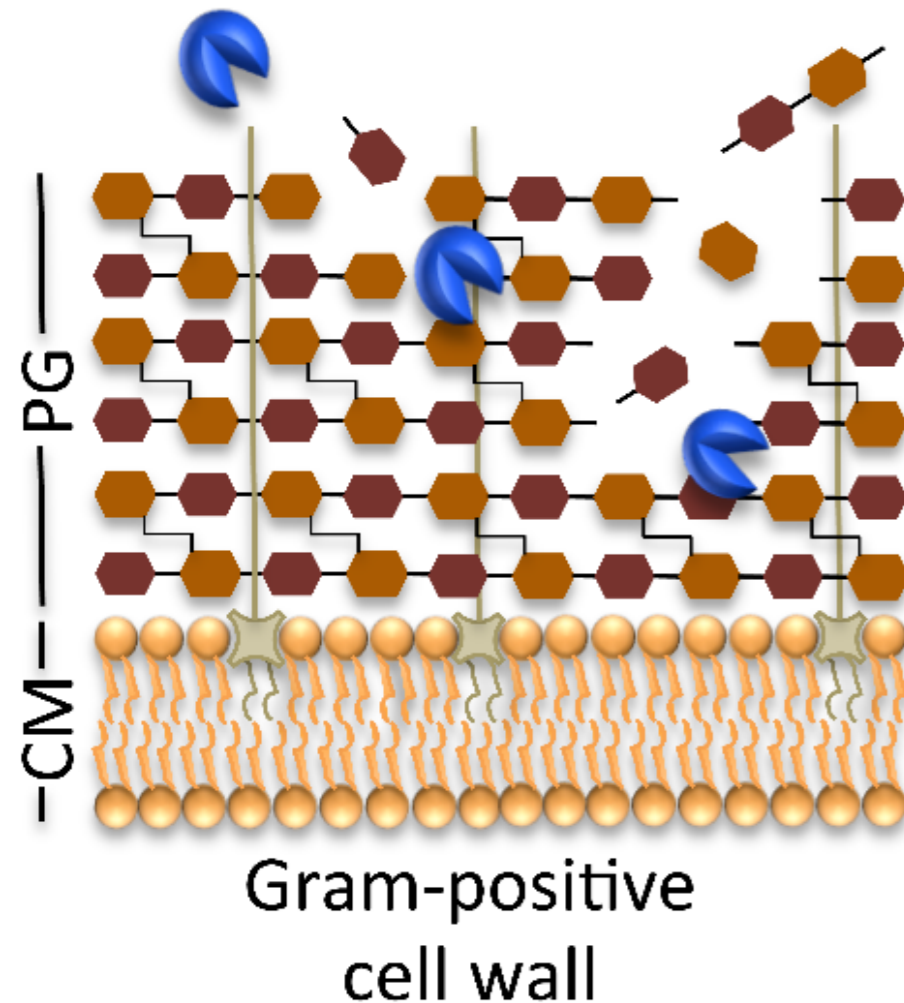


Host cell lysis by endolysins



Endolysins as antimicrobials

CM: cytoplasmic membrane
PG: peptidoglycan
OM: outer membrane
AG: arabinogalactan
MA: mycolic acids



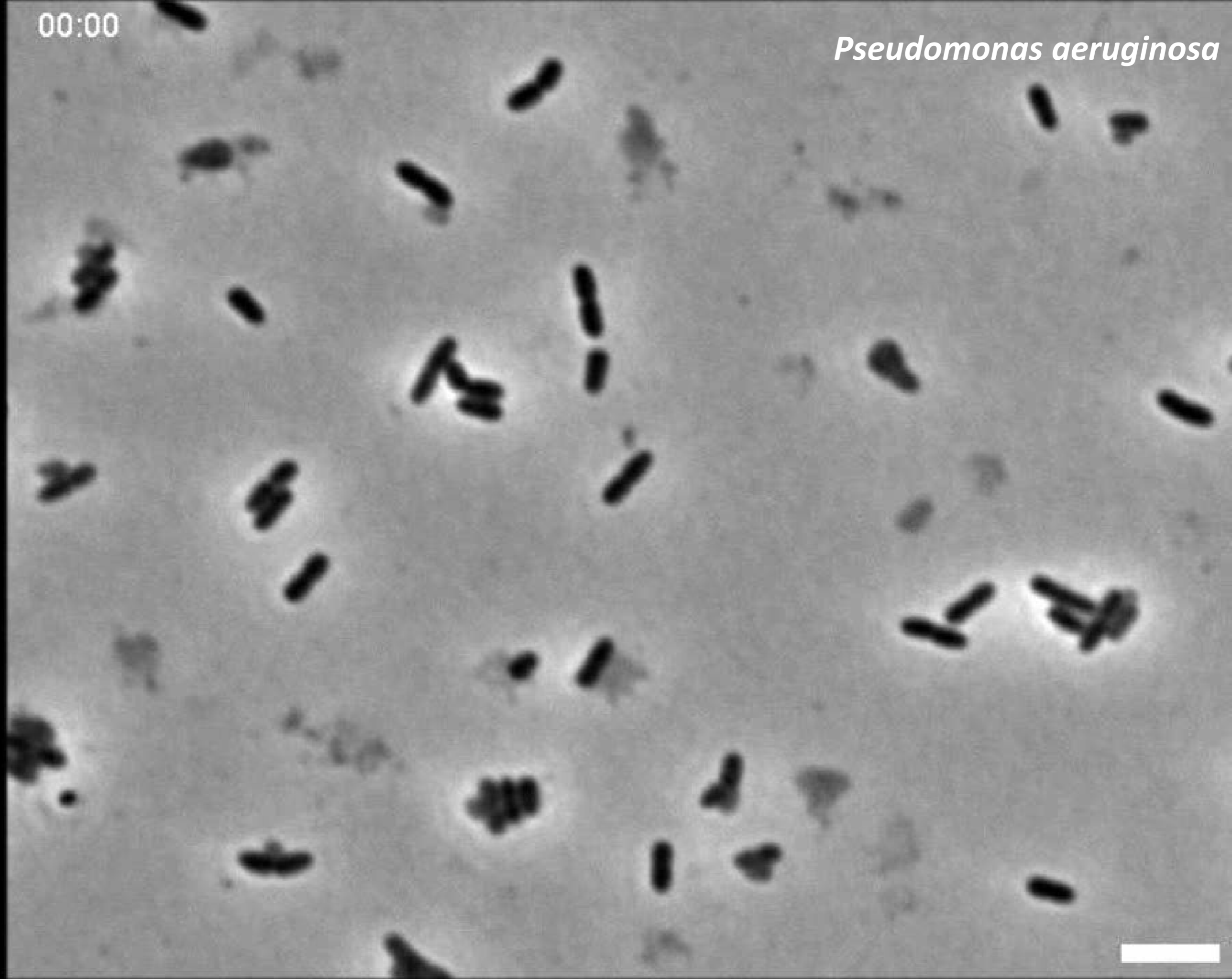
Current status:

