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# Phagen bei Multiresistenz

Dr. Holger Lößner

Abt. Mikrobiologie

FG Mikrobiologische Sicherheit

**22. ZSVA Hygiene-Forum Schleswig-Holstein, 29.10.2022**

# Disclaimer

Die dargestellten Informationen dieses Vortrages geben die persönliche Sicht und Einordnung des Autors wieder.

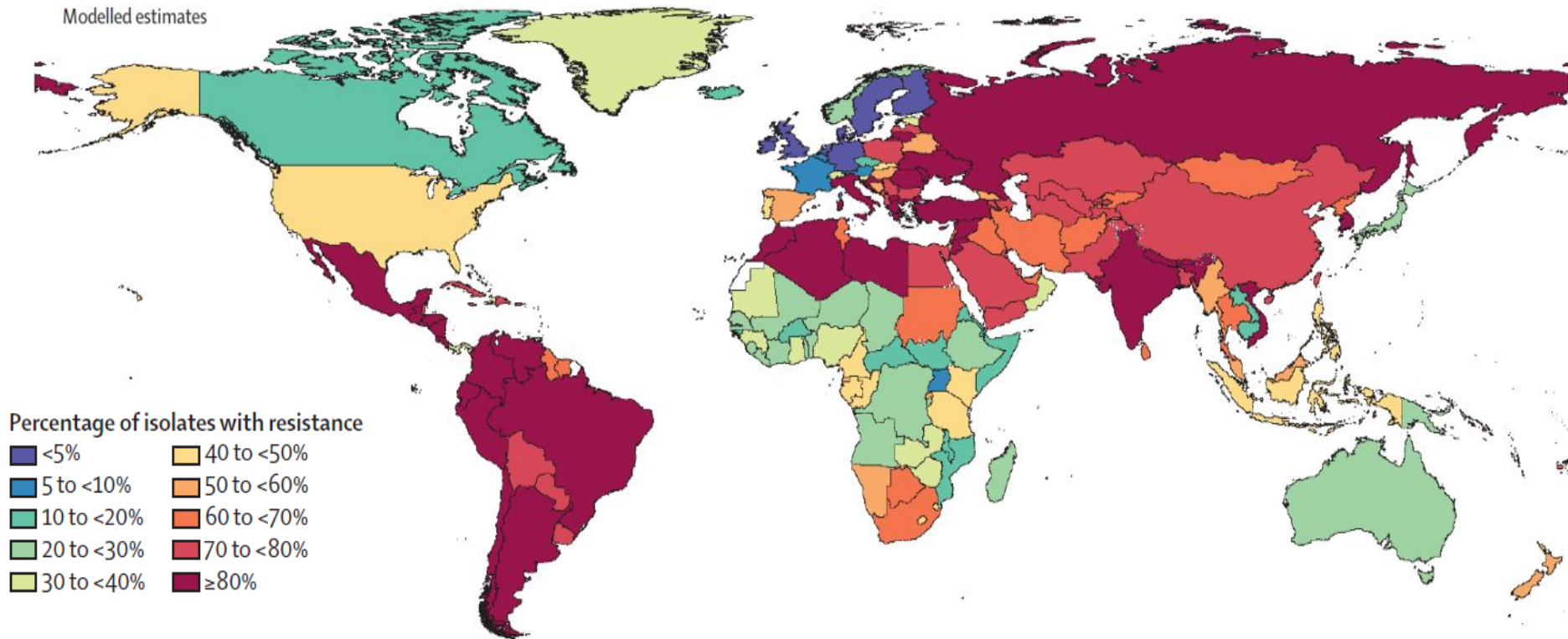
# Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

## AMR

Antimicrobial Resistance Collaborators\*

### D Carbapenem-resistant *Acinetobacter baumannii*

Modelled estimates



# AMR - Silent Pandemic

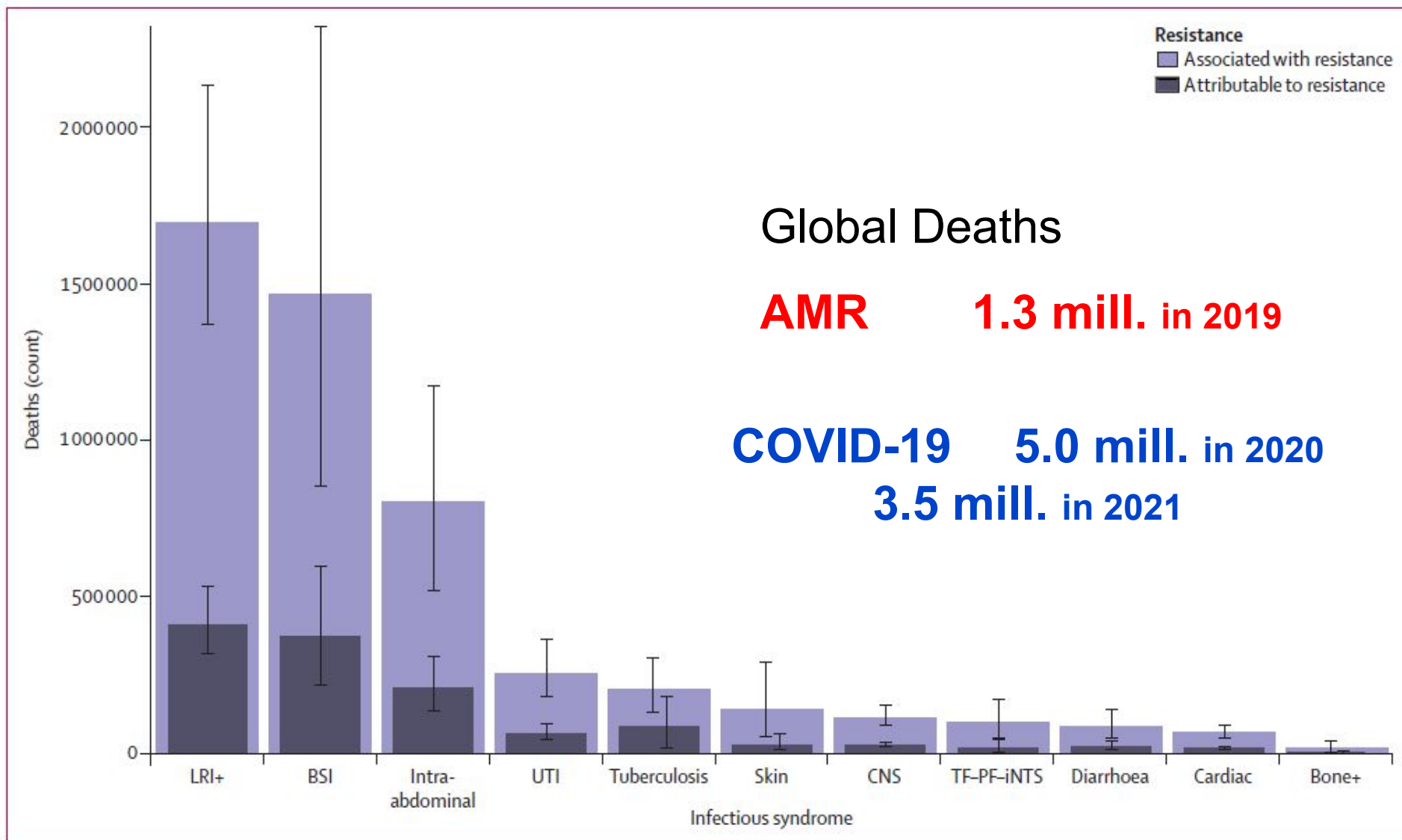
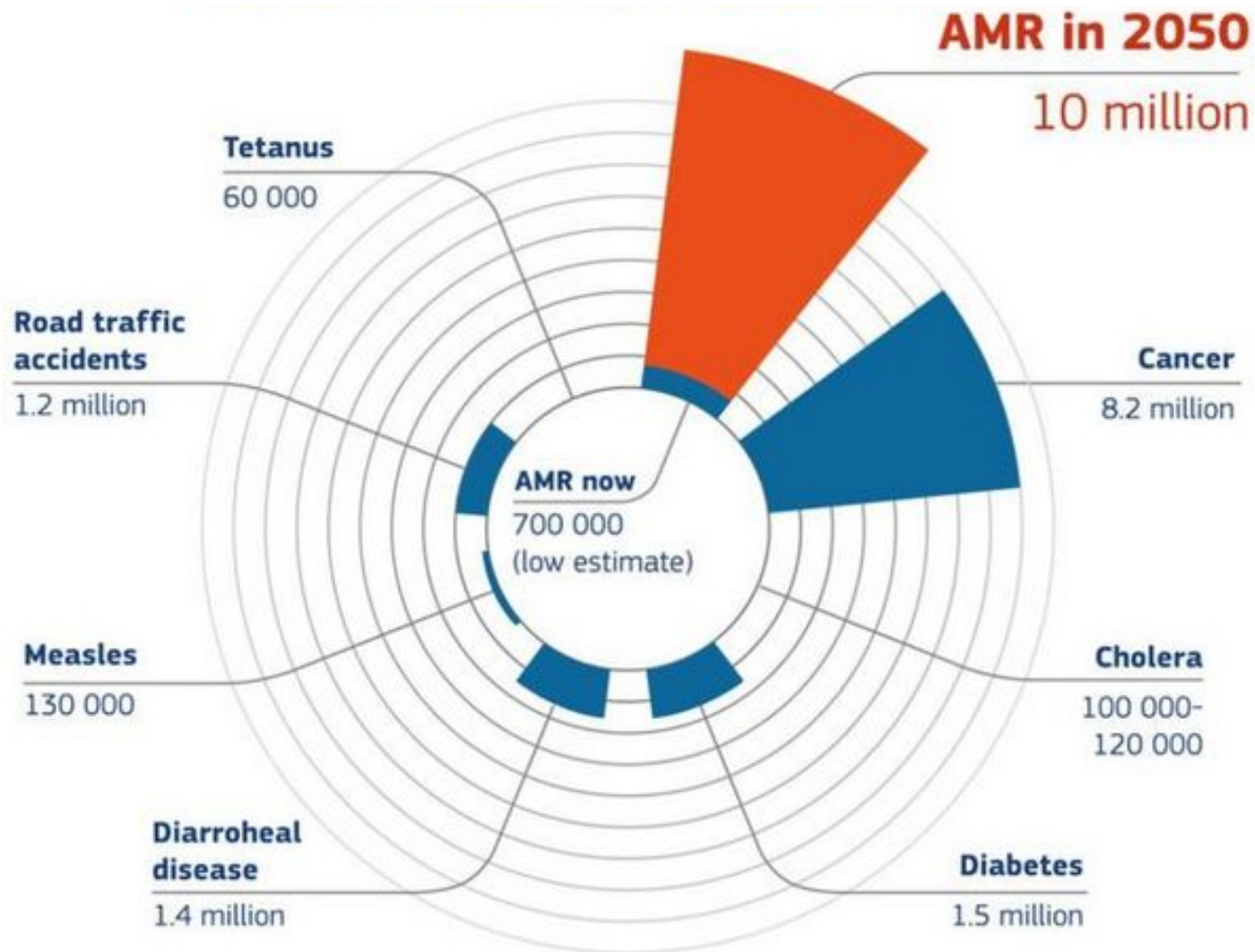


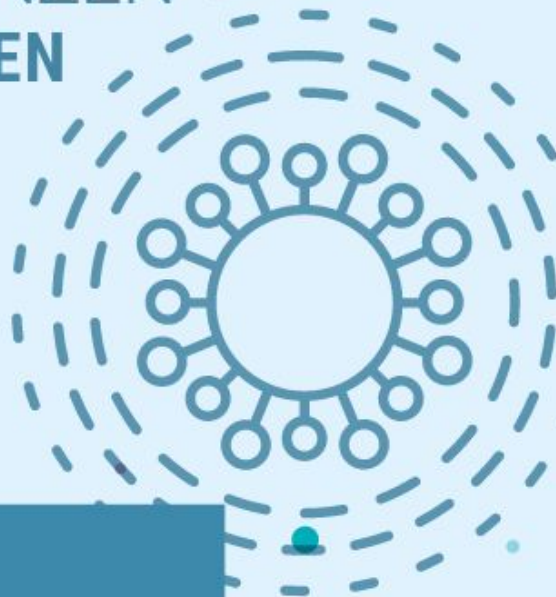
Figure 3: Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by infectious syndrome, 2019

# AMR - Silent Pandemic



Source: *The Review on Antimicrobial Resistance*, Jim O'Neill, 2014

# ANTIBIOTIKA RESISTENZEN VERMEIDEN



**DART 2020**

Vierter Zwischenbericht 2019

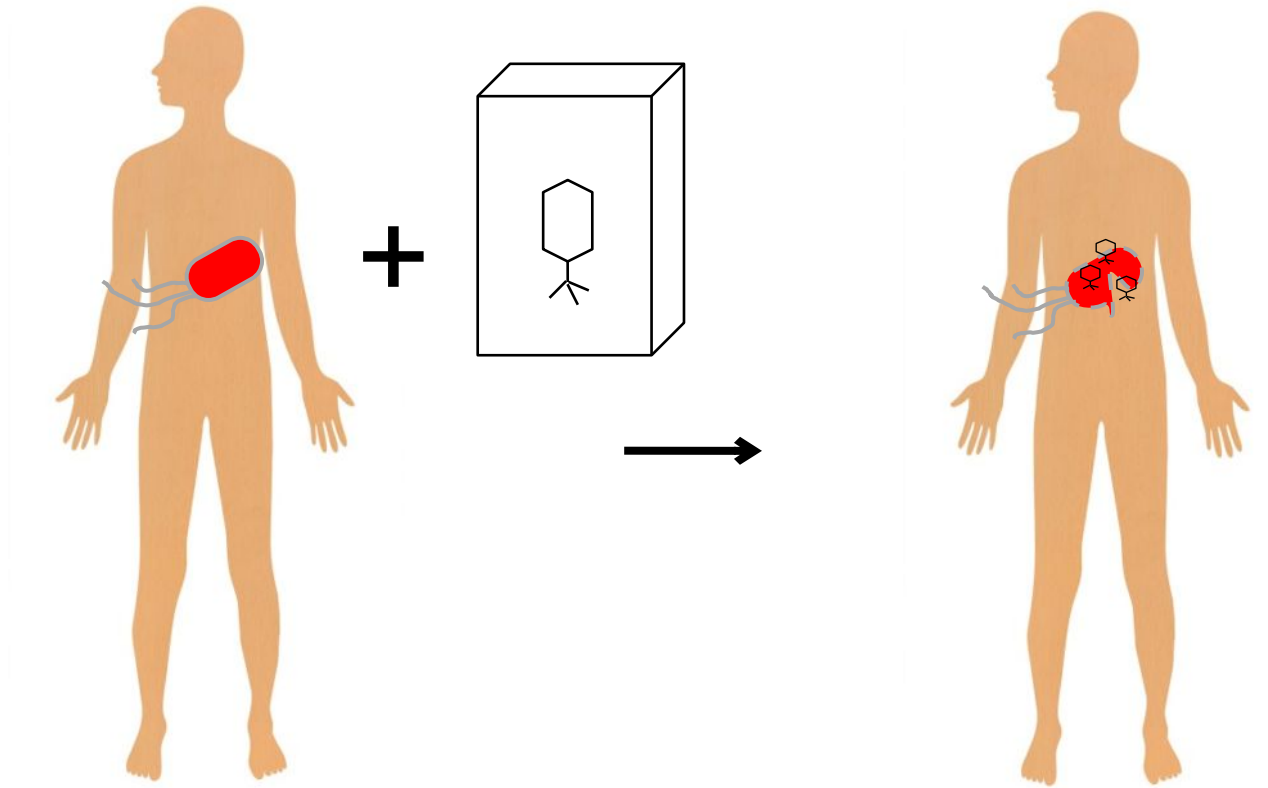
**Reduktion**

**Zielgenaue Bekämpfung**

...