Gram-positive pathogens: successful phase 1 and 2 clinical trials

Gram-negative pathogens: successful *in vivo* animal studies

00:00

Pseudomonas aeruginosa



Hallmark features of phage lysins

- Lysins are a rapidly acting novel class of antibiotics
- Lysins are highly bactericidal
- Lysins kill persisters
- Lysins kill multidrug-resistant strains
- Tunable specificity at genus, species or serovar level
- Lysins do not provoke resistance development
- Fit with regulatory framework for biologicals

Case study with dogs



8 days



Lysin
treatment



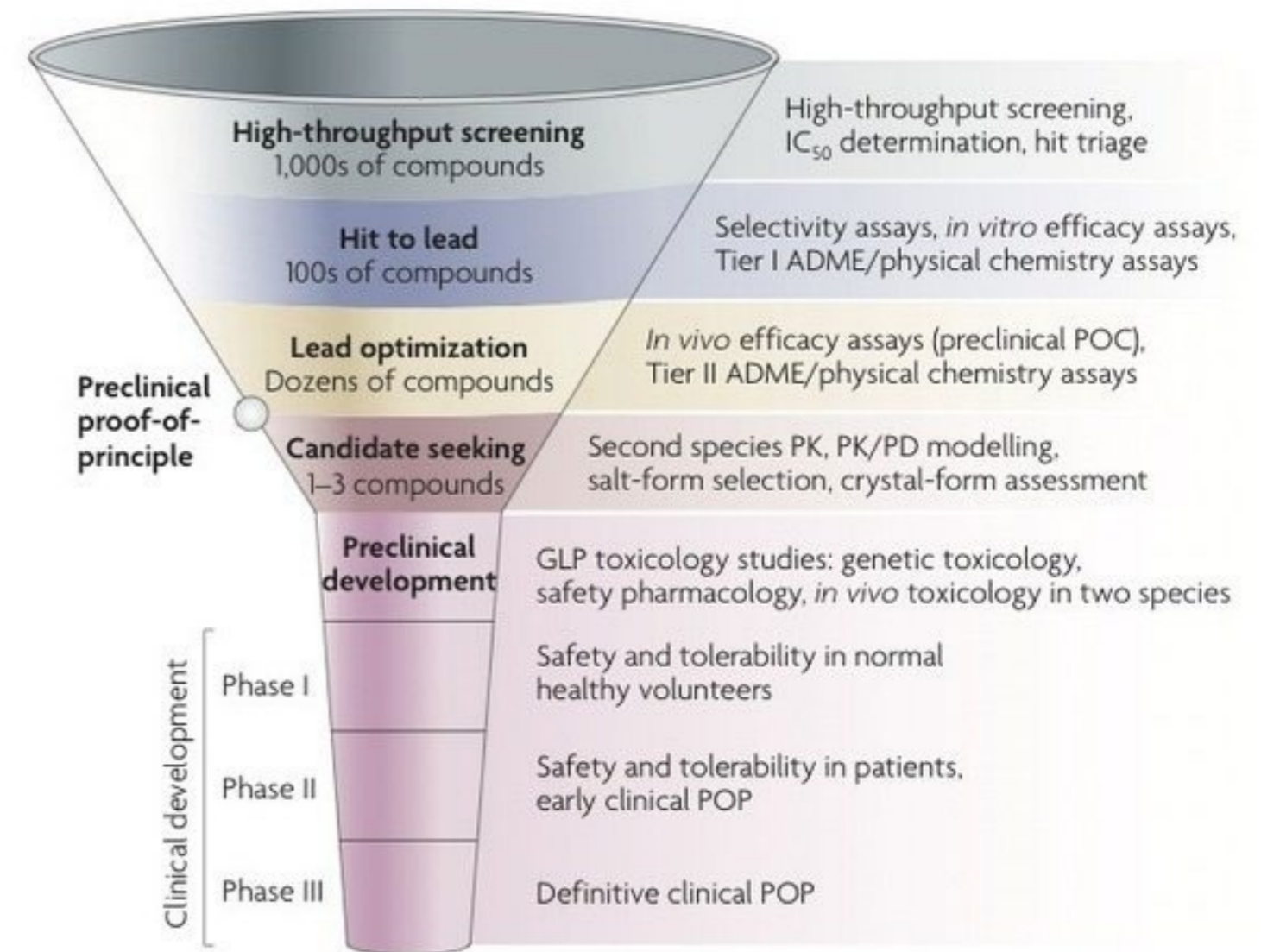
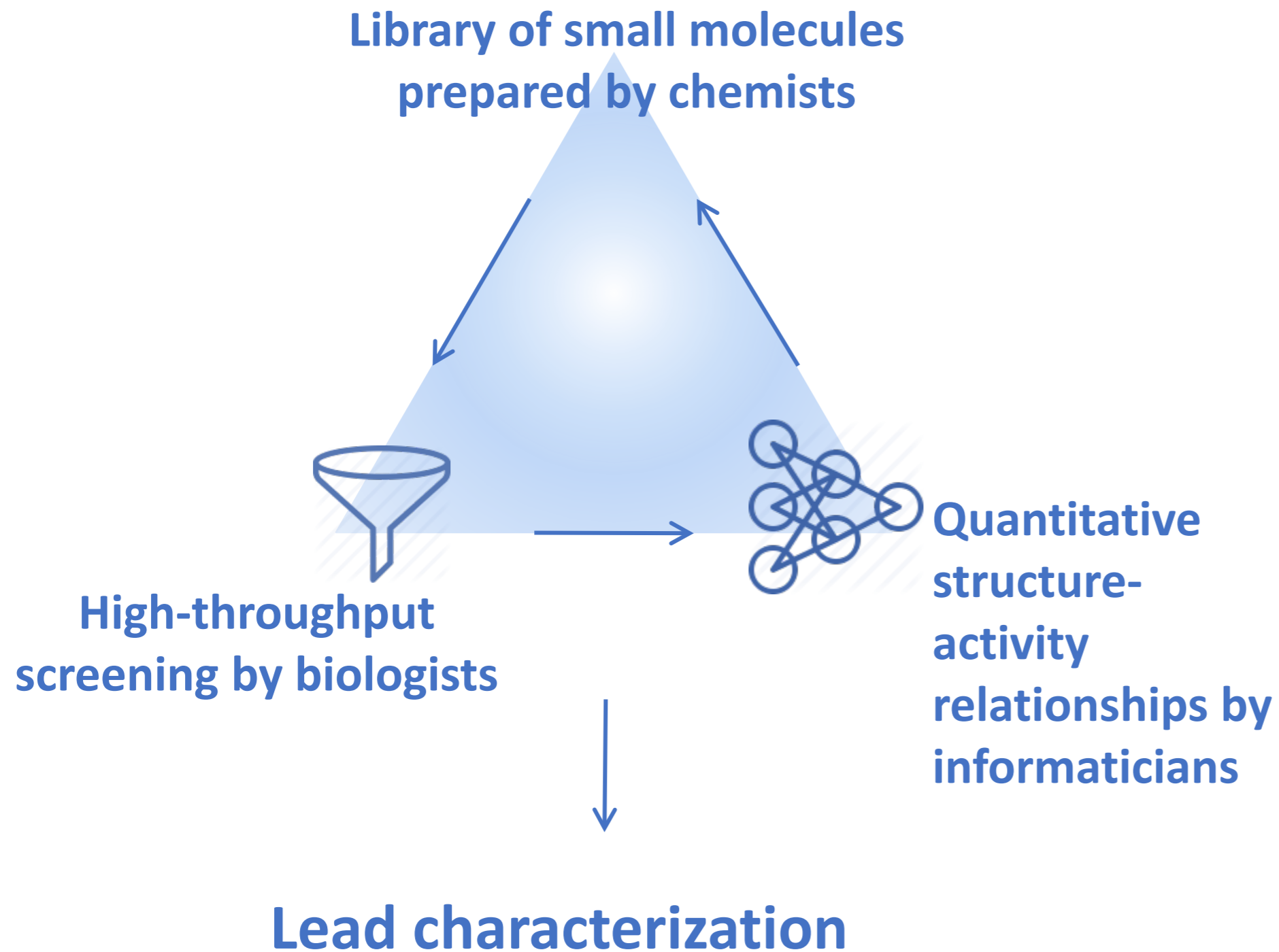


NEW SPINOFF

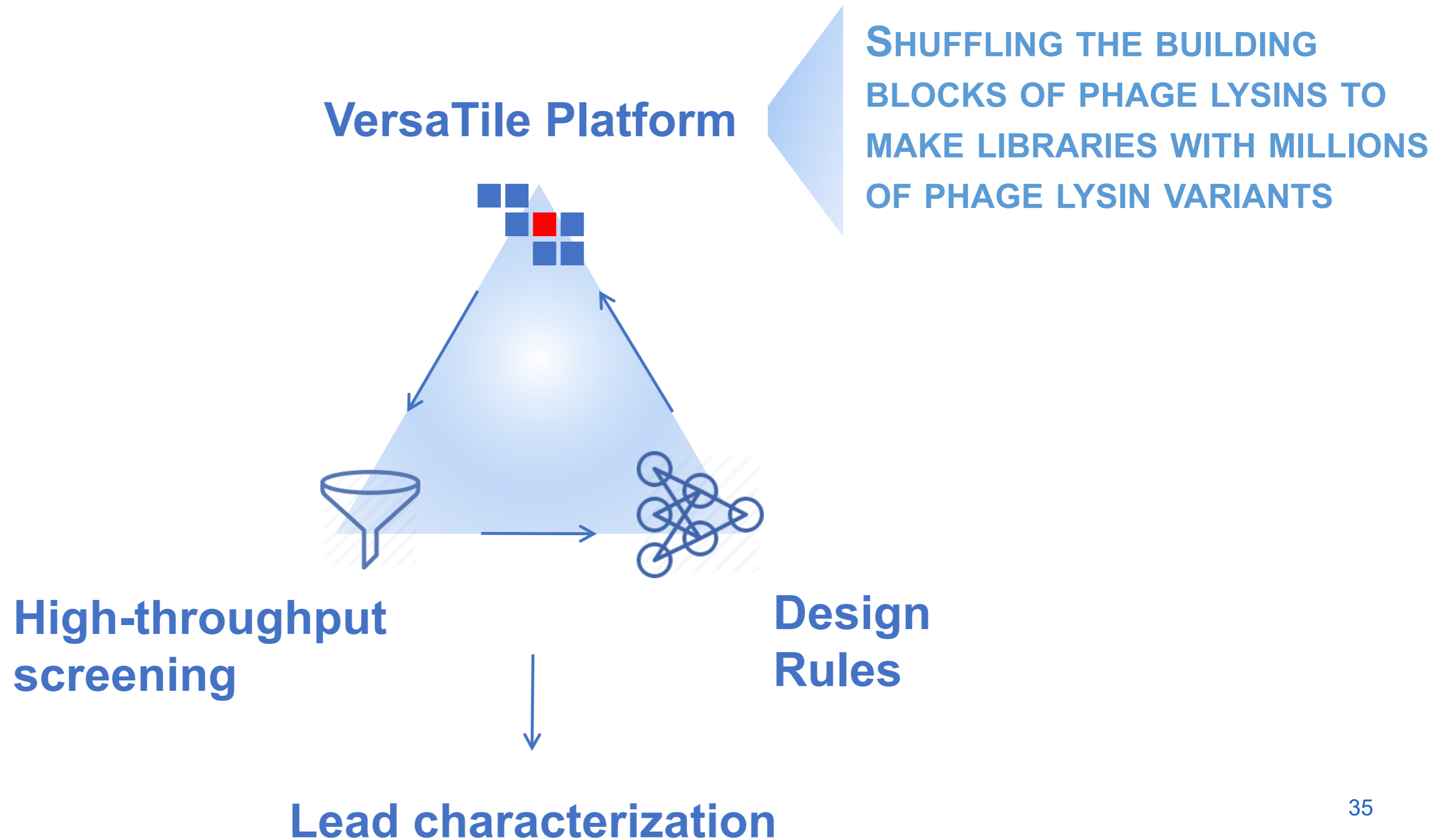
Obulytix

exploits the massive power of
natural bacteriophage lysins
to save the lives of countless patients
battling life-threatening conditions.