**Neue Antibiotika**

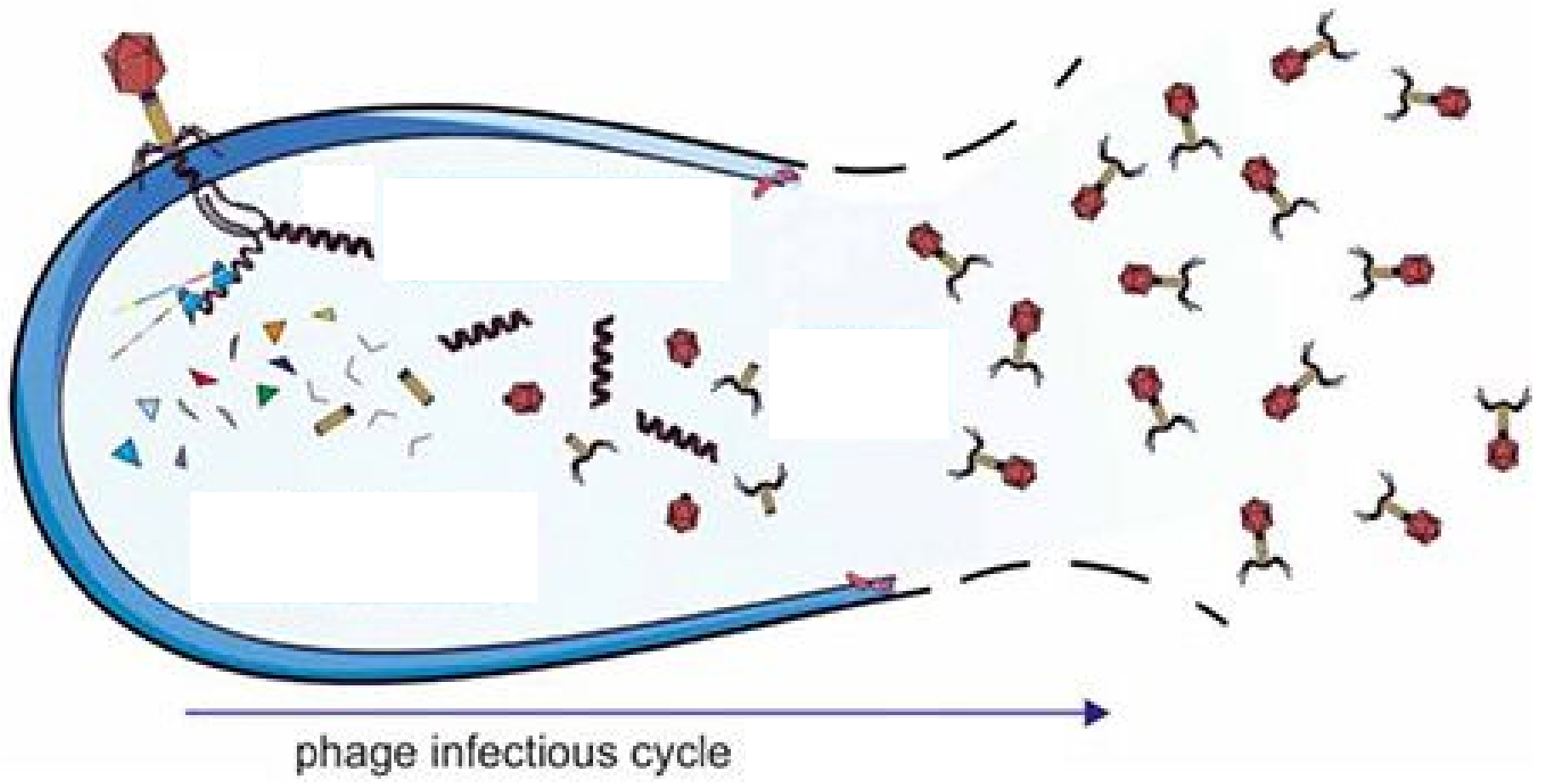
# Phagentherapie



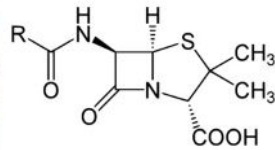
**„Last Resort“ gegen multiresistente Erreger (MRE)**