Hit-to-lead development process of small molecules in pharmaceutical industry



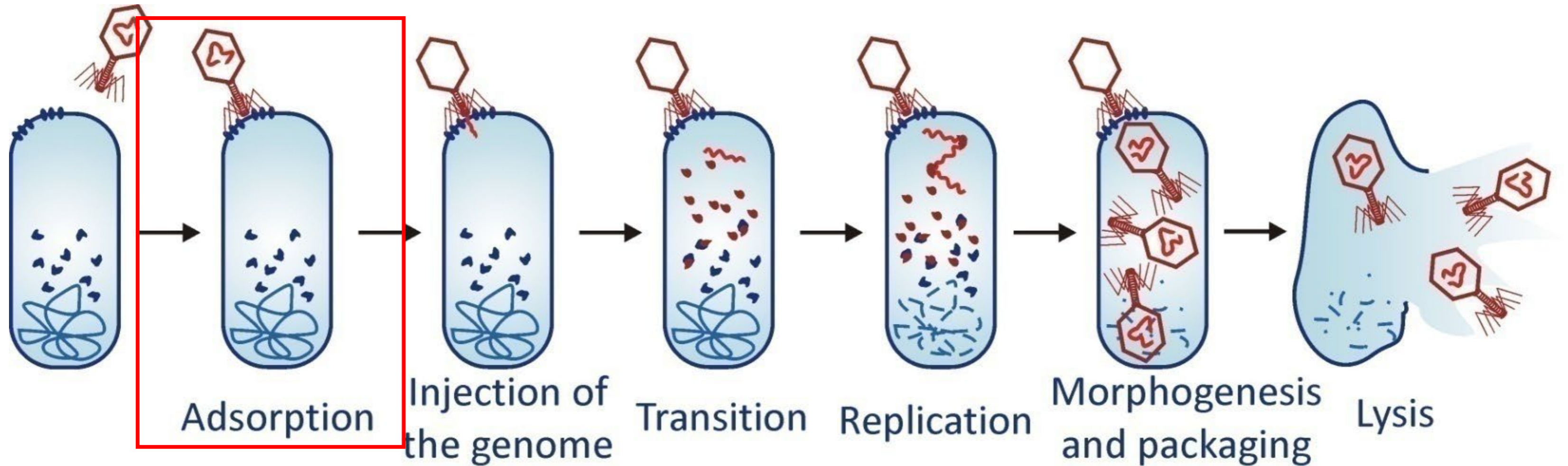
Approach



Phage-inspired antibacterials

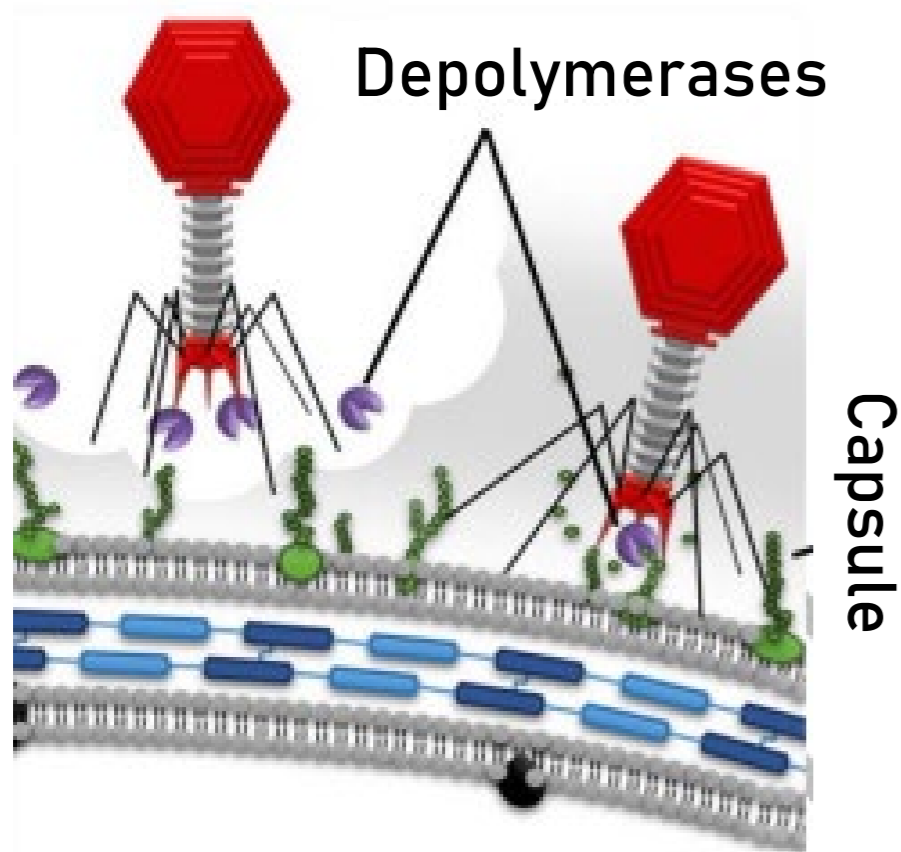
1. Phage lysins
2. Phage depolymerases
3. Tailocins

Phage depolymerases

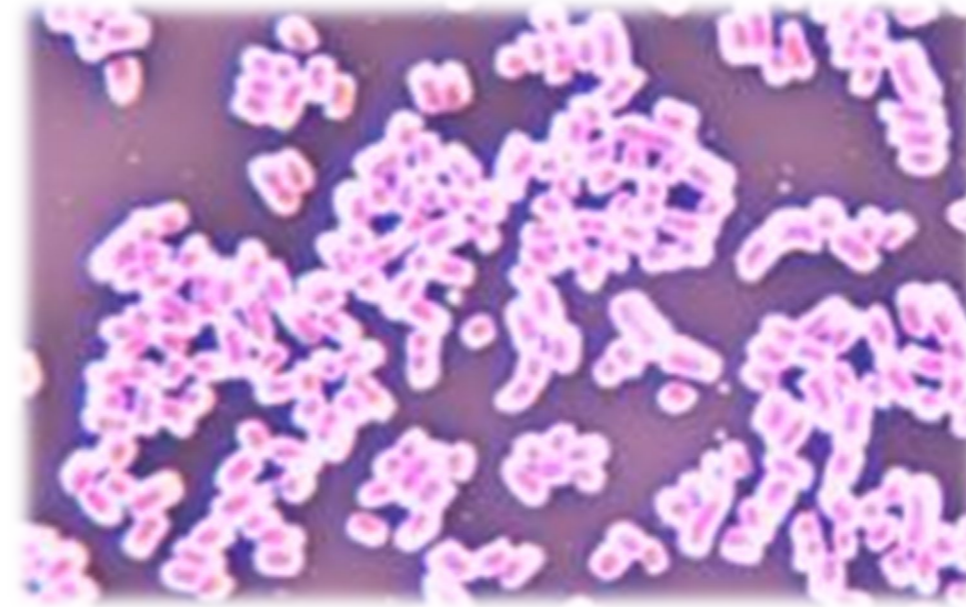


Phage receptor-binding proteins

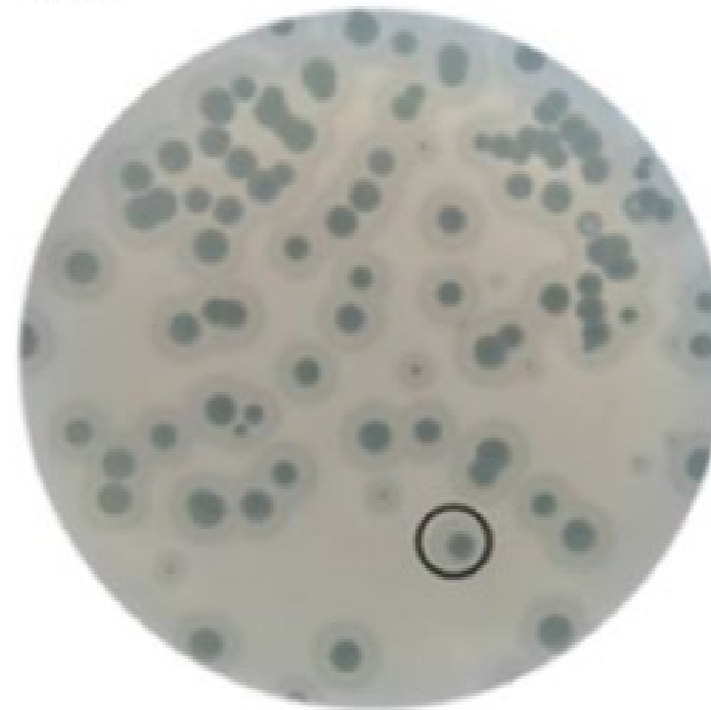
Phage depolymerases



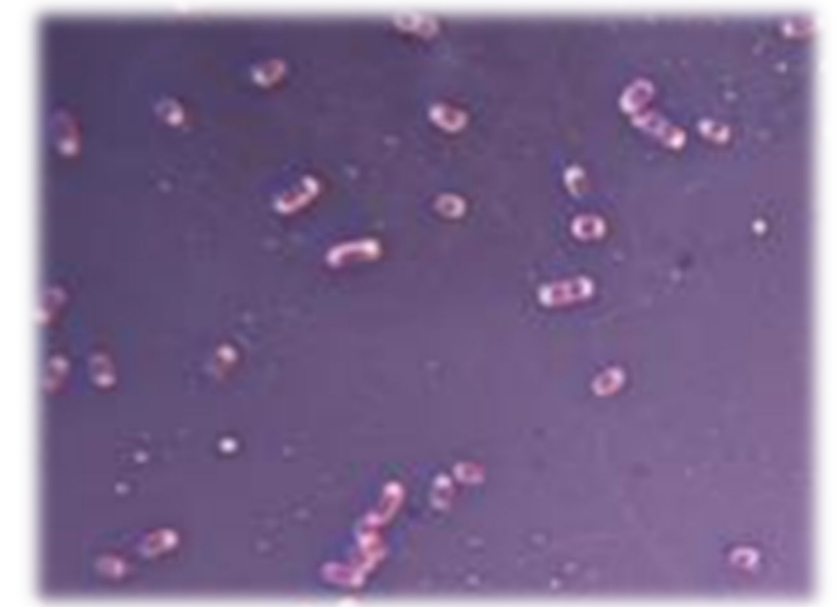
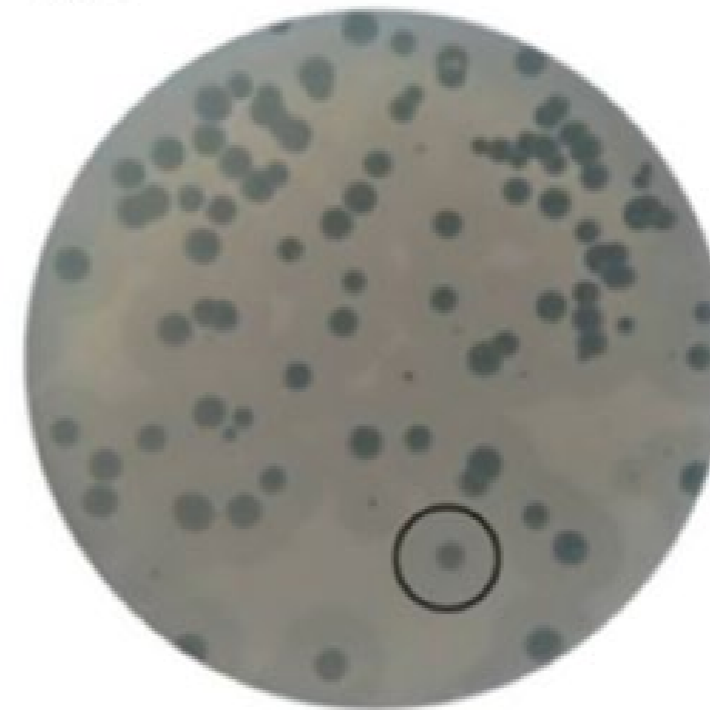
Phage depolymerases are phage receptor-binding proteins with enzymatic activity degrading the outer layers of bacterial cells (capsule, exopolysaccharides or LPS)