# 100 Jahre Phagentherapie



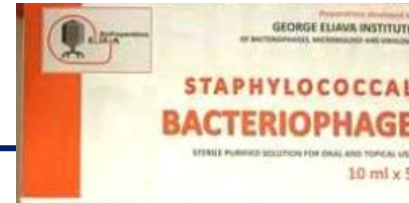
A. Fleming

1928

1945

AMR  
Microbiome

2000



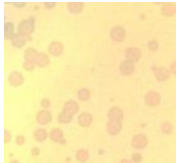
1915 / 1917

phage therapy

Frederick Twort

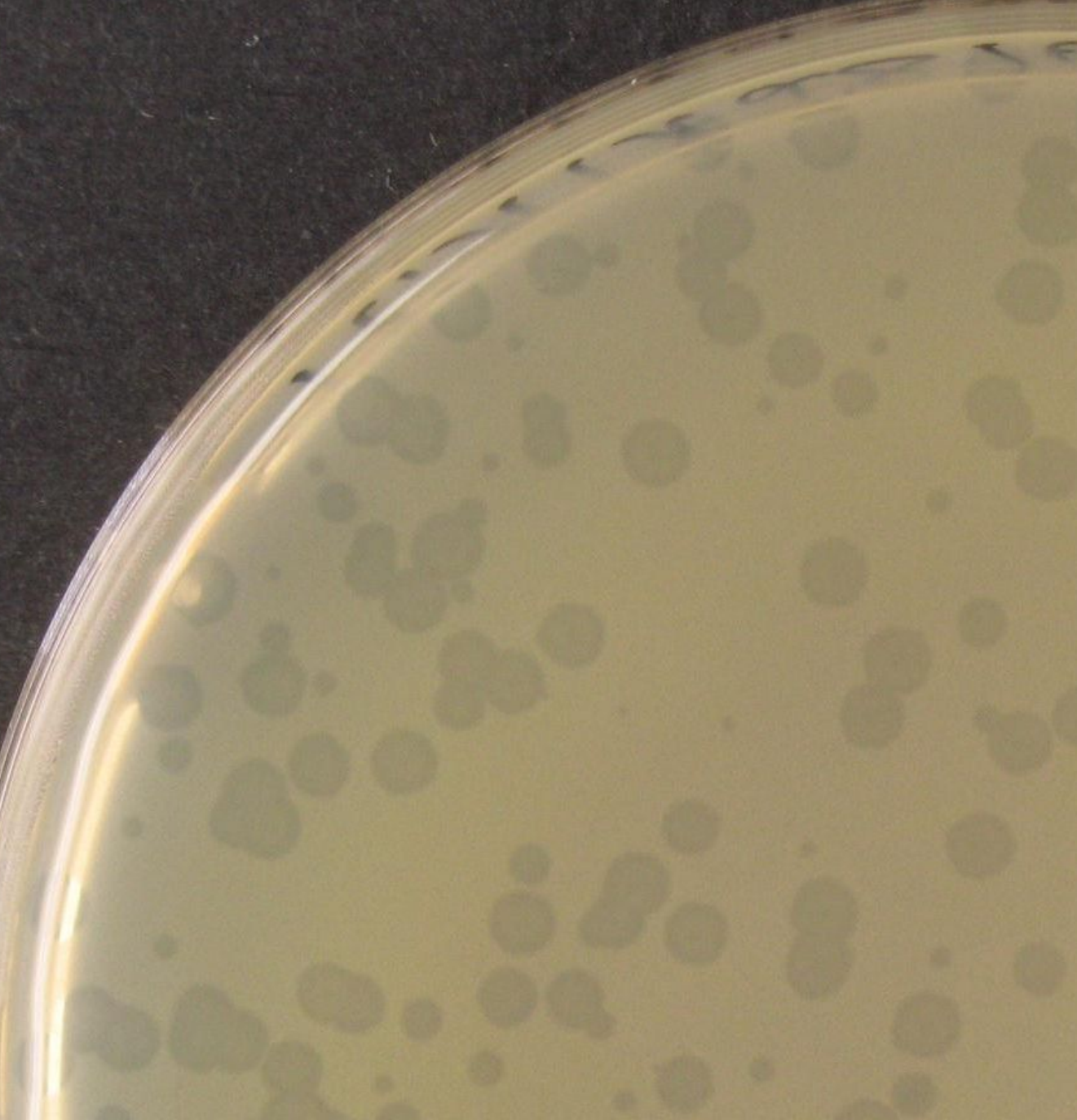
Georgi Eliava

Felix d'Herelle



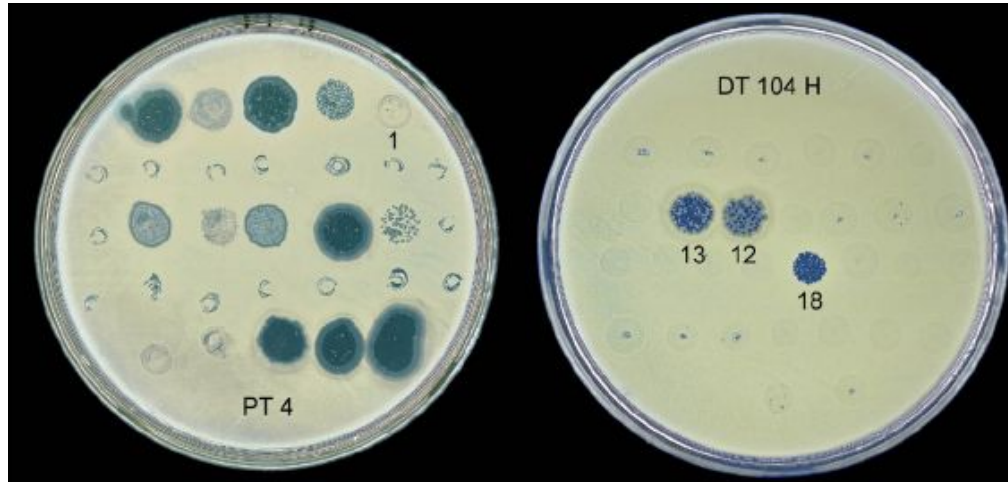
Anwendungen z.B. Diagnostik

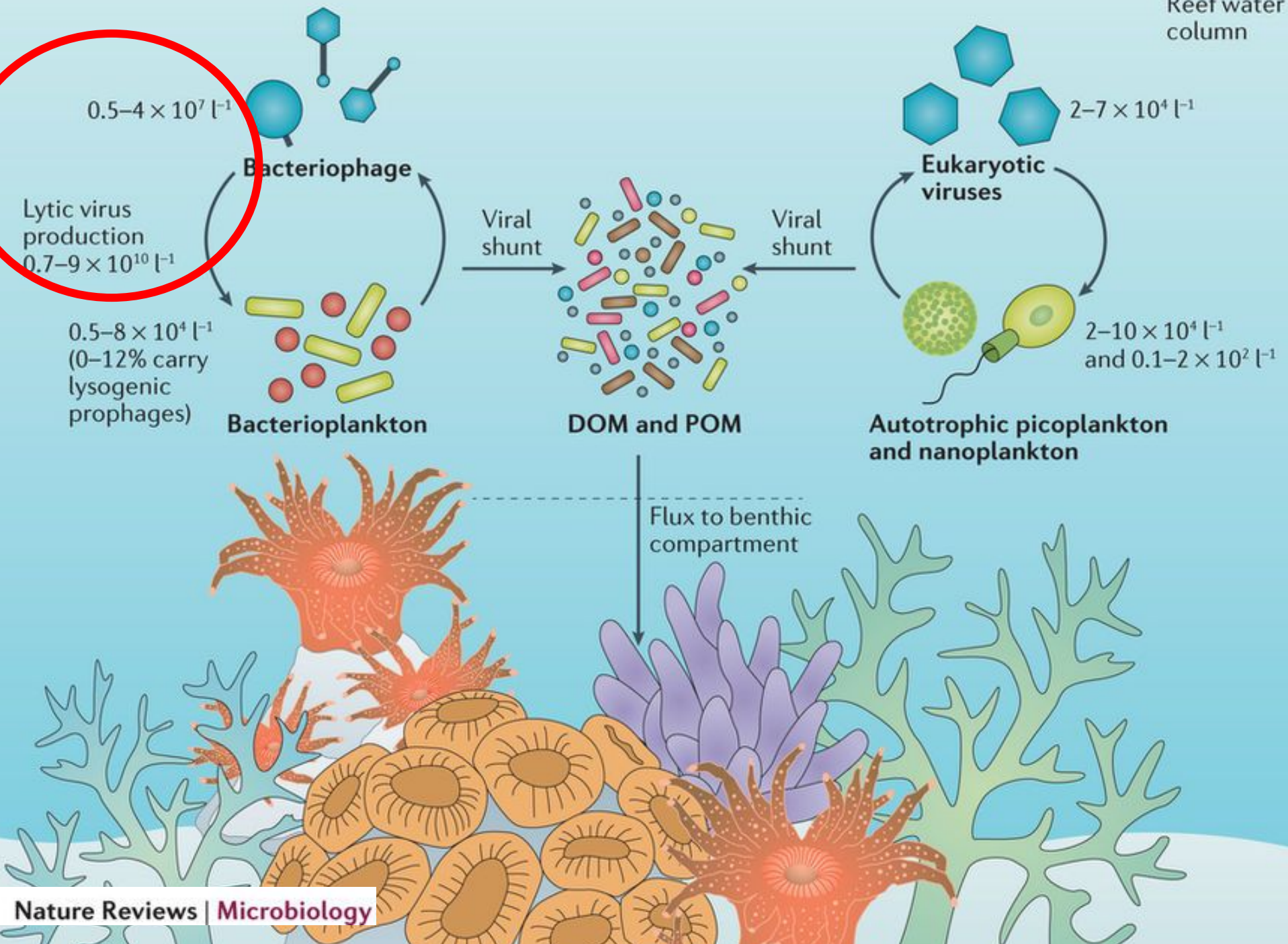
Molekularbiologie, Genetik

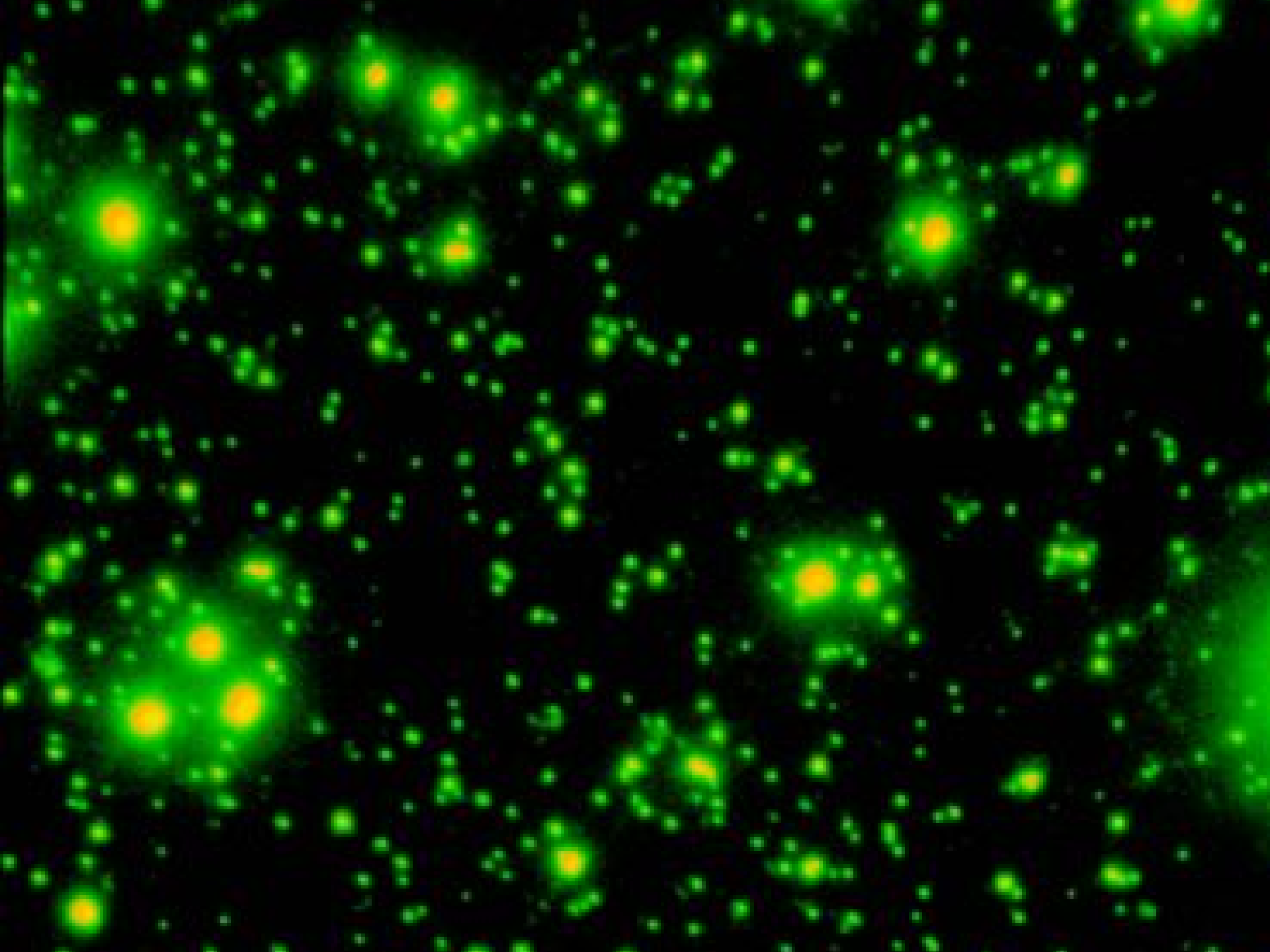


**Spezifität**

# Phagentypisierung von Bakterien

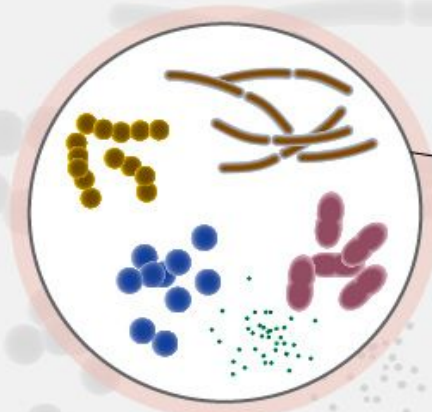






# Human microbiome

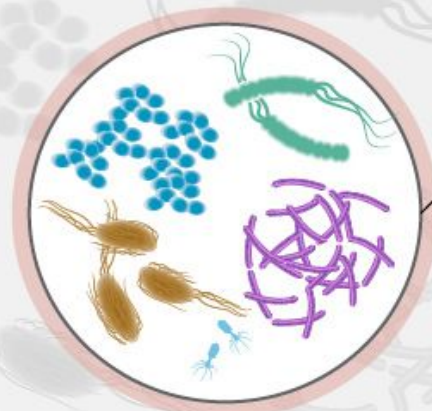
Archaea, bacteria, fungi and viruses



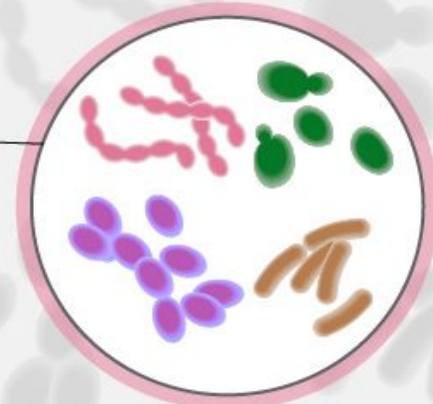
Mouth



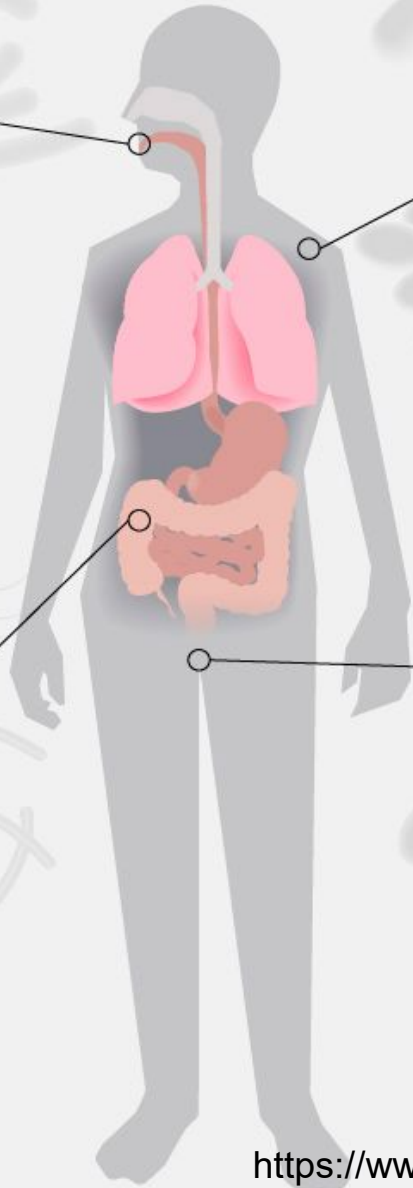
Skin



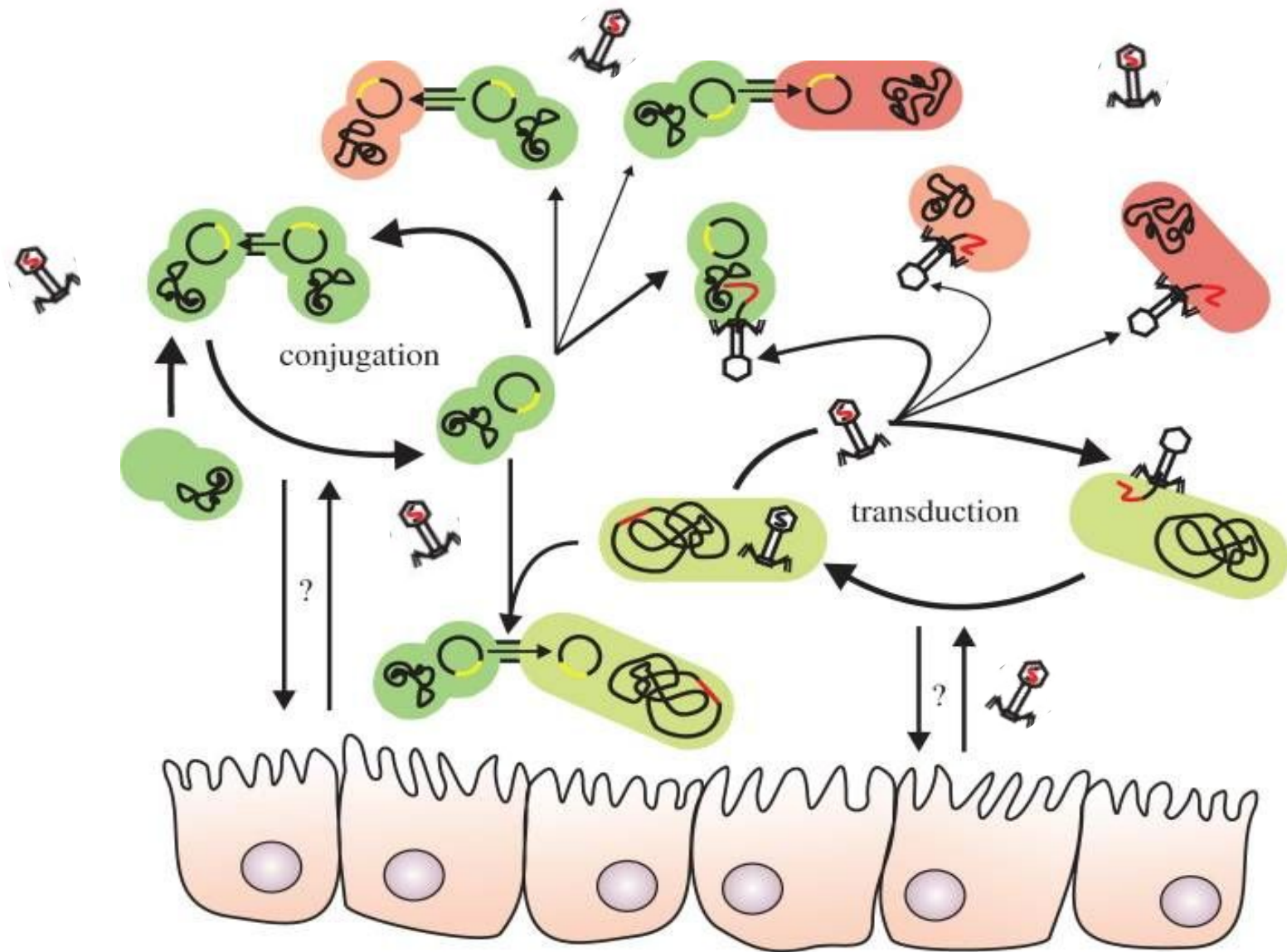
Digestive



Urogenital

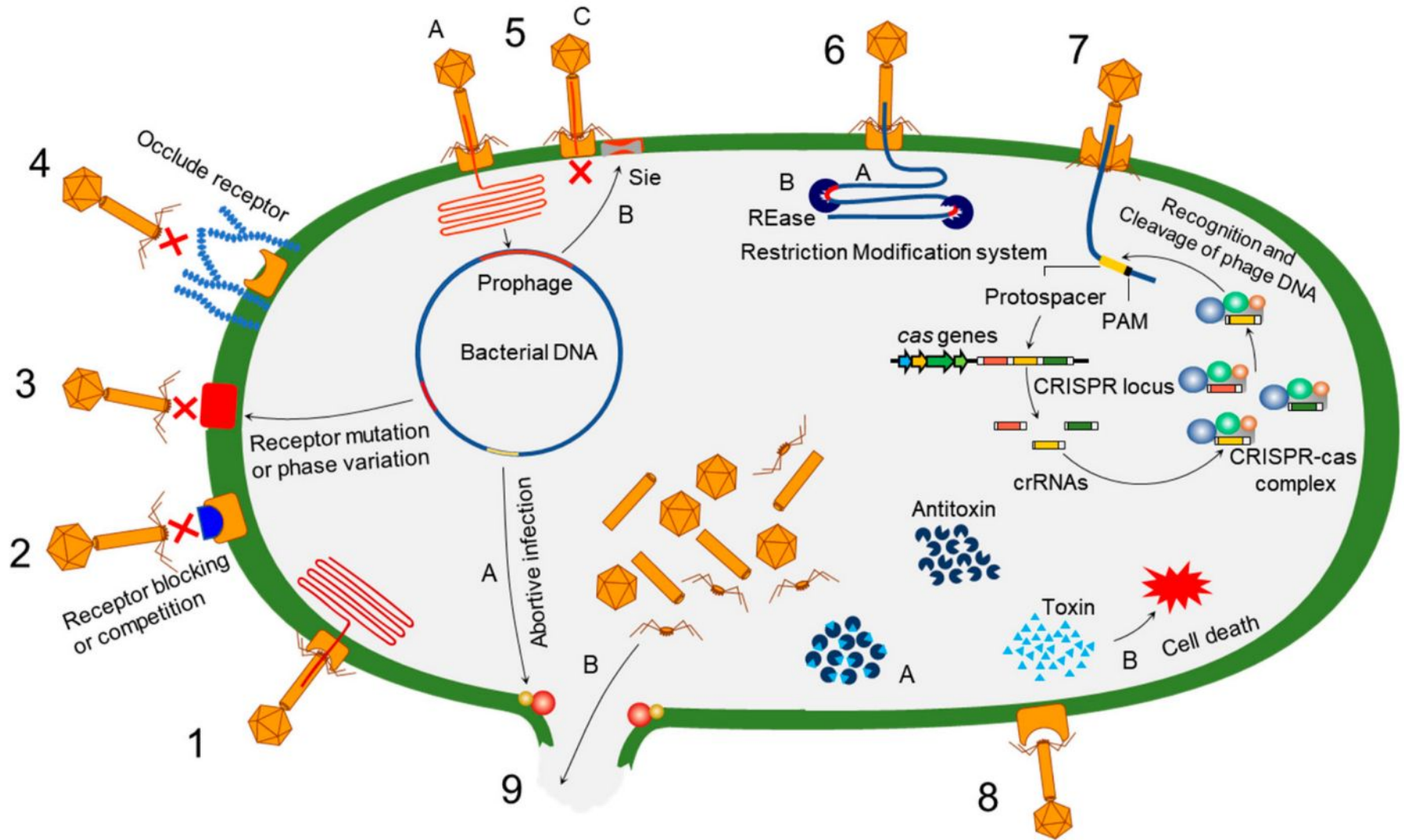


# Mikrobielle Evolution



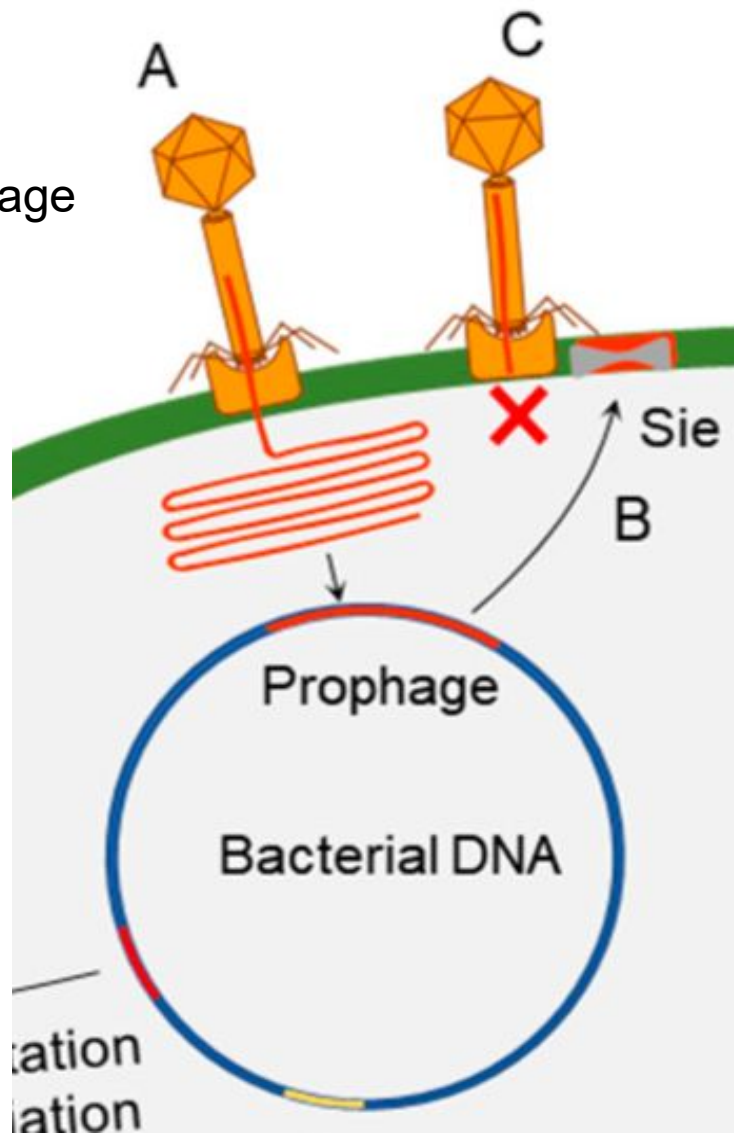


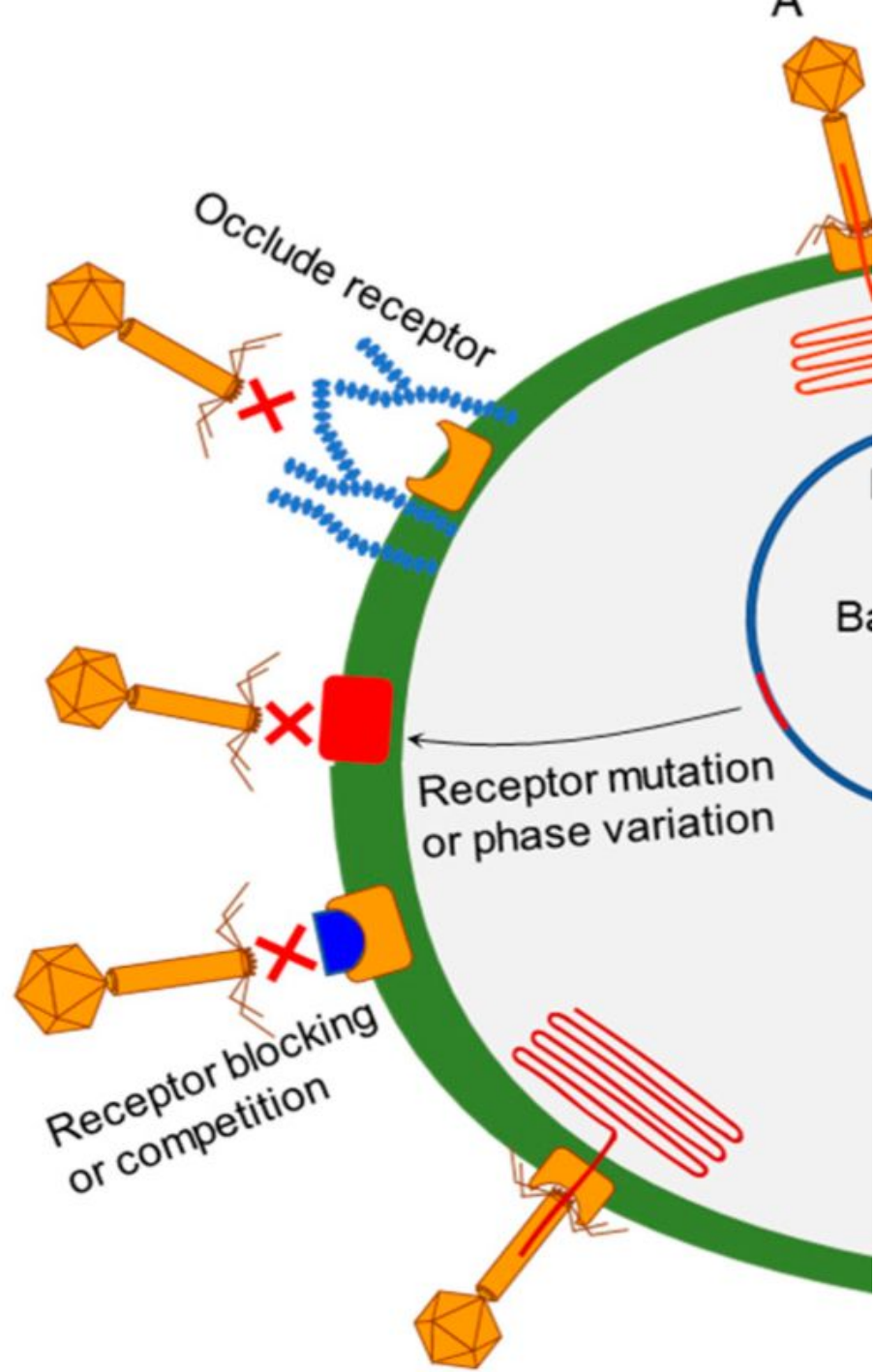
# Bakterielle Abwehrmechanismen

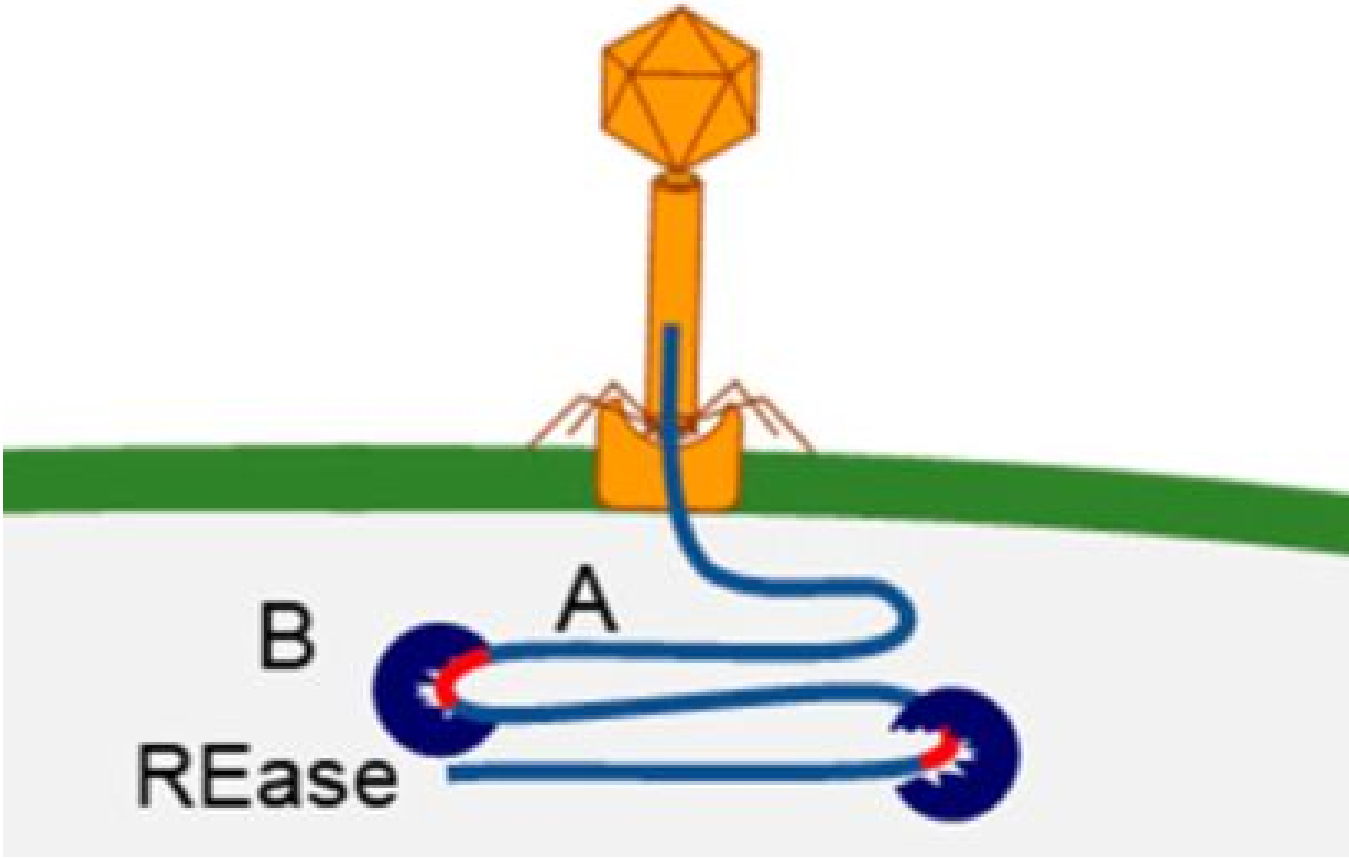


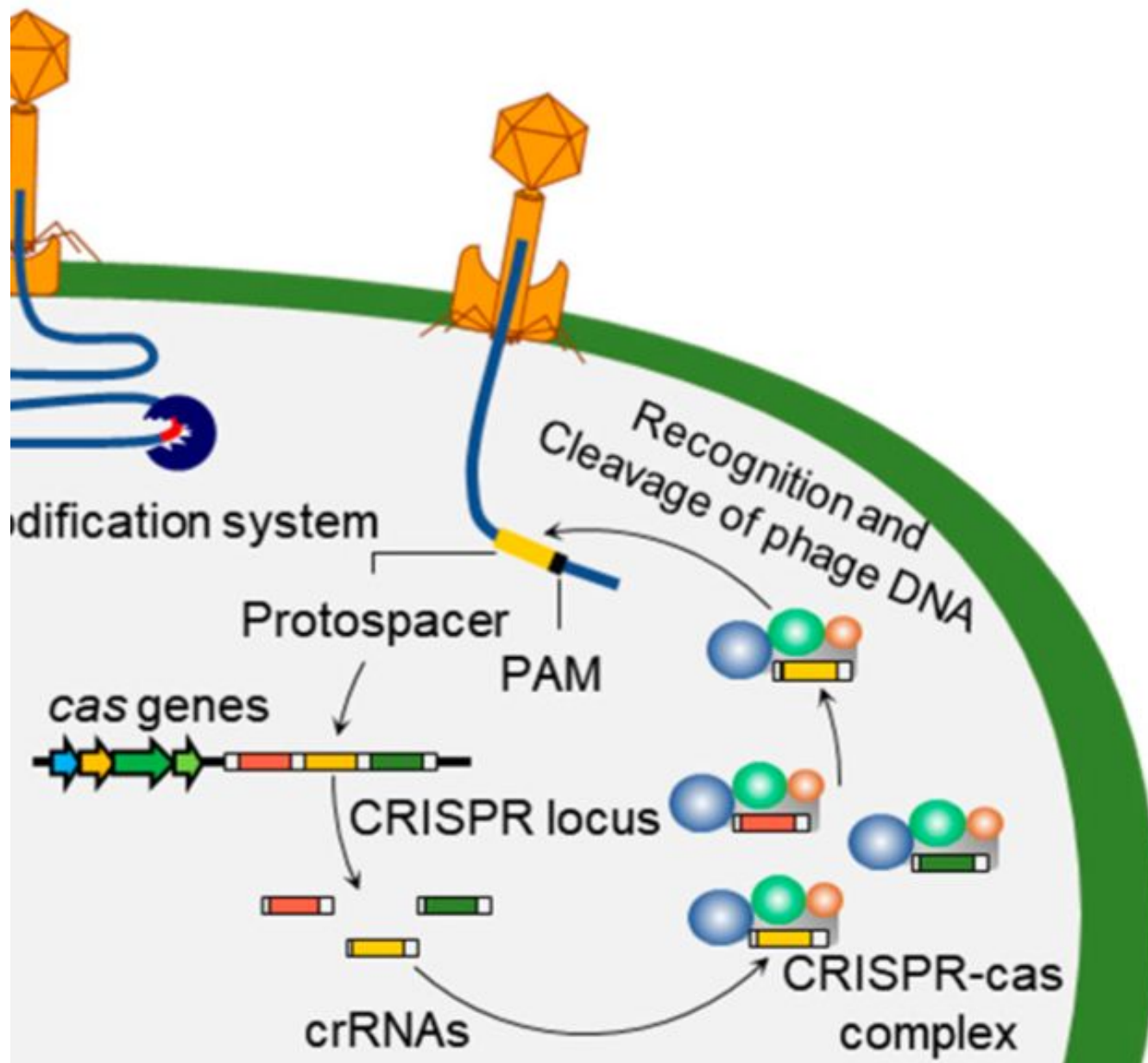
# Lysogenie

Temperenter Phage

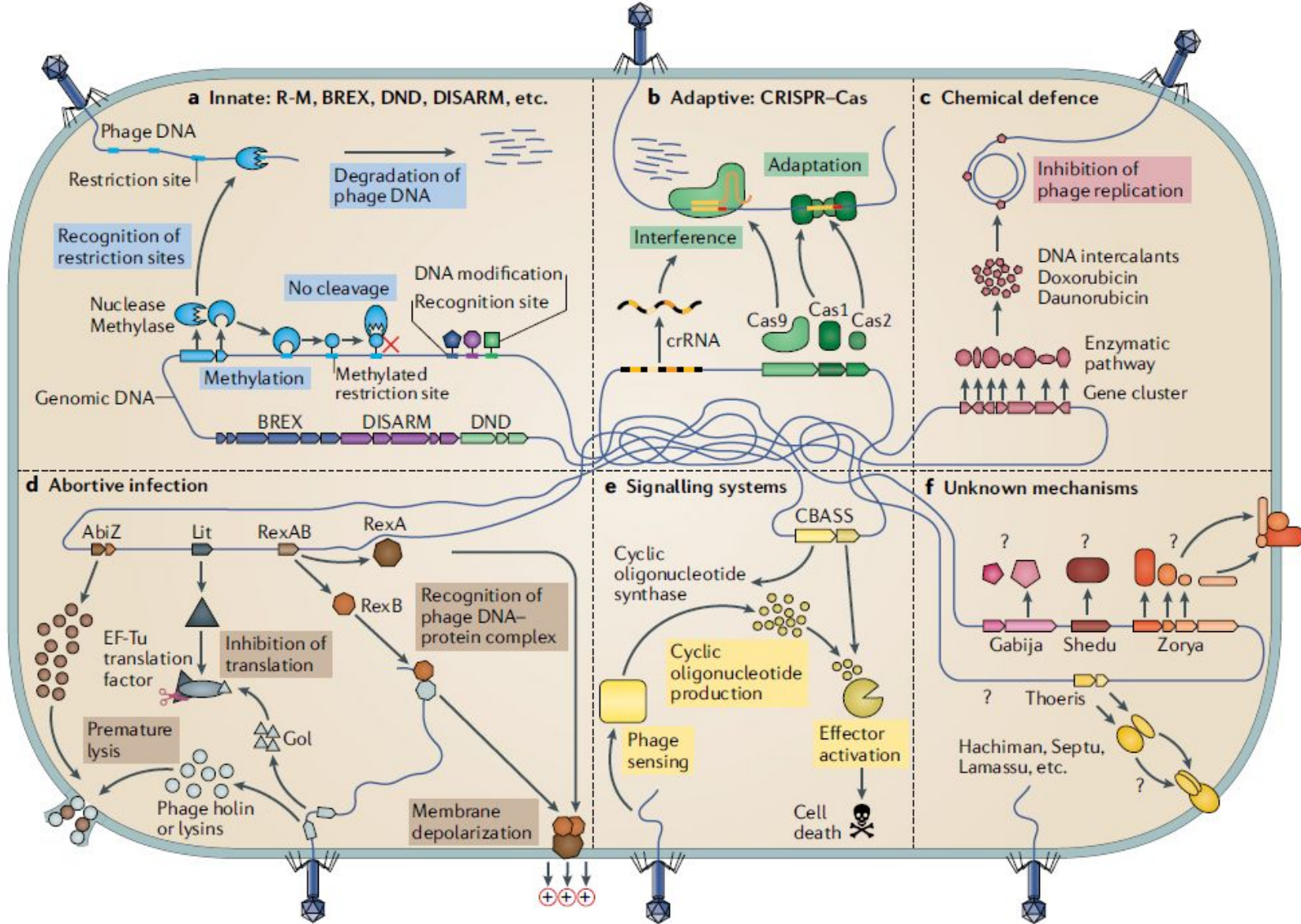




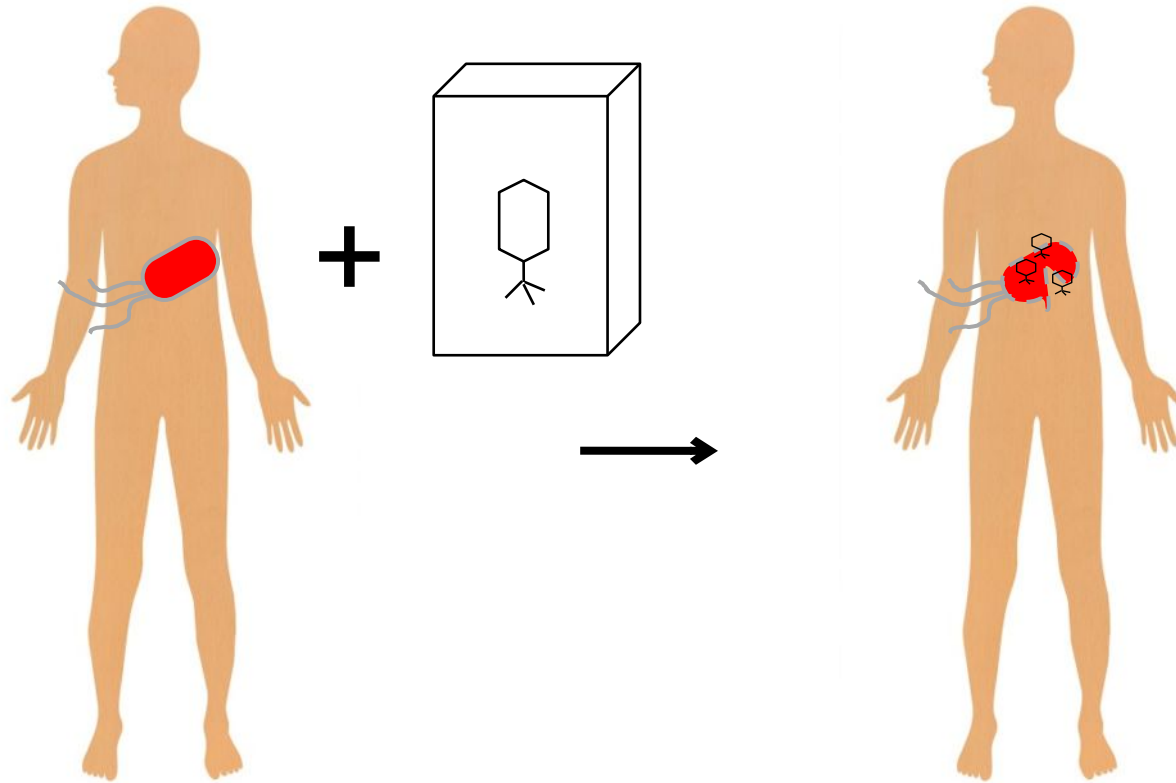




# ... viele neue bakterielle Immunmechanismen und Phagenausweichstrategien

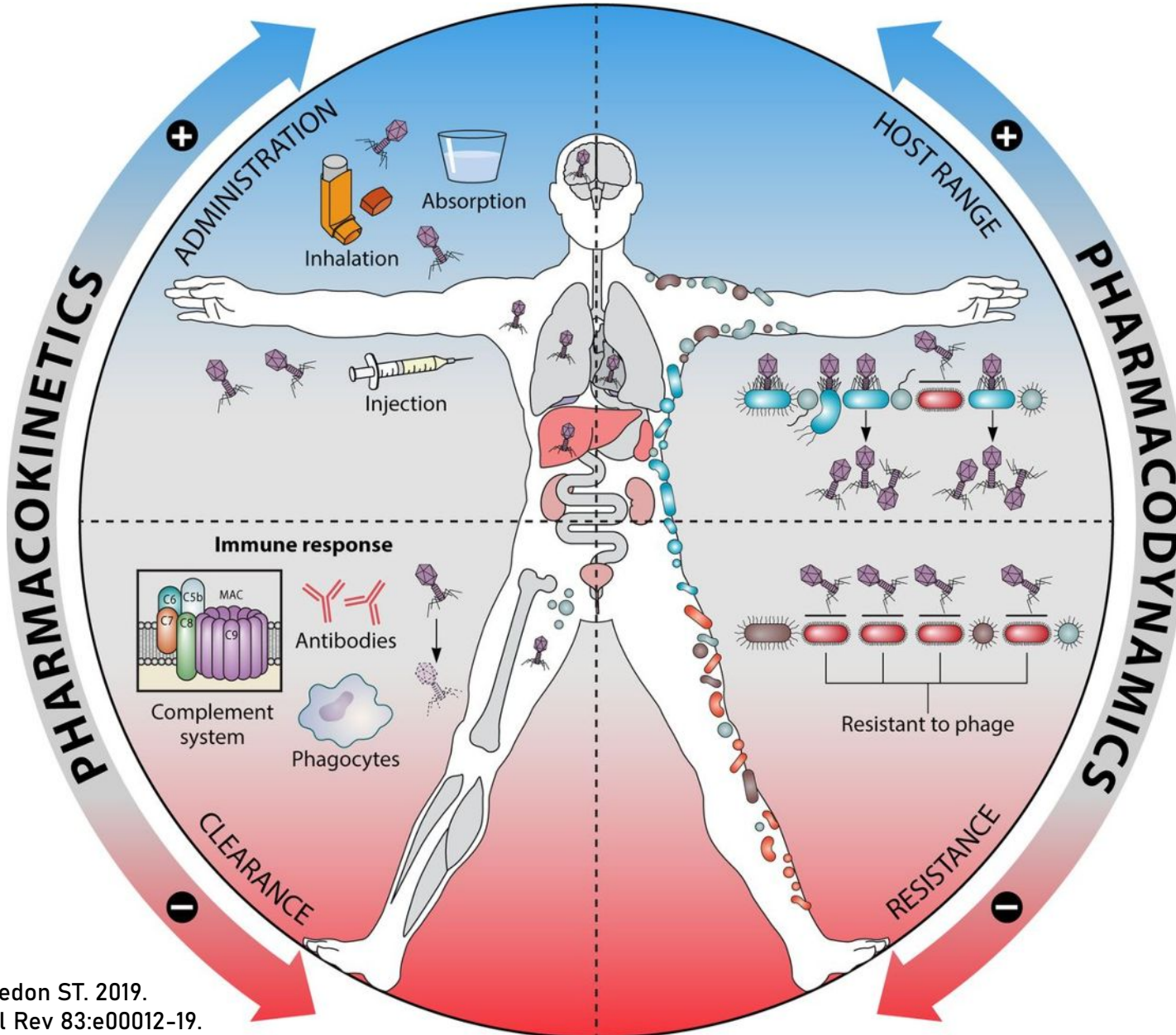


# Phagentherapie



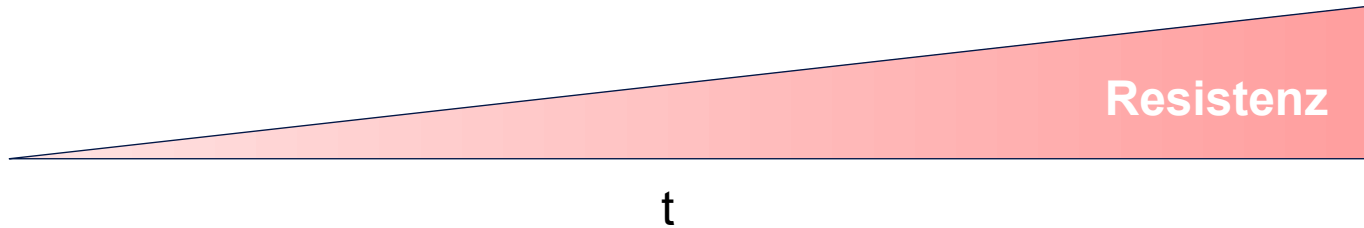
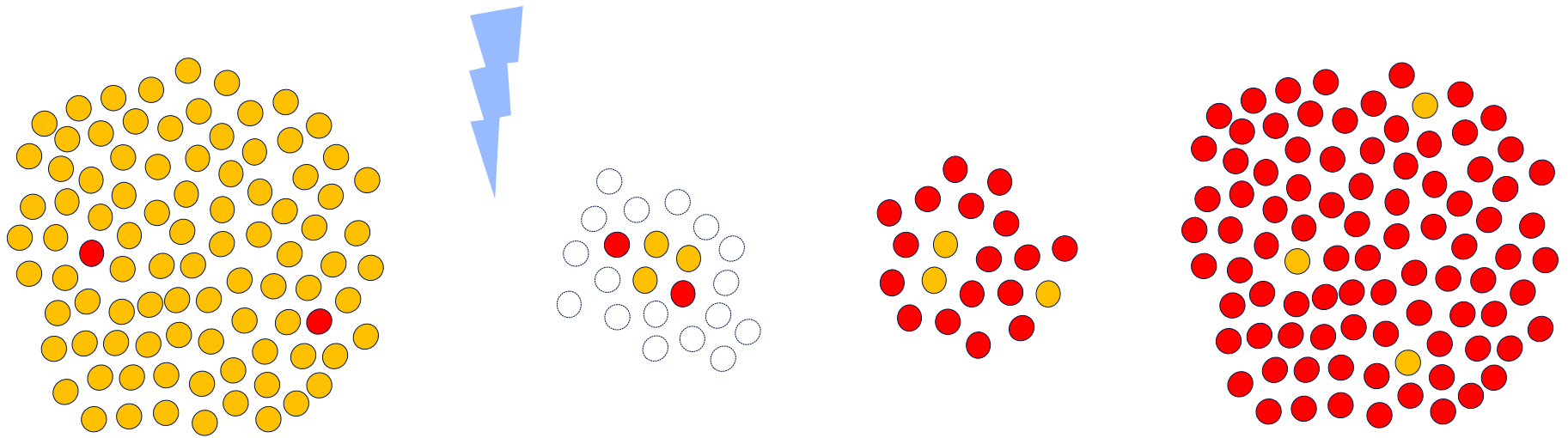