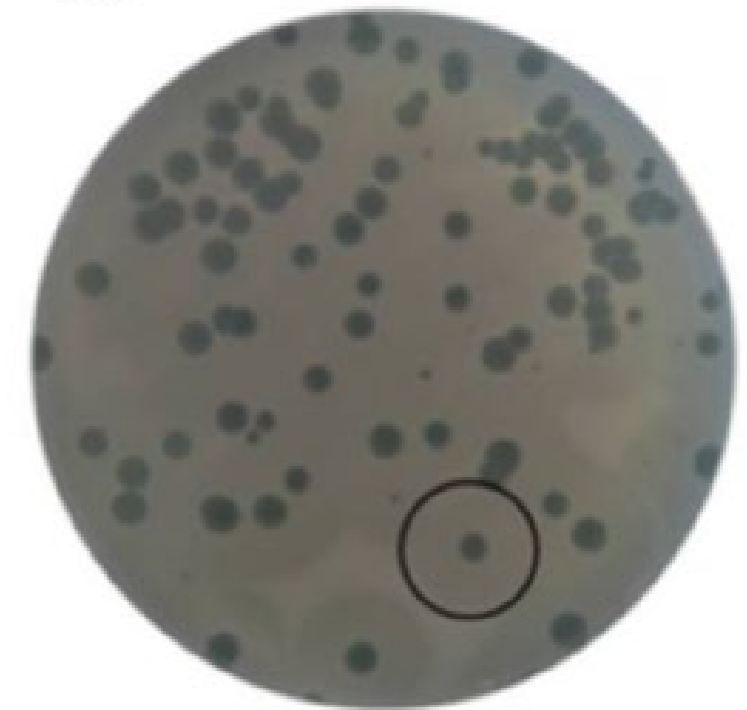
24 h



48 h



72 h



Hallmark features of phage depolymerases

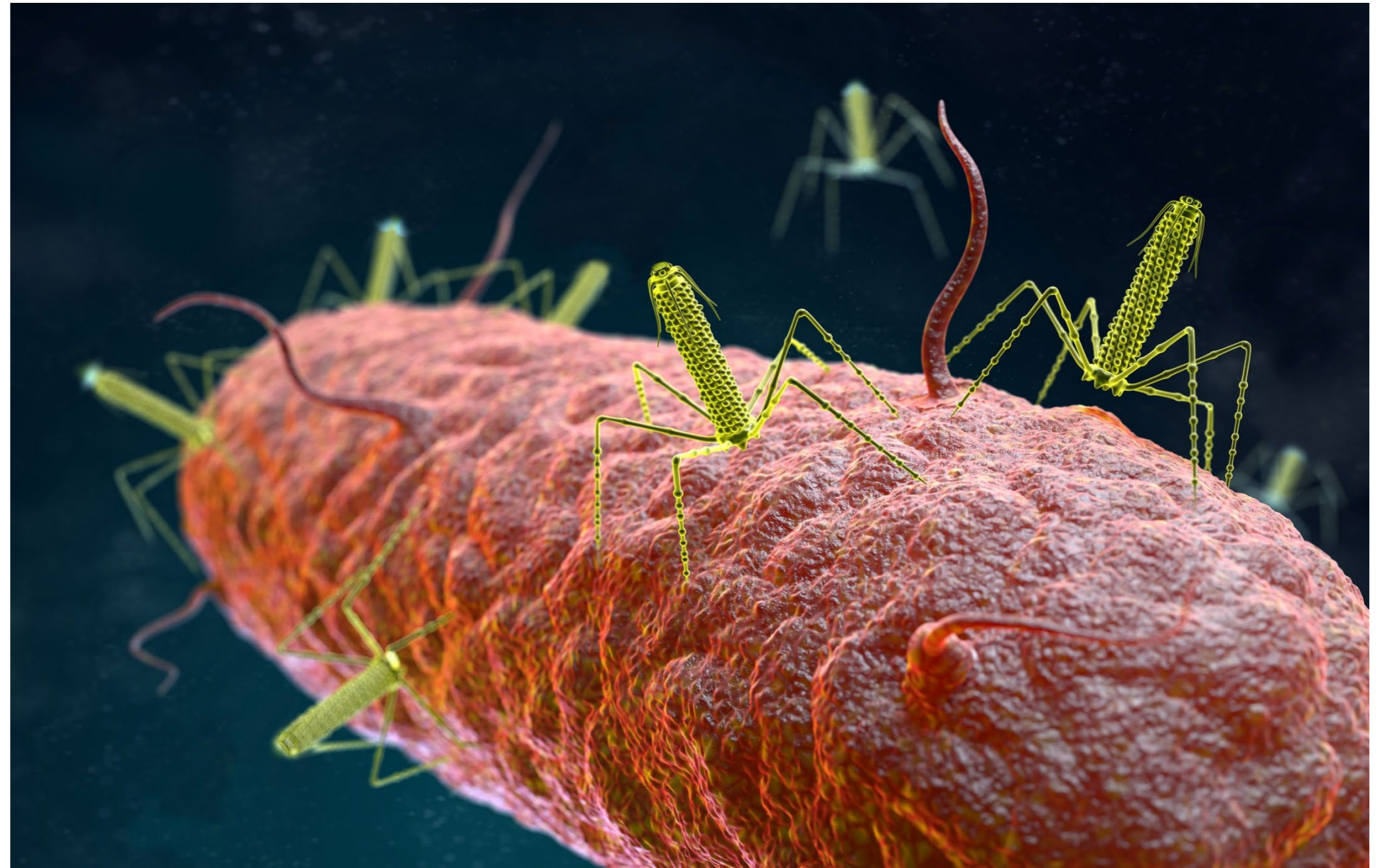
- Capsule or LPS removal eliminates the virulence of bacteria
- Phage depolymerases do not kill but disarm the cells
- Phage depolymerases can effectively disrupt biofilms
- Adjuvant potential enhanced standard-of-care antibiotics
- Upon treatment bacteria become more susceptible for serum and phagocytosis
- Serogroup specific (sub-species level)
- Successfully evaluated in mice infection models (targeting *K. pneumoniae*, *E. coli*, *A. baumannii*, *P. aeruginosa*,...)
- Fit with regulatory framework for biologicals