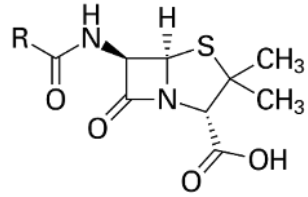
wirksam und sicher ?

# Phagentherapie - Wirksamkeit

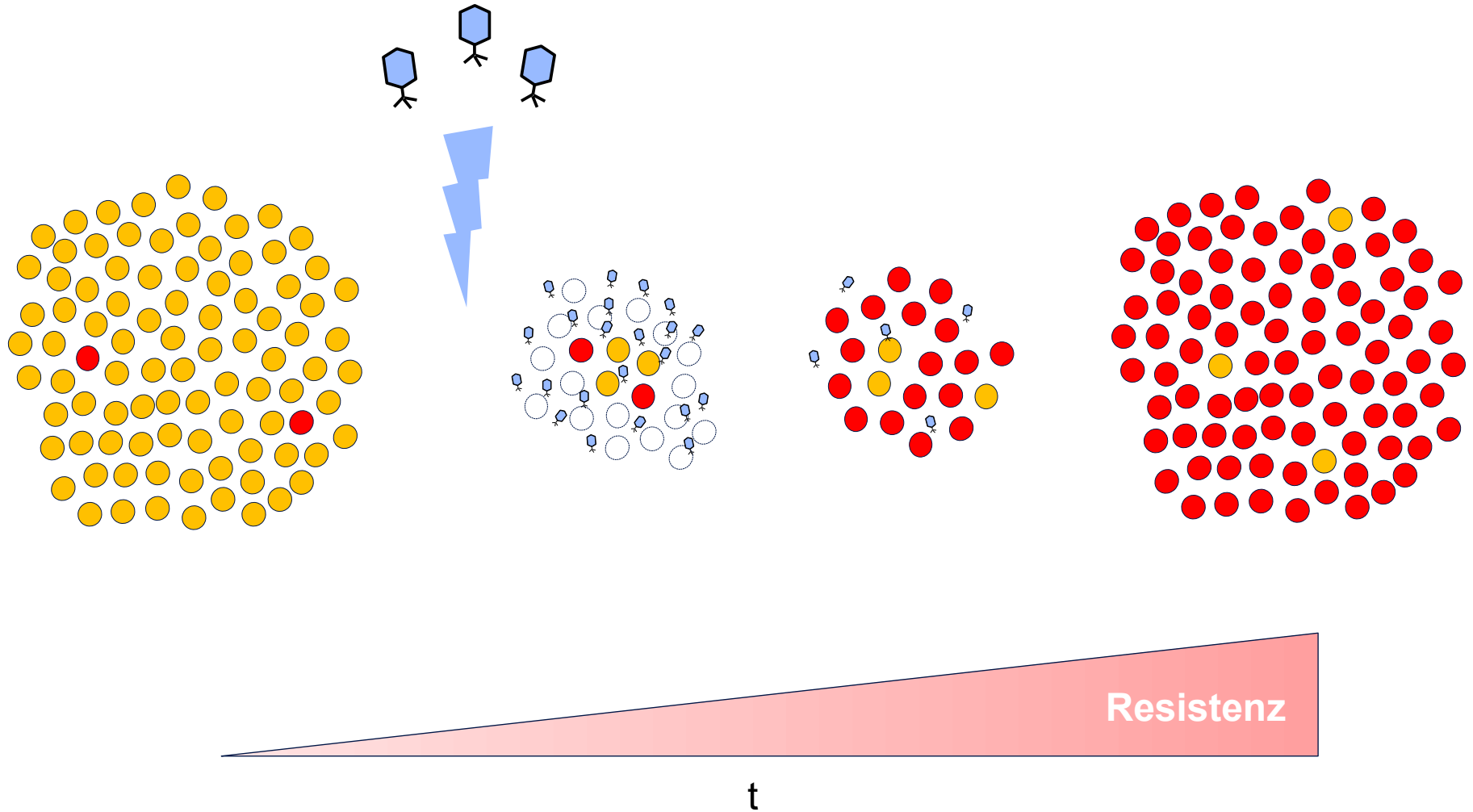




# Bakterielle Resistenzentwicklung

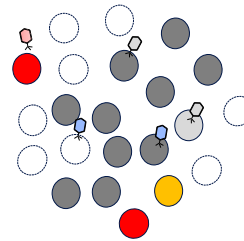
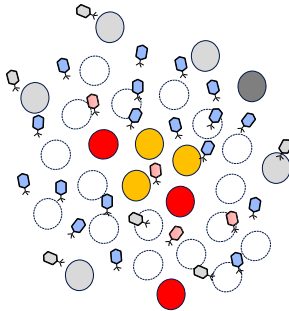
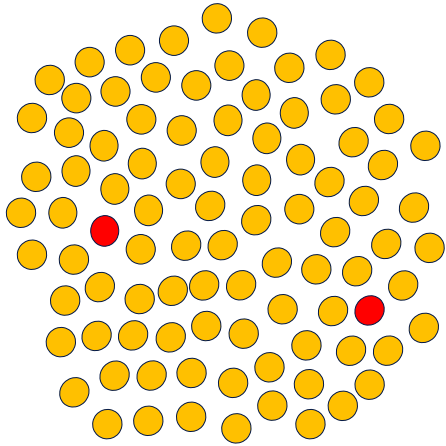
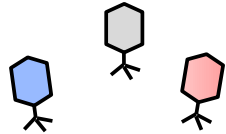


# Bakterielle Resistenzentwicklung



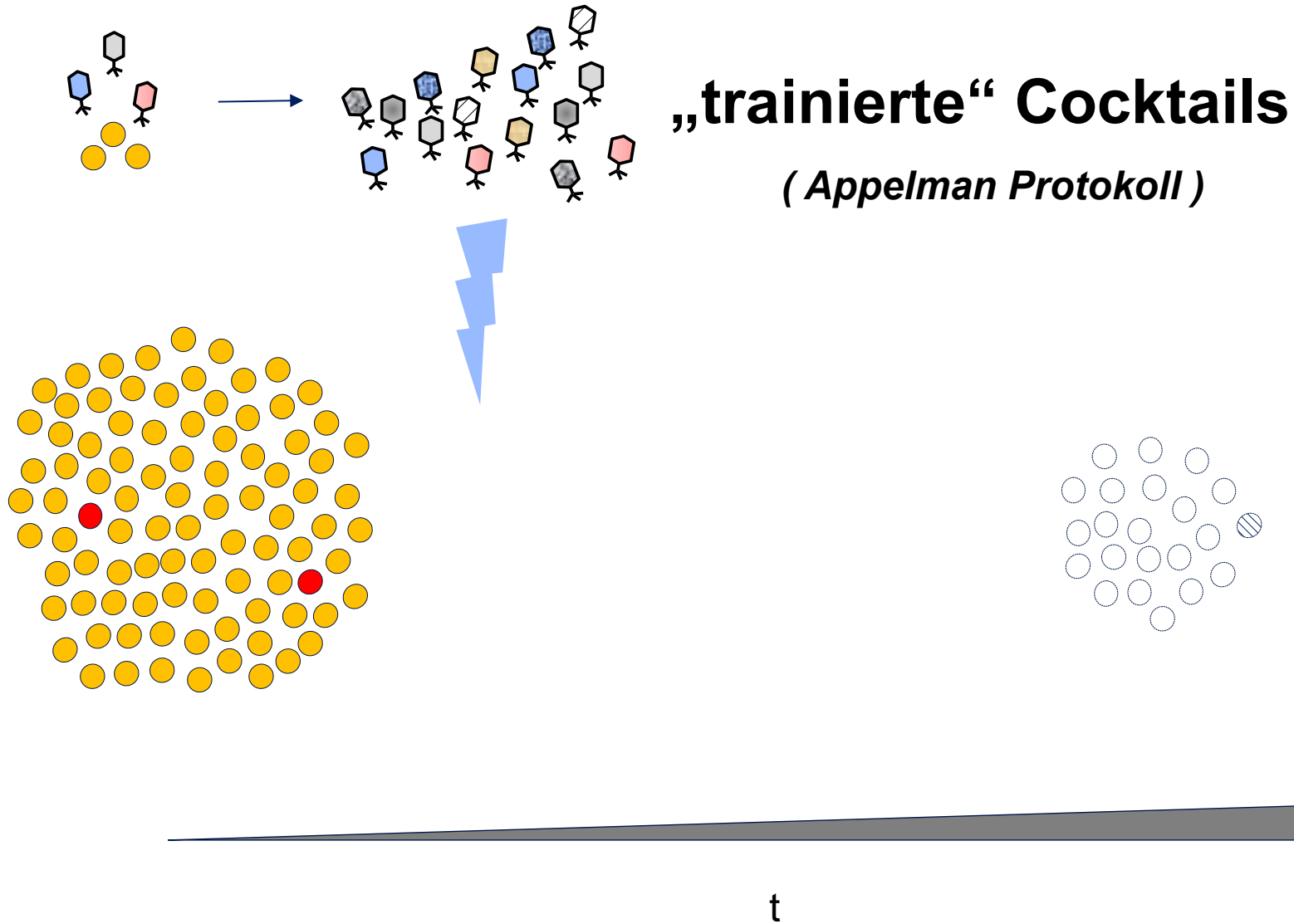
# Bakterielle Resistenzentwicklung

Cocktail



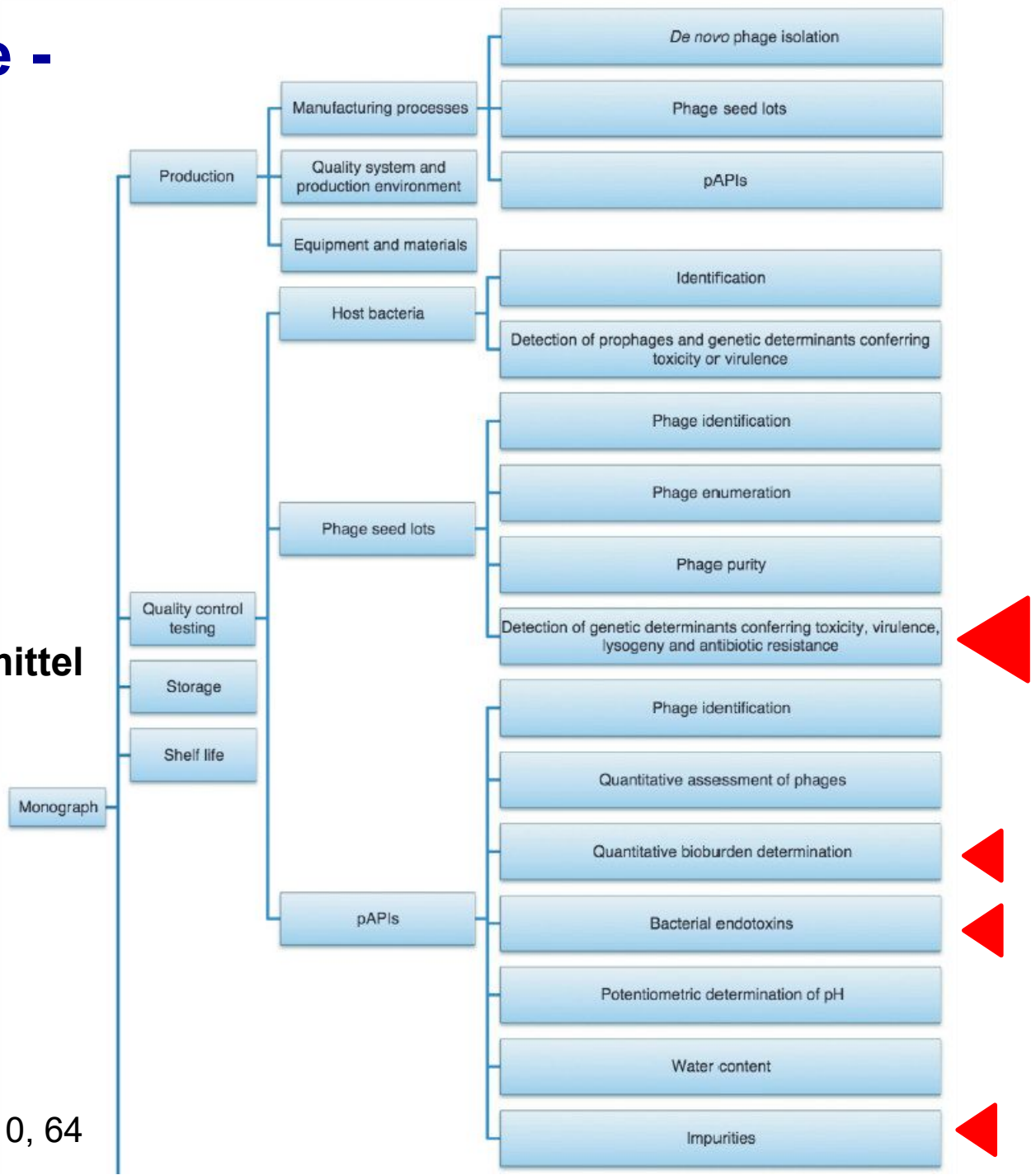
t

# Bakterielle Resistenzentwicklung

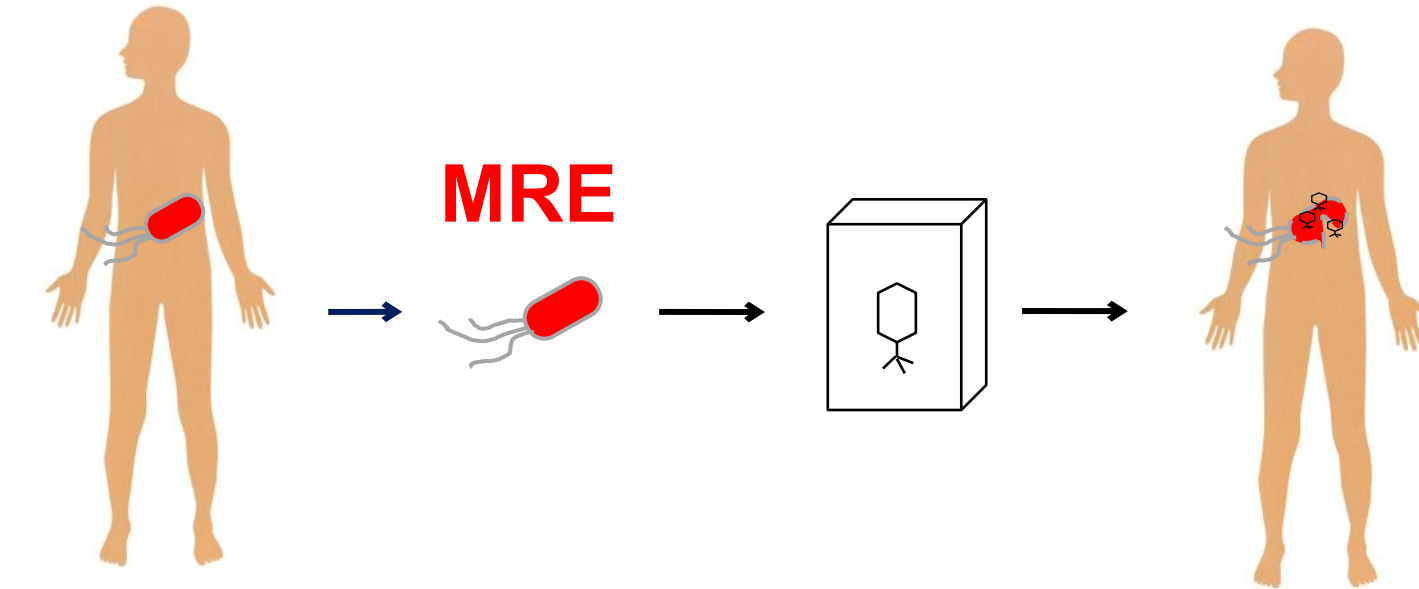


# Phagentherapie - Sicherheit

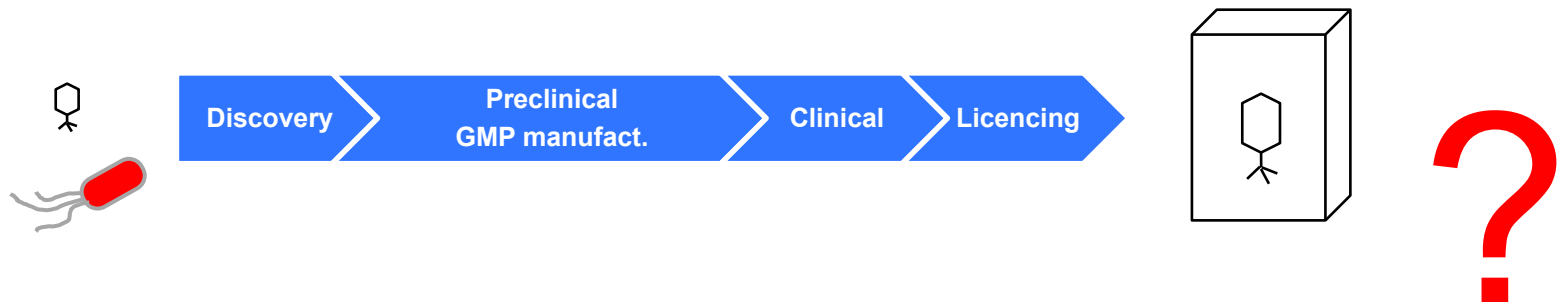
## BE – Monographie für Phagen-Rezepturarzneimittel



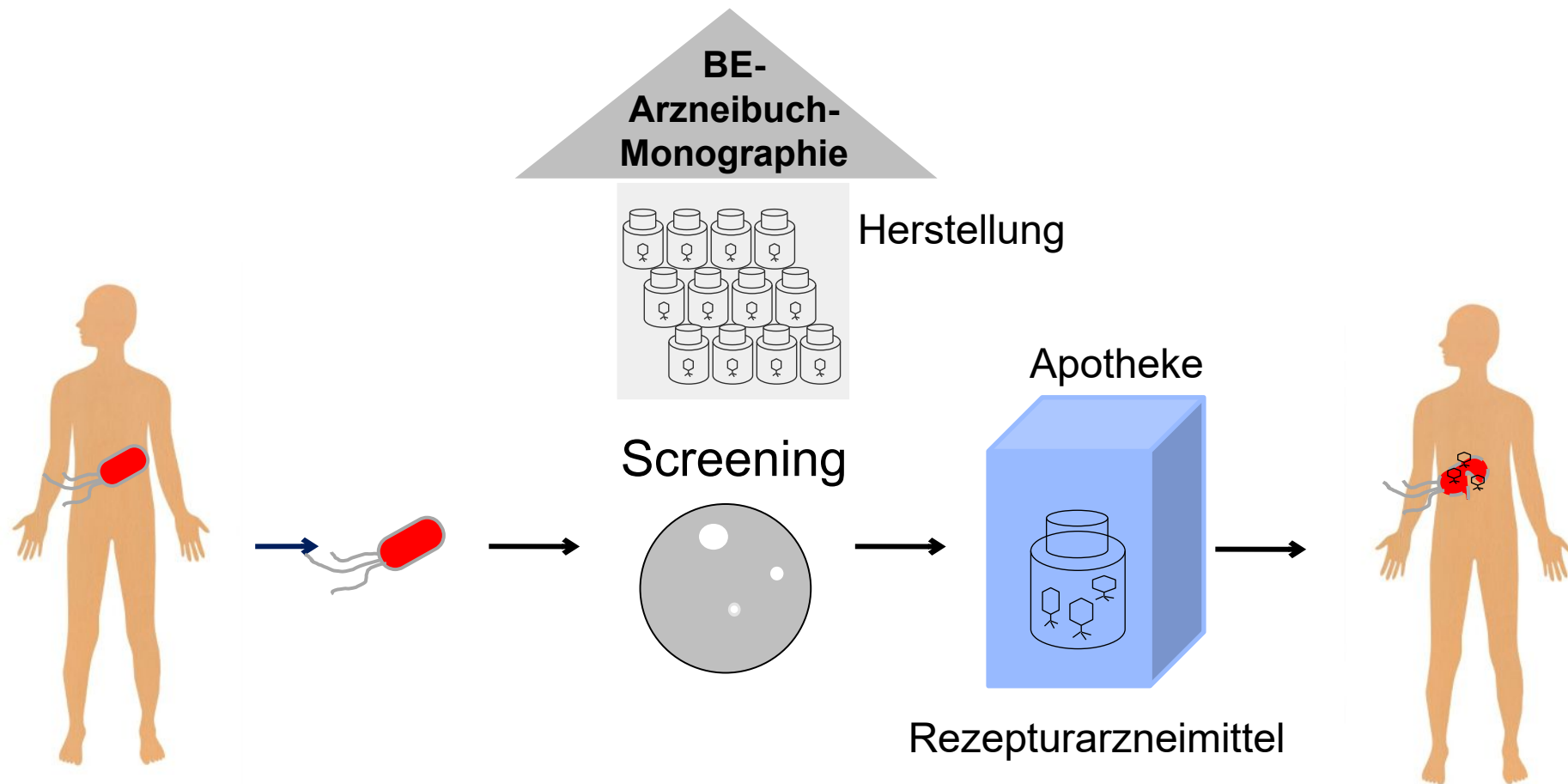
# Phagentherapie



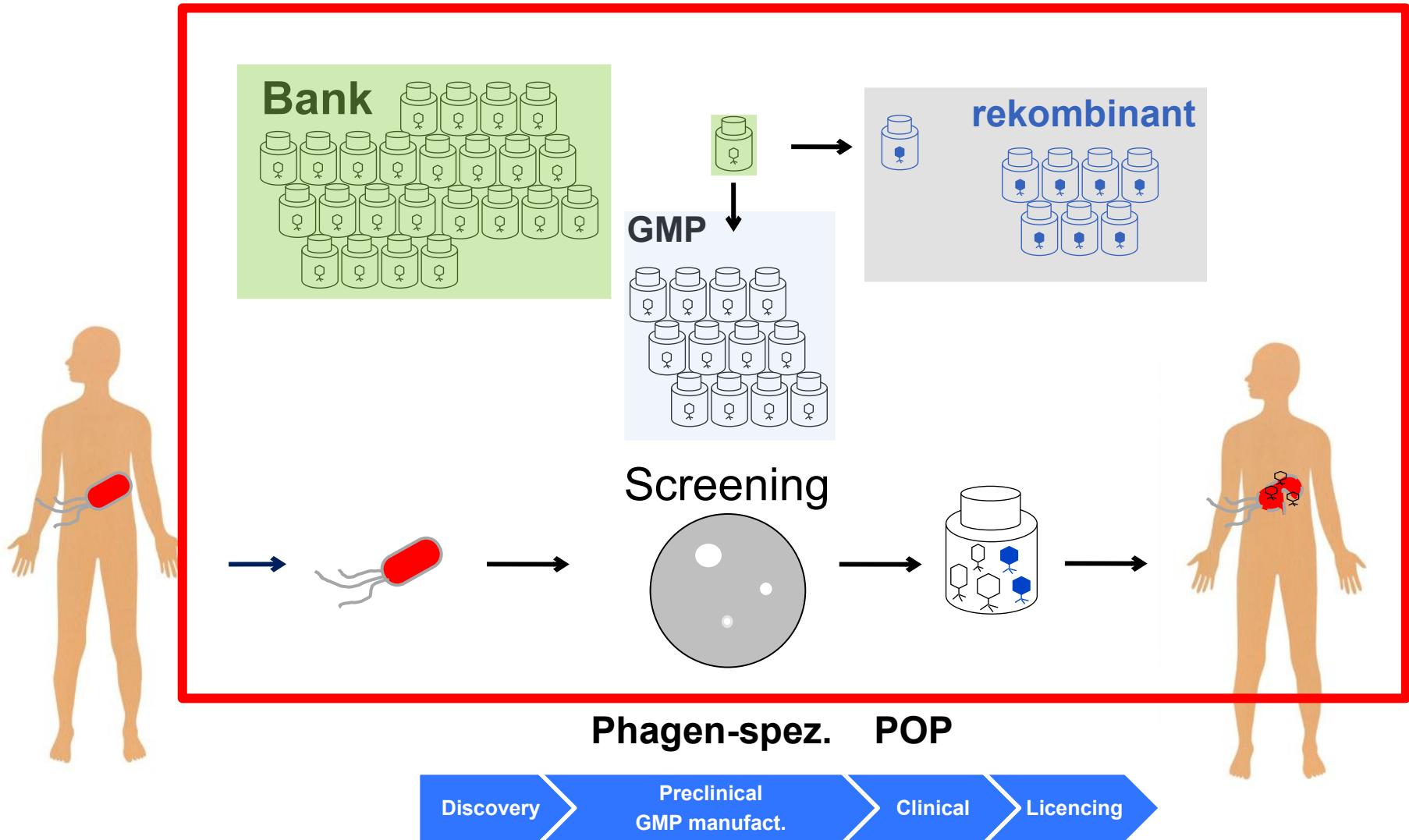
## Fertigarzneimittel



# Personalisierte Phagen-AM (Belgien)



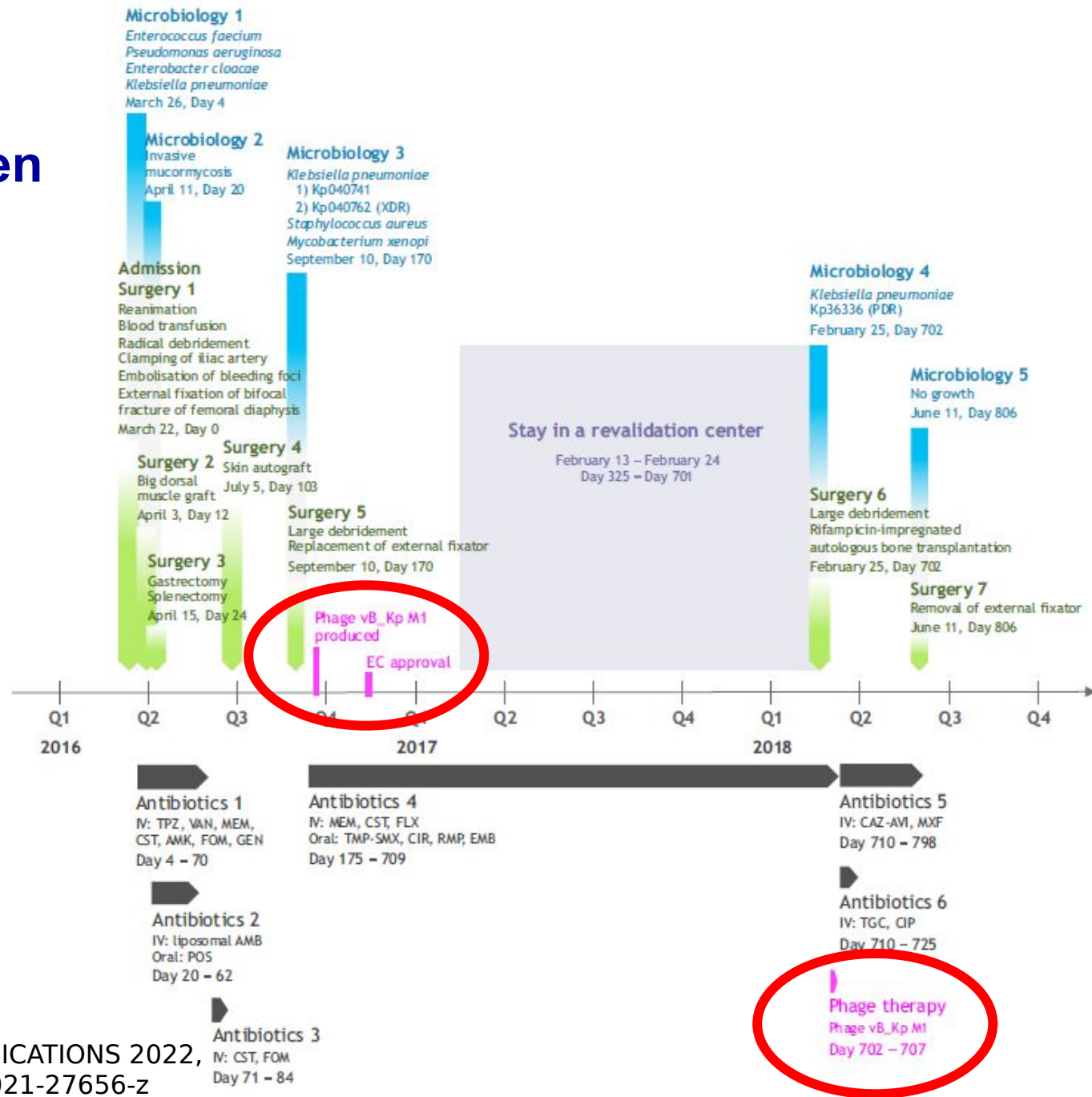
# Plattform für personalisierte Phagentherapie



**Plattform**



# Phagentherapie - last resort in MRE-Infektionen



## Safety and efficacy of phage therapy in difficult-to-treat infections: a systematic review



Saartje Uyttebroek, Baixing Chen, Jolien Onsea, Fred Ruythooren, Yves Debaveye, David Devolder, Isabel Spriet, Melissa Depypere, Jeroen Wagemans, Rob Lavigne, Jean-Paul Pirnay, Maya Merabishvili, Paul De Munter, Willy E Peetermans, Lieven Dupont, Laura Van Gerven, Willem-Jan Metsemakers

According to the latest reports from WHO, the incidence of antibiotic-resistant bacterial infections is increasing worldwide, resulting in increased morbidity and mortality and a rising pressure on health-care systems. However, the development of new antibiotics is an expensive and time-consuming process, urging scientists to seek alternative antimicrobial strategies. Over the past few decades, the concept of therapeutic administration of bacteriophages (also known as phages) has gained popularity worldwide. Although conceptually promising, the widespread implementation of phage therapy in routine clinical practice is restricted by the scarcity of safety and efficacy data obtained according to the strict standards of the applicable clinical trial regulations. In this systematic review, we list clinical data published between Jan 1, 2000 and Aug 14, 2021 on the safety and efficacy of phage therapy for difficult-to-treat bacterial infections, and provide an overview of trials and case studies on the use of phage therapy in several medical disciplines.

*Lancet Infect Dis* 2022; 22: e208-20

Published Online  
March 3, 2022  
[https://doi.org/10.1016/S1473-3099\(21\)00612-5](https://doi.org/10.1016/S1473-3099(21)00612-5)

Department of  
Otorhinolaryngology  
(S Uyttebroek MD,  
Prof L Van Gerven MD),  
Department of Trauma Surgery  
(B Chen MD, J Onsea PhD,  
E Ruythooren MD)

Uyttebroek et al., *Lancet Infect Dis*. 2022 Aug;22(8):e208-e220.