Phage-inspired antibacterials

1. Phage lysins
2. Phage depolymerases
3. Tailocins

Tailocins

Tailocins are morphologically similar to bacteriophages but lack a head and DNA, and can therefore not replicate.



Hallmark features of tailocins

- They kill cells in a single hit mechanism through membrane puncturing and membrane potential dissipation
- They are specific on the serotype level (sub-species) depending on their receptor-binding protein
- Swapping of the receptor-binding protein in a fixed scaffold allows to make tailormade tailocins
- They are investigated for human therapy (animal studies with *P. aeruginosa*, *B. cepacia*), for crop and food protection, and veterinary applications (e.g. *Salmonella*)
- Fit with regulatory framework for biologicals

Conclusions

Bacteriophages offer a non-traditional and rich armamentarium of antibacterials to complement or replace our current standard-of-care antibiotics, either as full virion therapy (phage therapy), its proteins (phage lysin or depolymerase therapy) or derivatives (tailocin therapy).

Conclusions

They have a vast diversity of application fields, wherever bacteria pose a problem

Human therapy

Veterinary therapy

Crop protection

Food conservation

...

Acknowledgments



All L.A.B. members!

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Michiel Stock
Bernard De Bets



Rob Lavigne

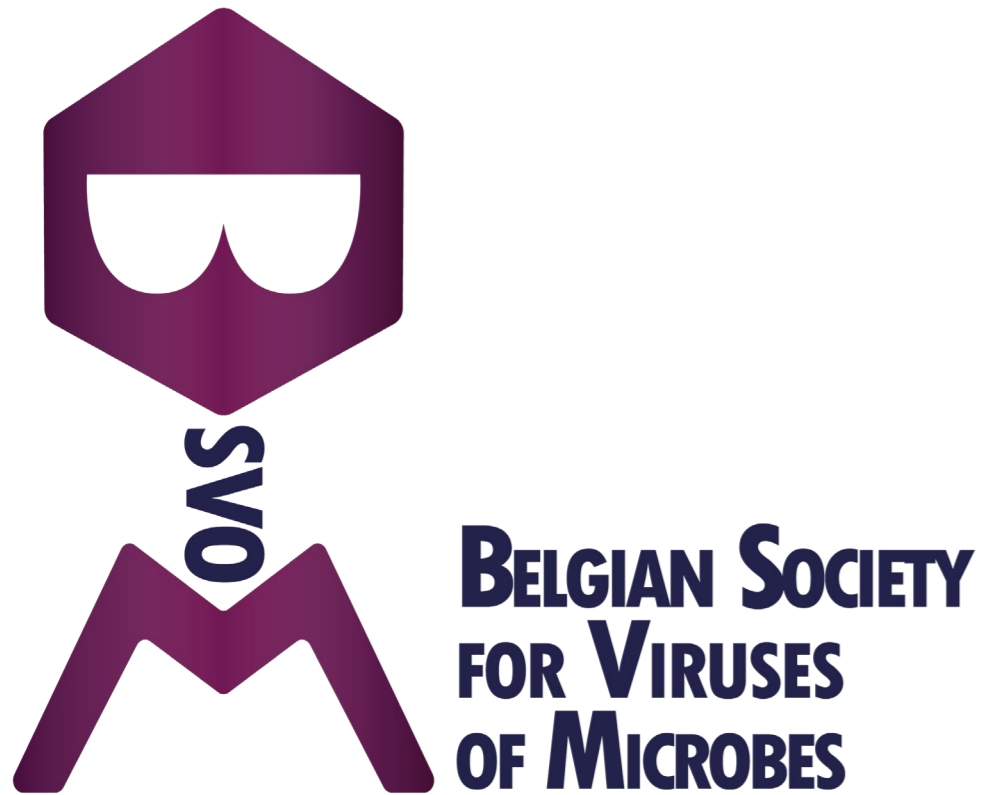


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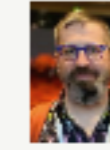
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