## Difficult-to-treat infections

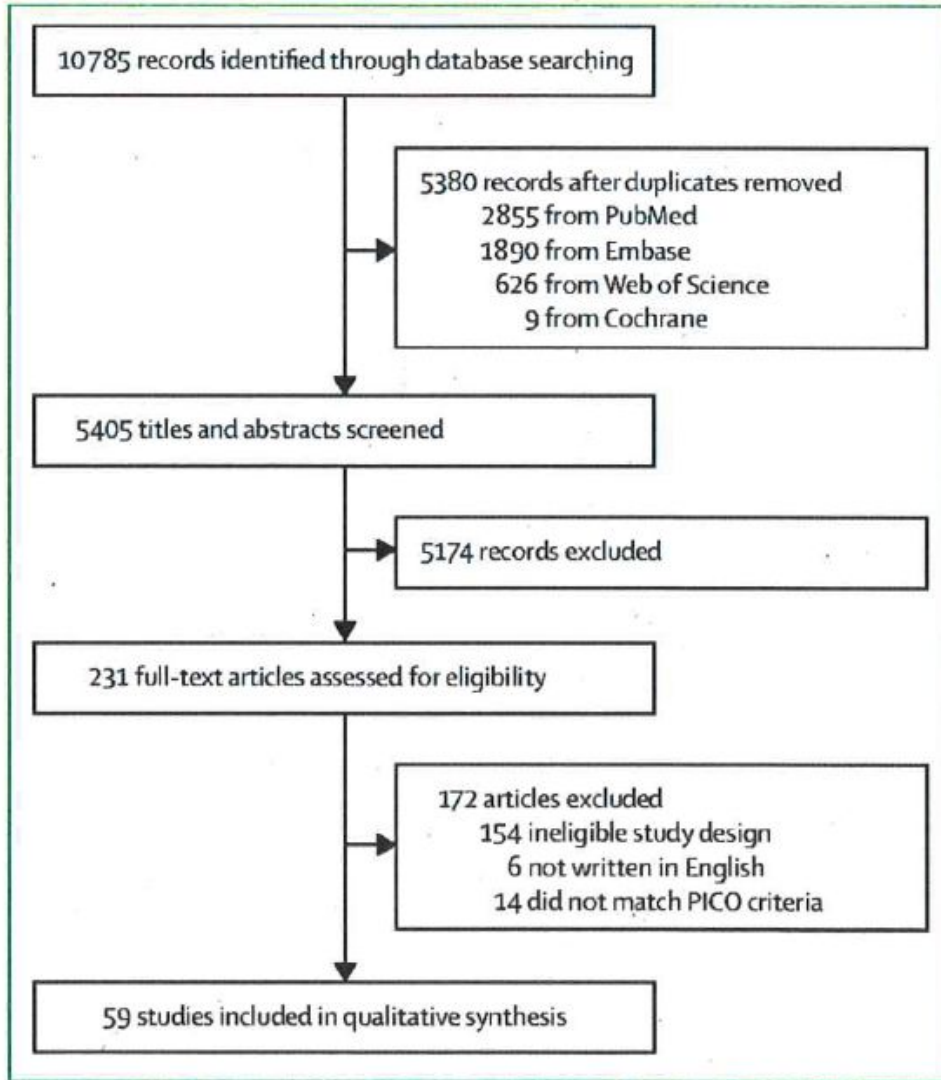


Figure: Study selection

### Panel: Inclusion criteria, based on a predefined population, intervention, comparator, outcome model

- Population: difficult-to-treat infections, with or without antimicrobial resistance, in which all previous standard-of-care (antibacterial, surgical, or both) treatments were not successful
- Intervention: application of phages
- Comparator: antibiotic regimens, other standard-of-care treatments, or placebo
- Outcome:
  - Safety: tolerability, short-term and long-term adverse events, and aberrant blood values, attributed to phage therapy
  - Efficacy: subjective or objective clinical improvement, or both; improvement in quality of life, reduction in bacterial load, and reduction in biofilm mass
- Study design: randomised controlled trial, observational studies, cohort studies, case series, or case reports
- Other criteria: English language; published between Jan 1, 2000 and Aug 14, 2021

## **Wirksamkeit**

**(klin. Erholung, bakt. Eradikation)**

Personalisierte Präparate

Cocktail

Stabilität

Dosis, Behandlungsdauer

## **Sicherheit**

**(Nebenwirkungen)**

Standardisierte Herstellung

Pharmazeutische Qualität

Ausschluss anhand Genomsequenz:

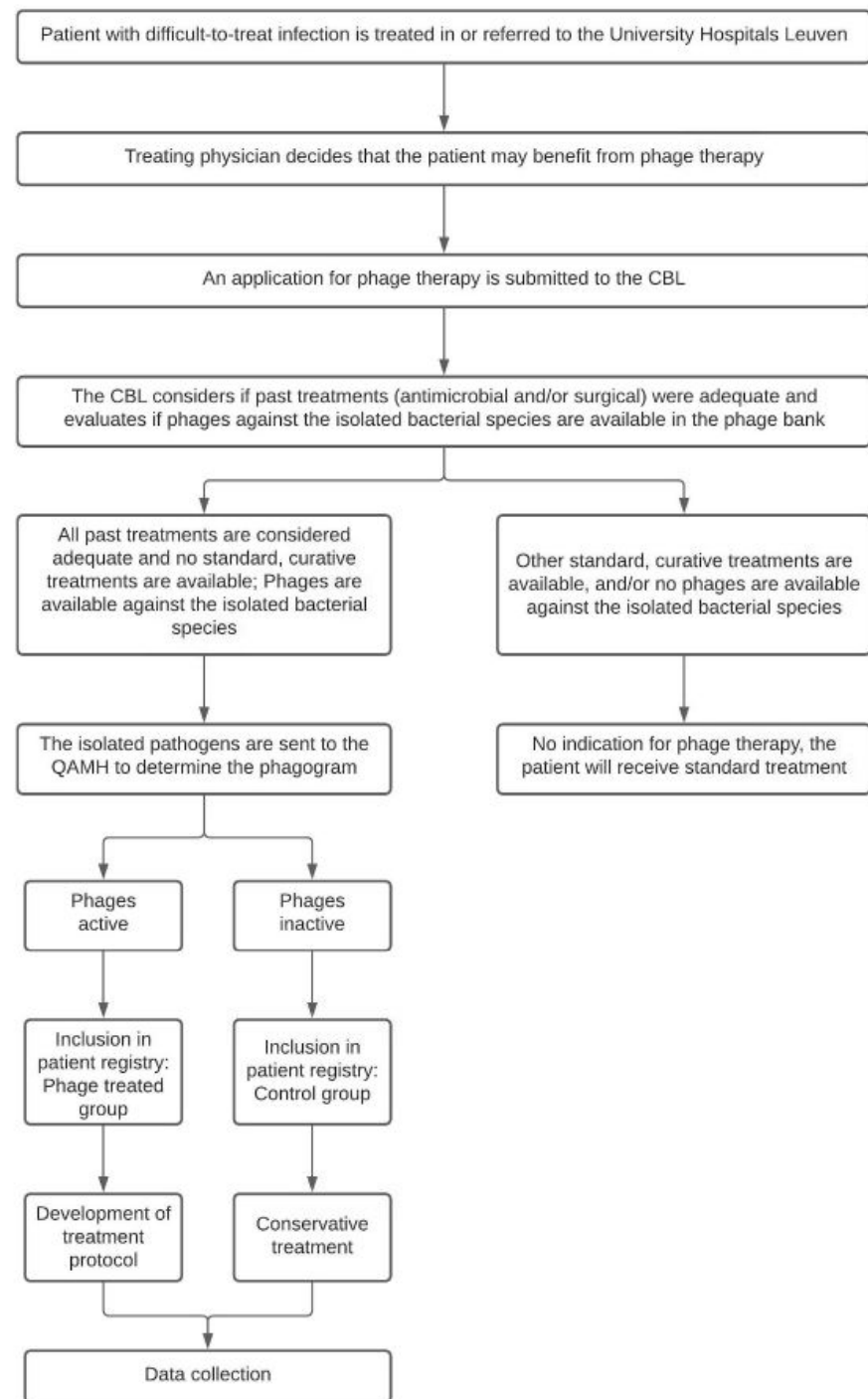
Phagen mit Lygenie-Modulen

Phagen mit AMR-/Virulenz-/Toxin-Genen

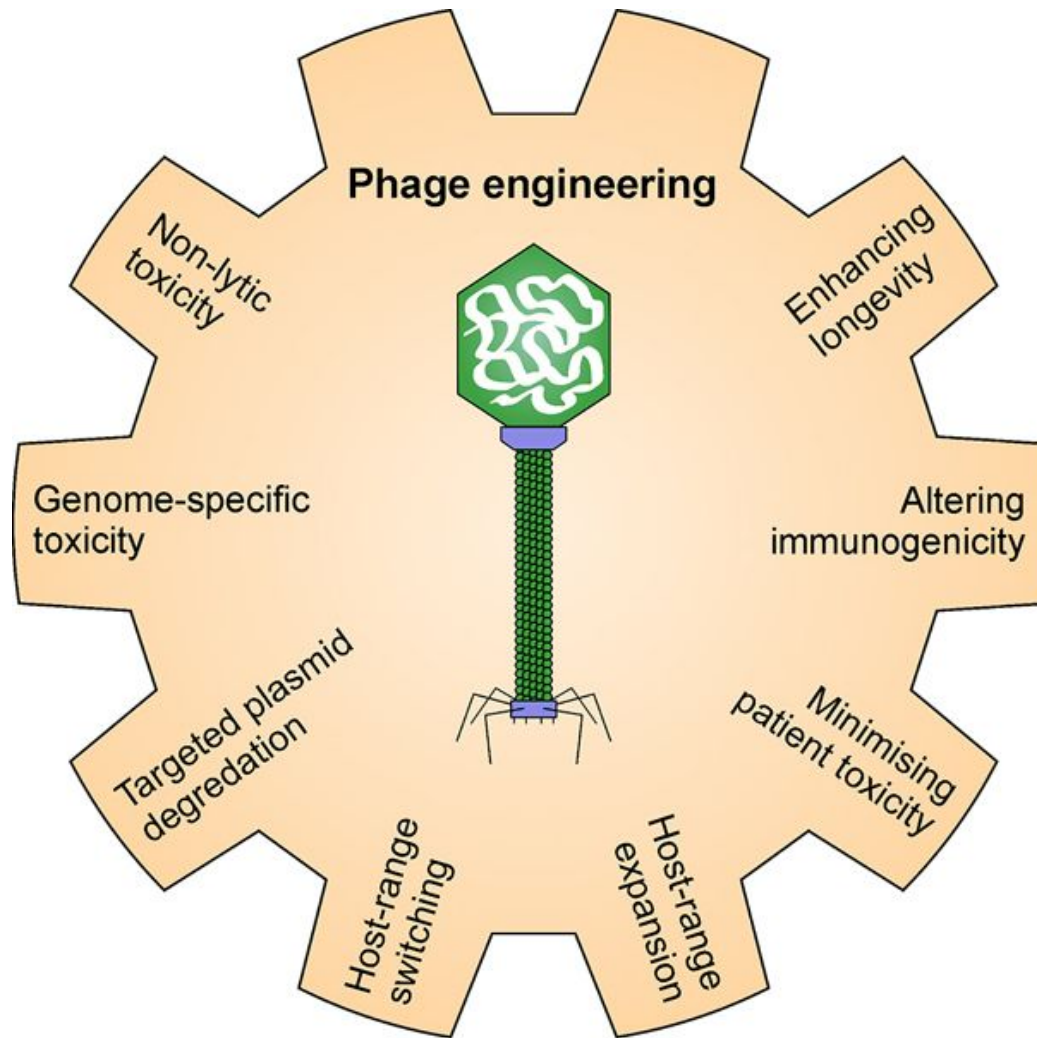
# Studiendesign für Personalisierte Therapie

## *PHAGEFORCE*

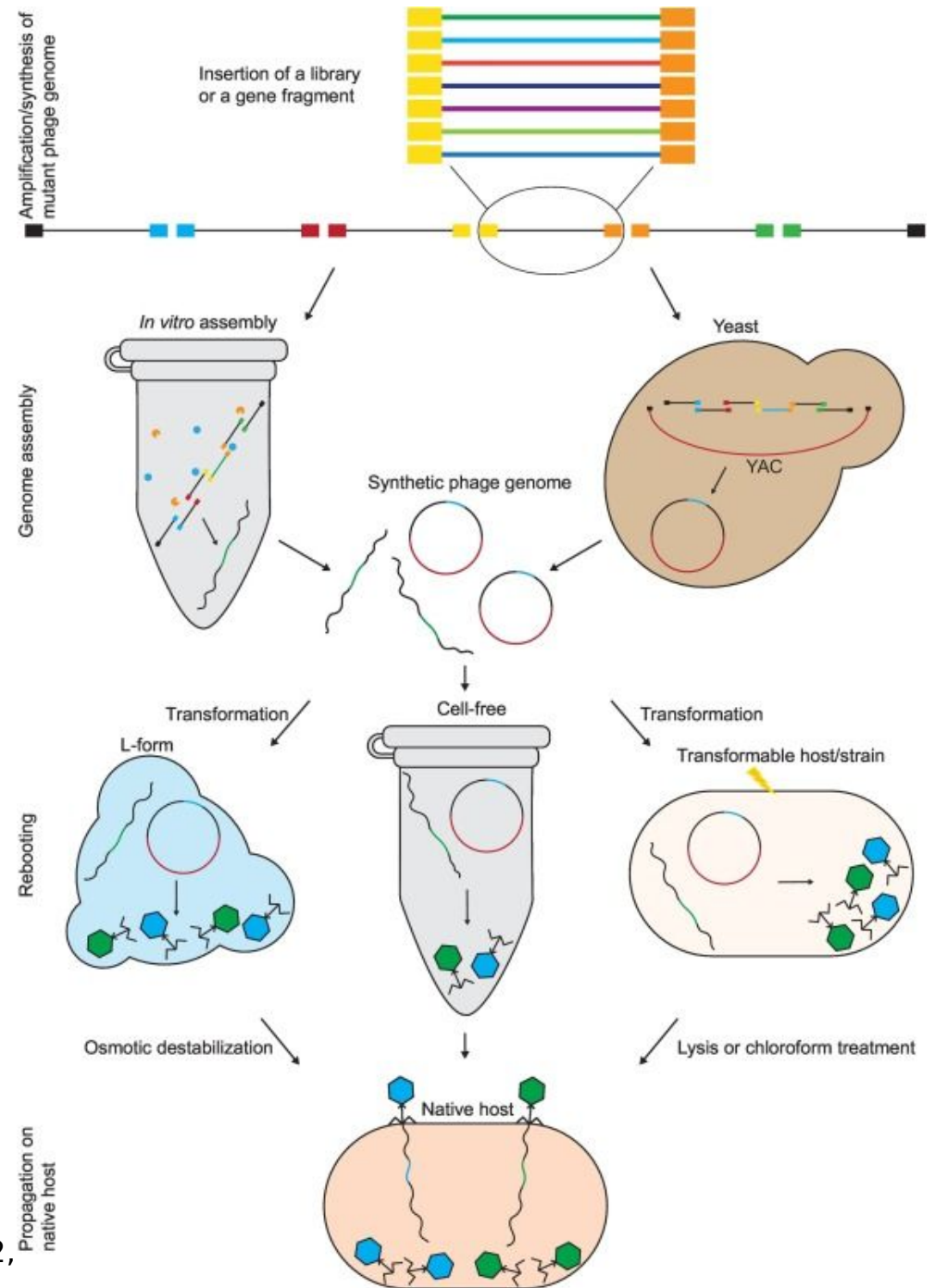
Onsea et al., Viruses 2021, 13, 1543.  
<https://doi.org/10.3390/v13081543>

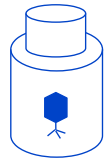
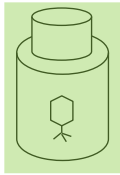


# Genmodifizierte Phagen



# Synthetische Phagen







lysogener Phage

lytischer Phage

## Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*

Rebekah M. Dedrick<sup>1,4</sup>, Carlos A. Guerrero-Bustamante<sup>1,4</sup>, Rebecca A. Garland<sup>1</sup>, Daniel A. Russell<sup>1</sup>, Katrina Ford<sup>2</sup>, Kathryn Harris<sup>2</sup>, Kimberly C. Gilmour<sup>2</sup>, James Soothill<sup>2</sup>, Deborah Jacobs-Sera<sup>1</sup>, Robert T. Schooley<sup>3</sup>, Graham F. Hatfull <sup>1\*</sup> and Helen Spencer <sup>2\*</sup>

**A 15-year-old patient with cystic fibrosis with a disseminated *Mycobacterium abscessus* infection was treated with a three-phage cocktail following bilateral lung transplantation. Effective lytic phage derivatives that efficiently kill the infectious *M. abscessus* strain were developed by genome engineering and forward genetics. Intravenous phage treatment was well tolerated and associated with objective clinical improvement, including sternal wound closure, improved liver function, and substantial resolution of infected skin nodules.**

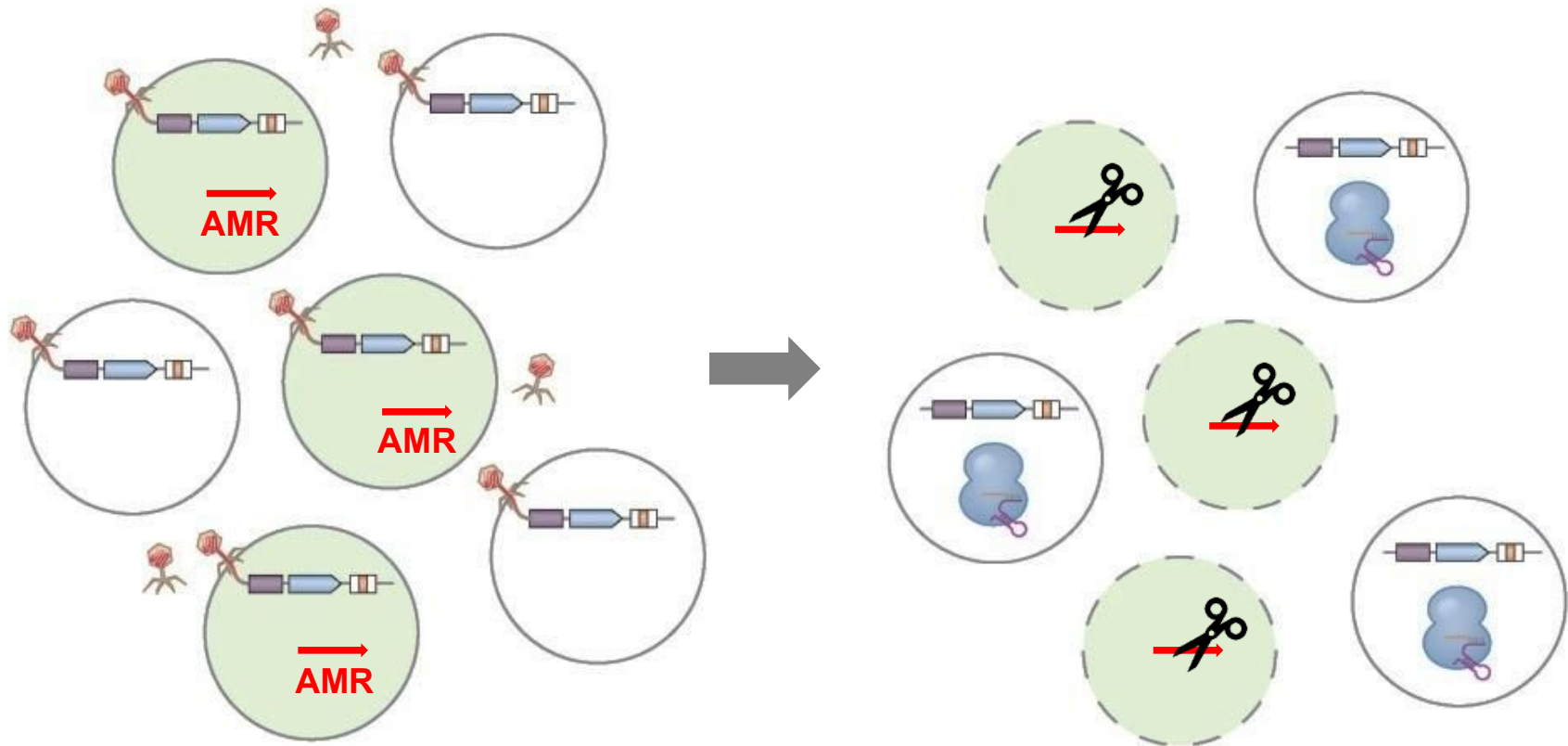
Mycobacterial infections impose a substantial global health

surgical incision. The chest X-ray showed consolidation, and *M. abscessus* grew from sputum (Supplementary Table 1). Clofazimine and bedaquiline were added and previous i.v. antibiotics were recommenced (Extended Data Fig. 1 and Supplementary Information). A positron-emission tomography (PET)-CT scan to evaluate ongoing abdominal pain, hepatomegaly, deranged liver function tests, and Epstein-Barr virus (EBV) viremia (11 million copies per ml) revealed fluorodeoxyglucose (FDG) activity in a 3.5 cm × 4 cm porta hepatis lesion and a destructive process at the sternum with abnormal adjacent soft tissue (Fig. 1b,c). Myconhenolate mofetil was

Dedrick et al., Nat Med. 2019 May;25(5):730-733.

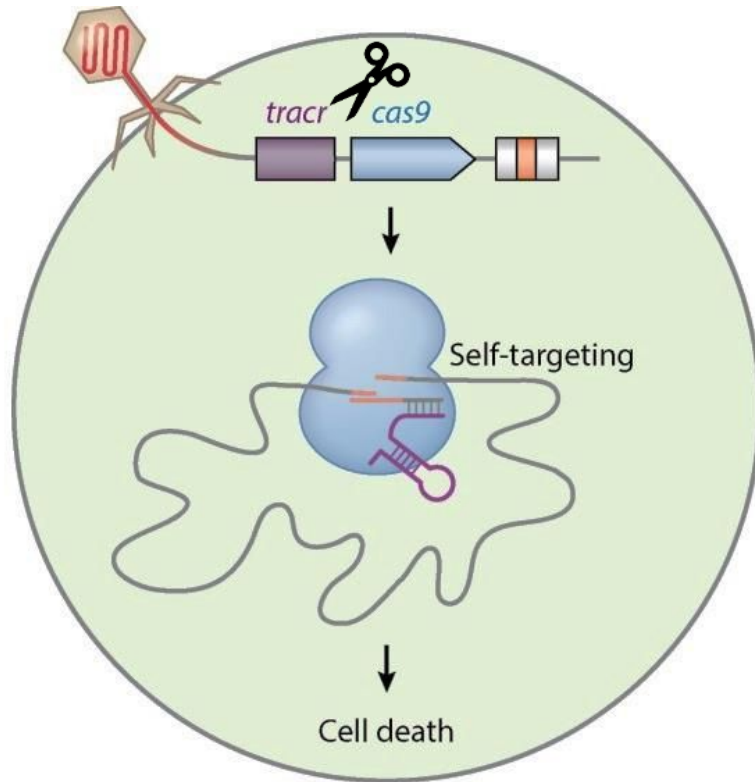


# Selektives Entfernen Resistenzgen-tragender Bakterien mittels CRISPR/Cas9-Phagen

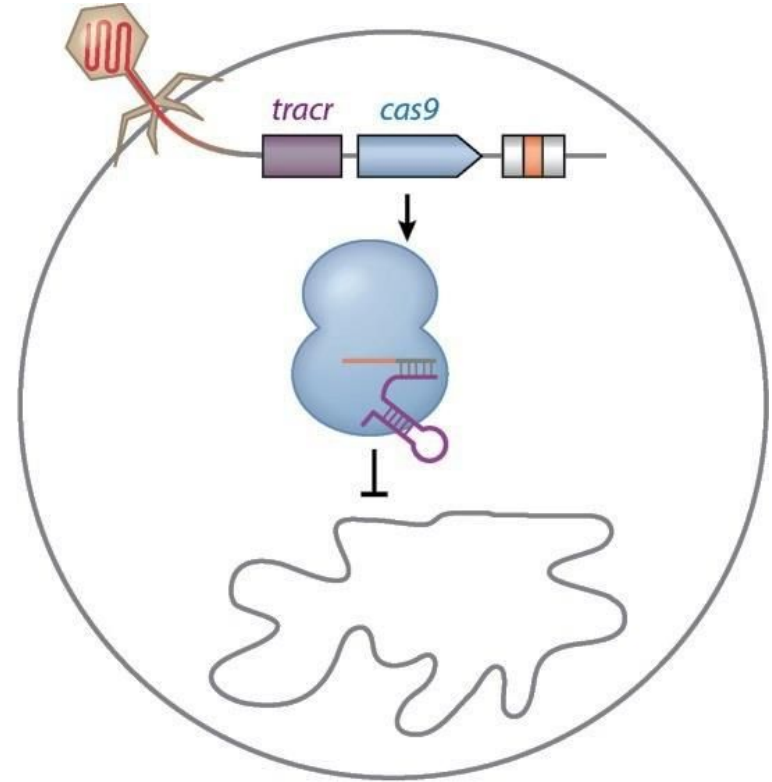


Jiang W, Marraffini LA. 2015.  
Annu. Rev. Microbiol. 69:209–28

# Selektives Entfernen Resistenzgen-tragender Bakterien mittels CRISPR/Cas9-Phagen



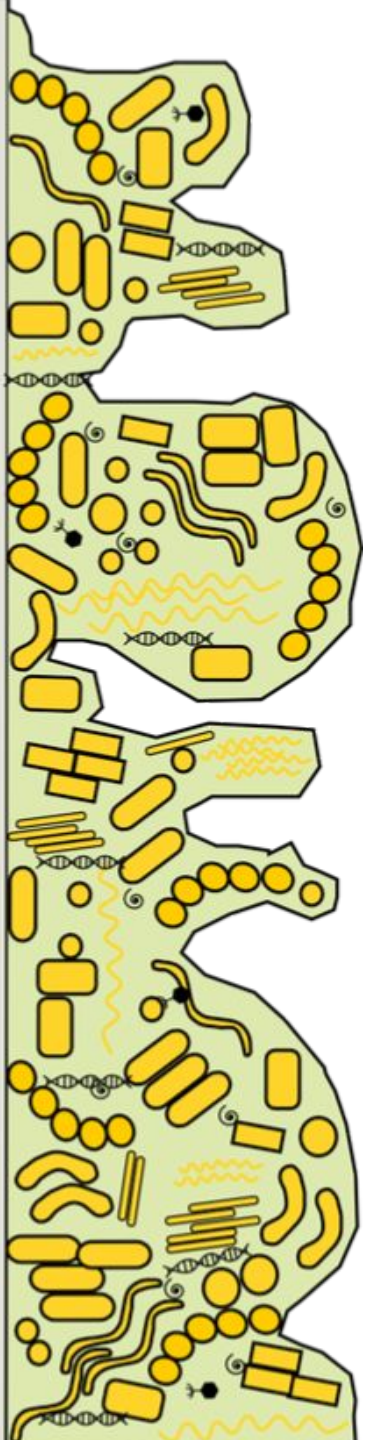
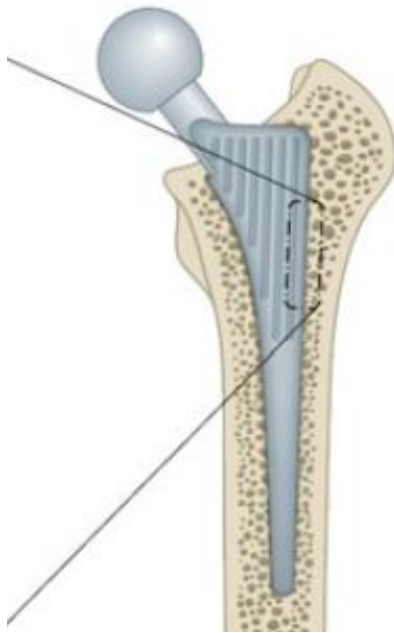
**Target cell**



**Nontarget cell**

Jiang W, Marraffini LA. 2015.  
Annu. Rev. Microbiol. 69:209–28

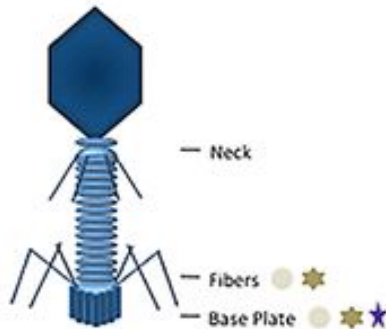
# Biofilmaktive Phagen



## Enzyme class

-  Sialidase
-  Levanase
-  Xylosidase
-  Dextranase
-  Alginate Lyase
-  Pectate/Pectin Lyase
-  Hyaluronate Lyase
-  Lipase
-  Peptidase

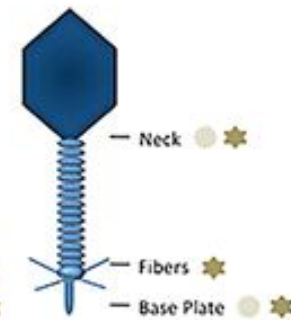
*Myoviridae*



*Podoviridae*



*Siphoviridae*



# **Ausblick Phagentherapie**

**Überwindung AMR, Synergien mit Antibiotika**

**Neue Wirkmechanismen, z.B. Biofilmaktivität**

**Nebenwirkungsarme, zielgenaue Erregerbekämpfung**

**Mikrobiota-Modulation: physiologische, immunologische,  
neurologische Indikationen ....**

**Prophylaktische Beseitigung von AMR-Bakterien**

**...**

**Personalisierte Therapie-Plattform**

# Gene therapy medicinal products (GTMP)

EU Directive 2009/120/EC

GTMP means a biological medicinal product which has the following characteristics:

- a. It contains an **active substance which contains or consists of a recombinant nucleic acid** used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;
- b. **Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence** it contains, or to the product of genetic expression of this sequence.

GTMP shall not include vaccines against infectious diseases.

**Recombinant nucleic acid**

**GM virus**

**GM cells**

**human  
animal  
microbial  
plant ....**



Bundesministerium  
für Gesundheit



Paul-Ehrlich-Institut

Bundesinstitut für Impfstoffe  
und biomedizinische Arzneimittel

AMG § 77



neuartige Therapien  
( ATMP )

Gen-  
therapeutika

Zell-  
therapeutika

Impfstoffe

Sera  
Antikörper

Bearbeitete  
Gewebe-  
produkte

„Virus“-Arzneimittel  
Personalisierte AM  
ATMP-Rahmen  
GVO-AM  
komplexe zelluläre AM  
...

Blut-  
produkte

Humane  
Gewebe

Allergene

# ATMP (advanced therapy medicinal product)

- Data-driven, flexible manufacturing **platforms**
- Heterogenous regarding origin, type and complexity of the product
- Combination with biomolecules/devices/companion diagnostics
- Genetically modified
- Personalised

Guideline on the **Risk-based approach** according to annex I, part IV of Directive 2001/83/EC applied to ATMPs (EMA/CAT/CPWP/686637/2011)

EudraLex Vol. 4 - Good Manufacturing Practice (GMP) guidelines part IV:  
**GTP for ATMP**

**Hospital Exemption** (...controversy)

# Ausblick: regulatorischer Rahmen für Phagen



**Erarbeitung Phagenkapitel EU-Arzneibuch**

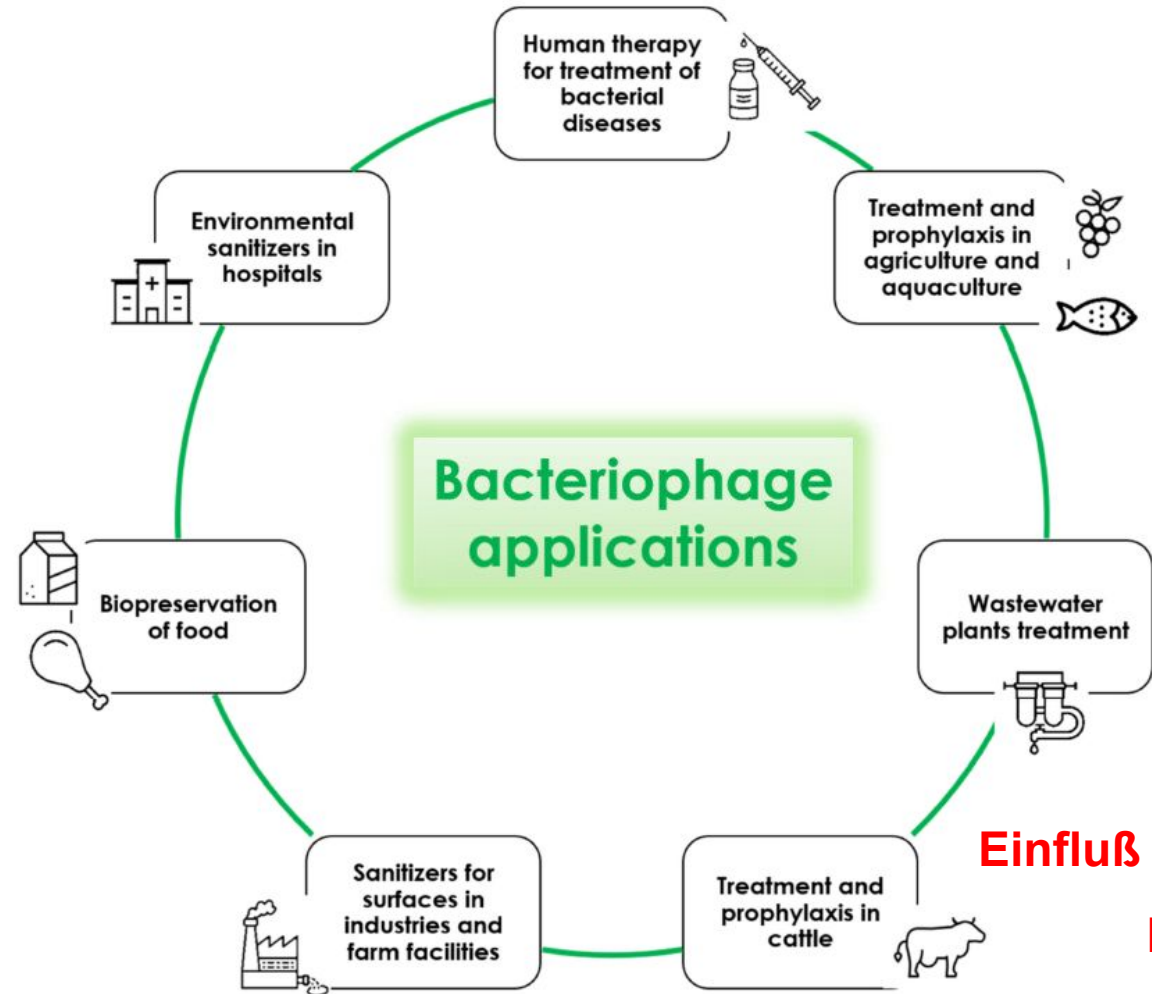
**Revision EU Pharma Legislation > passender regulatorischer Rahmen  
Phagen-Arzneimittel**



**Nationale Zwischenlösung für Phagen-Arzneimittel-Plattformen  
(z.B. BE-Modell, Krankenhausausnahme AMG 4b?)**



# Weitere Anwendungen lytischer Phagen



**CAVE**

**Resistenzentwicklung**

**Einfluß auf mikrobielle Gemeinschaften?**

**Horizontaler Gentransfer?**



# Phage Therapy in the Year 2035

*Jean-Paul Pirnay\**

*Laboratory for Molecular and Cellular Technology, Queen Astrid Military Hospital, Brussels, Belgium*



The emergence of multidrug resistant bacteria in both community- and hospital-acquired infections is recognized as a major public health threat. Phage therapy is increasingly mediatized and researched as an additional tool for combatting antibiotic resistant infections. However, phages exhibit a number of properties that differ from antibiotics and hamper their development as pharmaceutical products and their application in therapy. This paper advocates a paradigm shift in the development and application of infectious disease therapeutics to cater for personalized phage therapy, which could be realized by the year 2035. More specifically, it presents a sustainable and ethical supply chain of instant synthetic phages, based on a community effort,



**Vielen Dank**

Holger.Loessner@pei.de